Tools for Chemical Biology: New Macrocyclic Compounds from Diversity-Oriented Synthesis and Toward Materials from Silver(I) Acetylides

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Ph.D. Thesis

June 2010

Department of Chemistry
Technical University of Denmark

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Preface

This thesis describes the projects I have worked on during my Ph.D. studies from April 2007 to June 2010. Part I describes the results of the work carried out in the Clausen group at DTU, and Part II describes the results of the work conducted during a 6 months external stay from January to July 2009 in the Williams group at the University of Queensland (UQ), Brisbane, Australia.

Part I comprises four chapters. In Chapter 1, an introduction to diversity-oriented synthesis, and a review of diversity-generating strategies toward libraries of macrocyclic compounds, are given. Chapter 2 includes a description of the strategy for the project and the results which are rounded off by a conclusion in Chapter 3. Finally, Chapter 4 contains the experimental procedures used in this project.

Part II consists of Chapter 5, covering an introduction to single walled carbon nanotubes and techniques for their separation, and a description of the concept of the project and the results. Furthermore, the chapter contains a concluding part, summing up the results of the project and giving an outlook for the future, and finally an experimental section containing the procedures used in the project.

Appendix A contains a list of abbreviations used in this thesis.

Appendix B includes two published/submitted articles I have worked on during my Ph.D. studies.

In connection with this thesis, there are several people I would like to thank. First of all, I would like to express my gratitude to my supervisor Associate Professor Mads H. Clausen for fruitful discussions over the years and for always taking time for me. I would also like to thank my co-supervisor Associate Professor Charlotte H. Gotfredsen for her skilful assistance with currently ongoing structure analyses.

Current and former members of the MHC group are thanked for creating a great atmosphere and lots of fun, both in and outside the lab. Current and former co-students from other groups in building 201 are likewise thanked for a time I will miss. The following students who have been involved in the

project at DTU over the years are thanked for their valuable contributions: Marie V. Thrane, Martin Hansen, Jacob F. Kure, A. Emil Cohrt, Sarah M. Frankær, Martin Jonstrup, Kasper T. Madsen, and Casper J. Engelin. Current and former members of the technical staff in building 201 are thanked for their assistance.

Dr. Craig M. Williams is thanked for letting me work in his group at UQ and for his inspiring and enthusiastic supervision. I strongly hope I will be granted a postdoctoral fellowship so that I can return. The CMW group is thanked for creating a great atmosphere and for always being helpful. The technical staff at UQ is also thanked for their assistance.

DTU, the Lundbeck Foundation, the Torkil Holm Foundation, and the Augustinus Foundation are thanked for financial support for my Ph.D. studies. Furthermore, the Augustinus Foundation, the Otto Mønsted Foundation, Jorcks Foundation, Knud Højgaards Foundation, the Oticon Foundation, and Civilingeniør Frants Allings Legat are thanked for additional financial support for my external stay.

A special thanks goes to my fiancé Brian for his patience, love and support.

Charlotte Marie Madsen
Kgs. Lyngby, June 2010

Abstract

Part I

The formation of a library of diverse macrocyclic compounds with different functionalities and ring sizes in a few steps from two easily accessible α,ω-diol building blocks is presented. The building blocks are combined by esterifications in four different ways leading to the formation of four structurally isomeric diol precursors. These are then reacted with electrophilic reagents leading to 17-membered sulfites and 19-membered malonates in reasonable yields, and 20-22-membered phthalates and an 18-membered oxalate in low yields. Double-reductive amination of dialdehyde analogs of the diol precursors leads to 15-membered amines in yields ranging from 9 to 60%, reflecting large differences in reactivity based on steric environment. The convertion of the two least sterically hindered diols into diiodide analogs is also presented. However, the desired cyclizations of these precursors have not been successful.

Part II

The formation and subsequent coupling of a monosilver(I) acetylide of 2,3-diethynyltriptycene is presented. The silver(I) acetylide is formed in high yield from both 2,3-diethynyltriptycene and 2,3-di(trimethylsilylethynyl)triptycene by use of the same reagent. Coupling of the silver(I) acetylide with 1-iodoadamantane is demonstrated. Furthermore, attempts at the synthesis of 1,3-difluoro-5,7-diiodoadamantane from 1,3,5,7-tetraiodoadamantane are presented. Unfortunately, the reaction is found to be uncontrollable by use of two different reagents, giving a mixture of fluoro-iodoadamantanes. However, overall the results provide a good starting point for the synthesis of new triptycene and adamantane-containing molecules that can interact with carbon nanotubes.

Danish abstract

Part I

Dannelsen af et mangfoldigt bibliotek af makrocykliske stoffer med forskellige funktionaliteter og ringstørrelser i få trin fra to let tilgængelige α,ω-diol-byggeblokke bliver præsenteret. Byggeblokkene bliver kombineret ved esterificeringer på fire forskellige måder, der fører til dannelsen af fire strukturelt isomere dioler. Disse bliver derefter reageret med elektrofile reagenser, hvilket fører til 17-leddede sulfitter og 19-leddede malonater i rimelige udbytter, samt 20-22-leddede phthalater og et 18-leddet oxalat i lave udbytter. Dobbelt-reduktiv aminering af dialdehyd-analoger af diolerne fører til 15-leddede aminer i udbytter der ligger mellem 9 og 60%, hvilket afspejler store forskelle i reaktivitet baseret på sterisk miljø. Konverteringen af de to mindst sterisk hindrede dioler til diiodid-analoger bliver også præsenteret. Imidlertid er de ønskede cykliseringer af disse substrater ikke lykkedes.

Part II

Dannelse og efterfølgende kobling af et monosølv(I) acetylid af 2,3-diethynyltriptycen bliver præsenteret. Sølv(I) acetylidet dannes i et højt udbytte fra både 2,3-diethynyltriptycen og 2,3-di(trimethylsilylethynyl)triptycen ved anvendelse af samme reagens. Kobling af sølv(I) acetylidet med 1-iodadamantan bliver demonstreret. Desuden bliver flere forsøg på syntesen af 1,3-difluor-5,7-diiodadamantan fra 1,3,5,7-tetraiodadamantan præsenteret. Desværre har reaktionen vist sig at være vanskelig at kontrollere ved brug af to forskellige reagenser, der begge fører til dannelsen af en blanding af fluor-iodadamantaner. Imidlertid udgør resultaterne samlet set et godt udgangspunkt for syntese af nye triptycen- og adamantanbaserede molekyler, der kan interagere med kulstof-nanorør.

Contents

Preface **iii**

Abstract **v**

Danish abstract **vii**

I Tools for Chemical Biology: New Macrocyclic Compounds from Diversity-Oriented Synthesis 1

1 Macrocyclic drug discovery - from natural products to diversity-oriented synthesis 3
1.1 Lessons from nature 4
1.2 Diversity-oriented synthesis 5
1.2.1 Planning of DOS 5
1.3 Diversity-generating strategies toward libraries of new macrocycles 7
1.3.1 Multicomponent macrocyclizations 7
1.3.2 Ringclosures of combinations of building blocks 9
1.4 Modern techniques for macrocycle synthesis 12
1.4.1 Solid-phase synthesis 13
1.4.2 Fluorous synthesis 16
1.4.3 Preparation on DNA template 17
1.5 Concluding remarks 18

2 New macrocyclic compounds from diversity-oriented synthesis 19
2.1 Recent method development 19
2.2 The strategy 19
2.2.1 Choice of building blocks 20
2.3 Results and discussion 22

2.3.1 Synthesis of the building blocks 22
2.3.2 Synthesis of the diols 25
2.3.3 Synthesis of macrocyclic sulfites 25
2.3.4 Synthesis of macrocyclic malonates 26
2.3.5 Synthesis of macrocyclic phthalates 28
2.3.6 Synthesis of macrocyclic oxalate 29
2.3.7 Attempts at the synthesis of macrocyclic diether 30
2.3.8 Synthesis of macrocyclic amines 30
2.3.9 Attempts at the synthesis of macrocyclic sulfides . . . 36

3 Conclusion 39

4 Experimental section 41

II Toward Materials from Silver(I) Acetylides 65

5 Toward a spacer for carbon nanotube separation utilizing silver(I) acetylide chemistry 67
5.1 Carbon nanotubes - nanoscale electrical conductivity to be exploited 67
5.1.1 Single walled carbon nanotubes 67
5.1.2 Techniques for SWNT separation 68
5.2 The concept 70
5.2.1 Design of a molecular spacer 70
5.2.2 Synthesis outline 71
5.2.3 Alkynylation of adamantyl iodide by use of silver(I) acetylides 72
5.3 Results and discussion 73
5.3.1 Synthesis of the adamantane unit 73
5.3.2 Synthesis of the triptycene unit 75
5.3.3 Silver(I) acetylide chemistry 75
5.4 Summary and outlook 78
5.5 Concluding remarks 81
5.6 Experimental section 82

Bibliography 87

Appendix A 97

Appendix B 101

Part I

Tools for Chemical Biology: New Macrocyclic Compounds from Diversity-Oriented Synthesis

Chapter 1

Macrocyclic drug discovery - from natural products to diversity-oriented synthesis

Macrocyclic compounds are attractive compounds for drug discovery due to the fact that naturally occuring macrocycles often display diverse and interesting biological activities. These include for example antibiotic, antifungal, anticancer and immunosuppressive activities as seen for erythromycin (**1**),[1] amphotericin B (**2**),[2] epithilone B (**3**)[3] and rapamycin (**4**),[4] respectively (see Figure 1.1).

The reason for the biological activity can be found in several structural advantages characteristic for macrocyclic compounds. They are conformationally preorganized, enabling them to bind selectively to targets with minimal entropic loss. However, they have a certain flexibility, which, in combination with their functionally independent subregions, enables them to bind non-covalently to each other (e.g. **2**[5]) or to mediate the assembly of other macromolecules by non-covalent interactions (e.g. **4**[6]). Furthermore, they have the ability of burying away polar functionalities, leading to improved membrane permeability as compared to their linear analogs. Proteolytic and metabolic stability is also improved as a consequence of the reduced accessible conformational space.[7] An example of a synthetic macrocycle with improved target selectivity as compared to its linear analog is the cyclic compound **5**, which is a 17-fold more potent inhibitor of the matrix metalloproteinase MMP-8 than the linear analog **6** (Figure 1.2).[8]

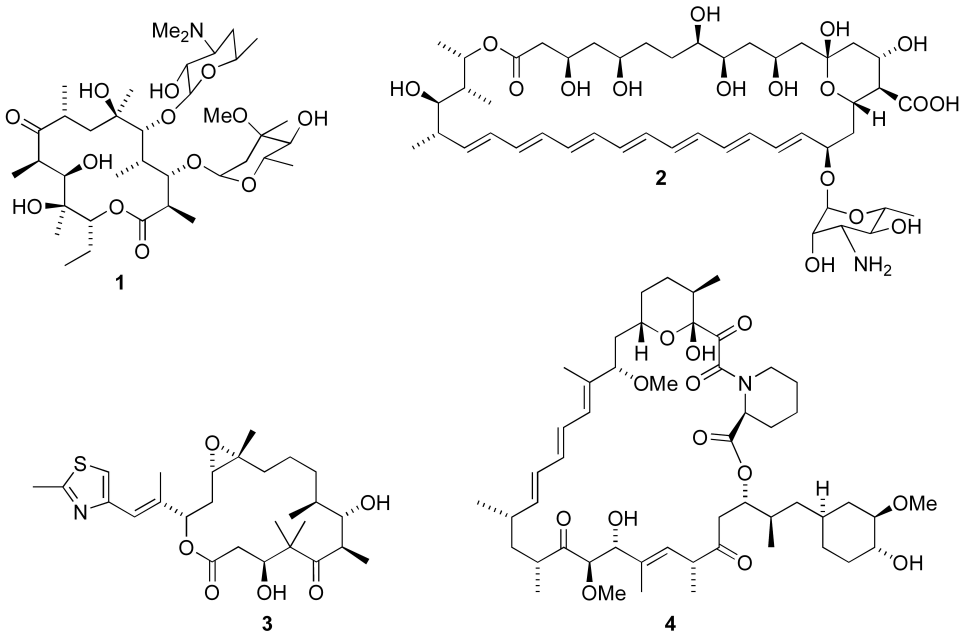


Figure 1.1: Structures of naturally occuring macrocyclic drugs: erythromycin (**1**), amphotericin B (**2**), epithilone B (**3**) and rapamycin (**4**).

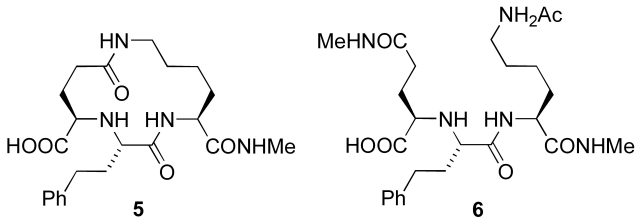


Figure 1.2: Compounds **5** and **6** are inhibitors of MMP-8, which is a member of the family of MMPs needed for maintenance of the extracellular matrix. The macrocyclic compound **5** is a 17-fold more potent inhibitor than the linear analog **6**.

1.1 Lessons from nature

Current macrocyclic drugs are almost exclusively derived from natural sources and are either identical to or closely related to naturally occuring macrocycles.[9] Despite the valuable characteristics described above for macrocyclic compounds and the proven success of more than a hundred marketed macrocyclic drugs, so far, this compound class has been poorly explored within drug discovery.[7] The main reason for this is the often complex structures of naturally occuring macrocycles and the synthetic effort thus required.

However, it is possible to prepare significantly less complex synthetic macrocycles, and valuable inspiration for this can be found in nature. Hence, it has been found that some substructures are frequently present in naturally occuring macrocycles. These are, for example, polyketides, heterocycles, peptide, biphenyl and (bi)aryl ether domains.[10]

An approach, combining natural product drug discovery with combinatorial chemistry has been suggested.[11,12] This strategy relies on the design of synthetic compounds from easily accessible building blocks containing naturally occurring substructural motifs, and hence it gives rapid access to synthetic libraries of compounds resembling natural products.

1.2 Diversity-oriented synthesis

In recent years, a field named diversity-oriented synthesis (DOS) has been employed within chemical biology.[13,14] Whereas target-oriented synthesis (TOS) aims to access a single target structure with known or predicted properties, and combinatorial chemistry aims to access a collection of analogs of such a structure, the aim in DOS is to populate chemical space* broadly with complex and diverse structures having unknown properties (Figure 1.3).[14]

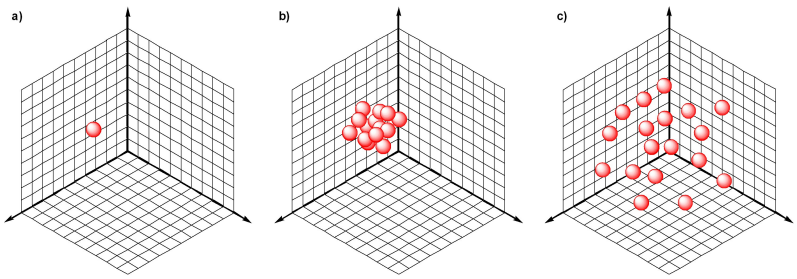


Figure 1.3: Illustration of the difference between TOS (a), combinatorial synthesis (b), and DOS (c) in terms of the occupation of chemical space.

1.2.1 Planning of DOS

TOS comprises linear and convergent synthetic pathways, which are planned in the reverse-synthetic direction by using retrosynthetic analysis, going from complex→simple. In contrast, DOS is planned by using forward-synthetic

*Chemical space is multidimensional. Each dimension is defined by a descriptor, which can be of biological or chemical nature.[14]

analysis,[15] going from simple and similar→complex and diverse, leading to branched and divergent synthetic pathways.[14]

Complexity and diversity-generating reaction pathways, including pairwise relationships, where the product of one complexity and diversity-generating reaction is the substrate for another, are valuable in the planning of DOS and can lead to highly complex and diverse products in just a few synthetic steps starting from simple and similar building blocks.[14]

Complexity-generating reactions

Based on the structures and functions of natural products, it is suggested that structural complexity may have a positive influence on macromolecule-perturbing function and specificity of action. Hence, the aim of DOS is to access small molecules with complex molecular skeletons,* and moreover, to access more globular or spherical molecular skeletons as compared to the relatively flat molecular skeletons often used in combinatorial chemistry. To maximize efficiency, synthetic pathways in DOS should be no more than three to five steps.[14]

Diversity-generating reactions

The desired diversity obtained from diversity-generating reactions can be divided into three distinct diversity elements: appendage diversity, stereochemical diversity and skeletal diversity.[14]

Appendage diversity: Obtained through the use of coupling reactions to attach different appendages to a common molecular skeleton, leading to the generation of all possible combinations of the skeleton and the used appendages. This process is identical to the central process in combinatorial chemistry.[14]

Stereochemical diversity: Achieved through the use of enantio- or diastereoselective reactions, ideally producing a combinatorial matrix of stereoisomeric products in a process analogous to the above.[14]

Skeletal diversity: Obtained through two different strategies; a reagent-based approach and a substrate-based approach (Figure 1.4). In the first approach, a common substrate is transformed into a collection of products having different molecular skeletons through the use of different reagents (Figure 1.4a).[13,16,17] The second approach involves the transformation of a collection of substrates having different appendages that pre-encode skeletal

*The overall three-dimensional shape of a complex molecular skeleton is defined by a large number and/or variety of rigidifying elements: covalent bonds, non-covalent bonds, and non-bonding interactions.[14]

information (called σ elements) into a collection of products having different molecular skeletons by the use of common reagents (Figure 1.4b).[18]

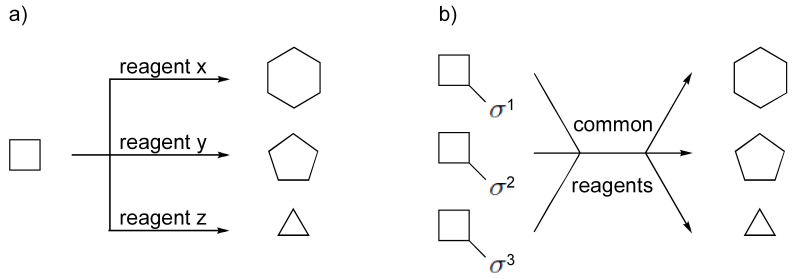


Figure 1.4: Illustration of the two general approaches for the generation of skeletal diversity: (a) the reagent-based approach and (b) the substrate-based approach.

Simultaneous generation of complexity and diversity

To achieve high levels of both complexity and diversity, an approach incorporating complexity-generating reactions into stereochemical and skeletal diversity-generating reactions has been suggested to be effective.[19] Moreover, there has recently been a growing interest in the development of a systematic and general strategy for achieving this goal.[20]

1.3 Diversity-generating strategies toward libraries of new macrocycles

The formation of macrocyclic compounds rather than cyclic or linear oligomers is challenging. Specifically, the conformation of the precursor has a large influence on macrocyclizations,[21] and it is often necessary to tailor reaction conditions to individual substrates.[22,23] Hence, the synthesis of macrocycles within DOS is difficult as it requires a cyclization method that is practical and general enough to work reliably with a wide variety of substrates and functional groups. Moreover, the minimization of steps and hereby the demand to avoid protection groups is difficult. However, strategies toward this goal have been developed.[24]

1.3.1 Multicomponent macrocyclizations

The use of multicomponent reactions (MCRs) involving bifunctional building blocks is an efficient approach for DOS. In particular, the Ugi reac-

tion has been proposed to give the structural variation required for such an approach.[25] A strategy for the one-pot assembly of diverse and complex macrocycles, mainly employing the Ugi four-component reaction (Ugi-4CR), has been proposed by Wessjohann.[26] This strategy has been termed 'multiple multicomponent macrocyclization including bifunctional building blocks' (MiB).[26]

The Ugi-4CR is a reaction between an isonitrile, an aldehyde, an amine, and a carboxylic acid to form a dipeptide (Figure 1.5a). It is possible to achieve highly diverse products by varying the substituents of each of the four components. When this reaction strategy is expanded to involve two or more MCRs for the formation of macrocycles, the resulting products may be described as uni- or bidirectional (Figure 1.5b+c). The unidirectional product is the result of an MiB involving unsymmetrically* bifunctional building blocks and basically a higher homolog of the single Ugi macrocyclization (Figure 1.5b), whereas the bidirectional product is the result of an MiB involving symmetrically bifunctional building blocks (Figure 1.5c).[26]

Recently, Wessjohann and co-workers demonstrated that the above strategy is suitable for the rapid generation of diverse bidirectional macrocycles with exocyclic substituents resembling natural products, e.g. **7** (Figure 1.6).[28] In order to obtain appendage diversity by introducing natural-product-like side chains in the one-pot process, carboxylic acid building blocks with appended amino acids or carbohydrates were used. These were combined with formaldehyde as the aldehyde building block, and different diamines and diisocyanides as the bifunctional building blocks, containing biaryl ether, heterocycle, heterofunctionalized chain or benzene moieties. The diisocyanides were synthesized in two steps from the corresponding commercially available diamines.[28]

Very recently, a new protocol for synthesizing cyclic peptides of type **8** (Figure 1.7) based on the Ugi-4CR was introduced by the group of Yudin.[29] Amphoteric amino aldehydes with the nucleophilic center at the α-position were shown to aid in high-yielding and stereoselective formation of cyclic peptides. Initially, an imine was formed from the amino aldehyde and a linear peptide. Subsequent cyclization of the resulting zwitterion with *tert*-butyl isonitrile followed by transannular attack of the amine onto the mixed anhydride yielded the cyclic peptides **8**. Further diversification by ring opening of the aziridine ring is possible.[29]

*The term 'unsymmetrically bifunctional' refers to a building block with two different MCR reactive functional groups on either side of the molecule, whereas the term 'symmetrically bifunctional' refers to a building block with two identical MCR reactive functional groups on both sides of the molecule. This terminology is independent of the symmetry or asymmetry of the core of the building block.[26]

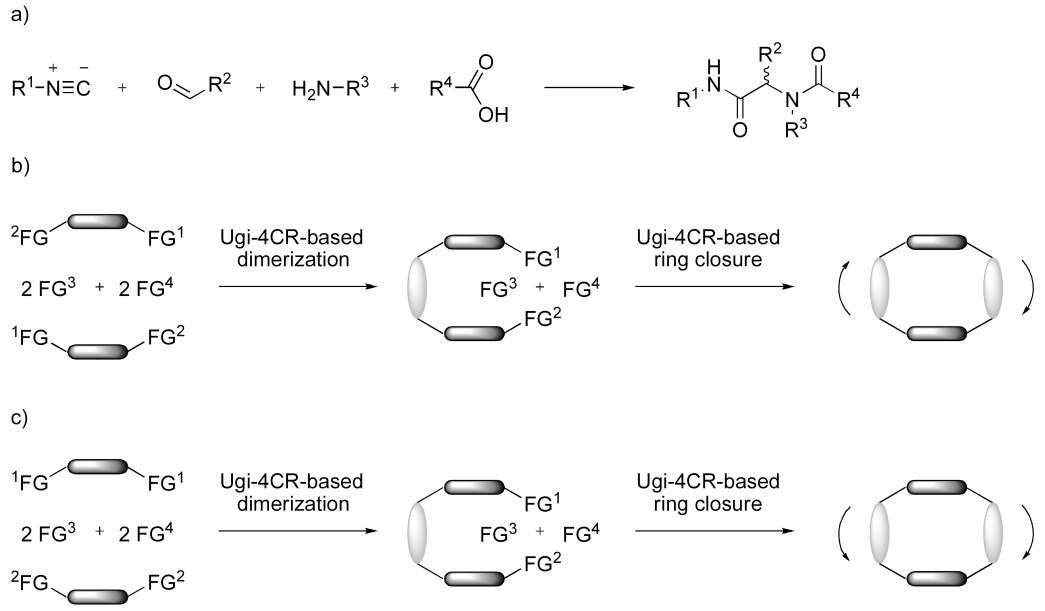


Figure 1.5: Illustration of: (a) the Ugi-4CR forming a dipeptide, (b) the use of unsymmetrically bifunctional building blocks in Ugi-4CR MiB to obtain a unidirectional product, and (c) the use of symmetrically bifunctional building blocks in Ugi-4CR MiB to obtain a bidirectional product. FG^{1-4} refer to the Ugi-4CR reactive functional groups (-NC, -CHO, $-NH_2$, -COOH) in any combination.[27]

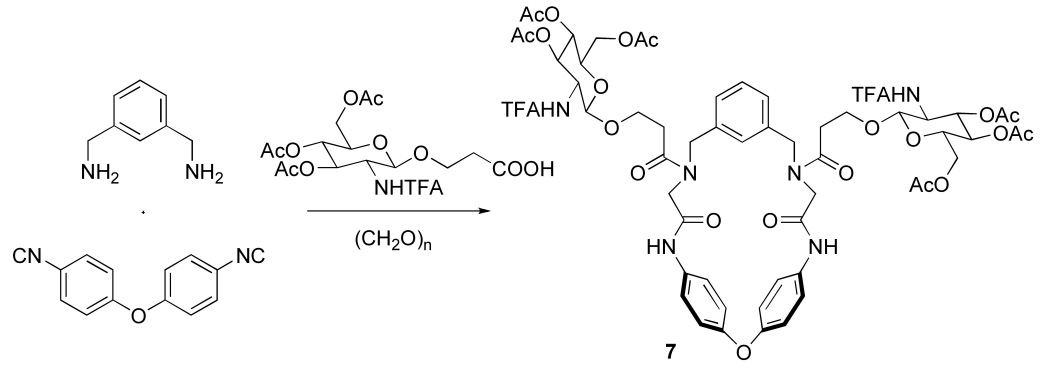


Figure 1.6: The formation of bidirectional macrocycle **7** with carbohydrate (aminoglucose) moieties.

1.3.2 Ringclosures of combinations of building blocks

A majority of approaches to DOS of macrocycles has been based on the formation of cyclization precursors in a few steps from easily accessible building blocks followed by cyclization by use of an established method, examples of

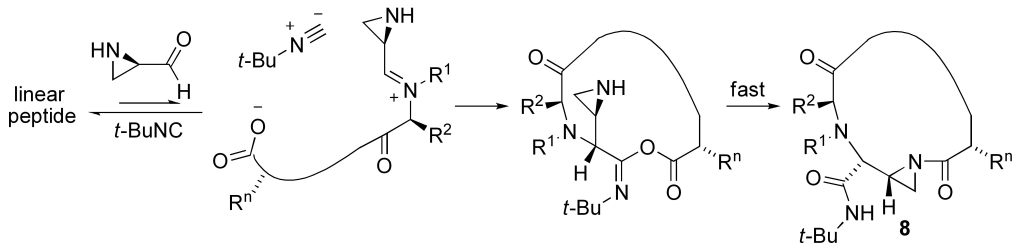


Figure 1.7: Stereoselective formation of **8**.

which are described below.

Macrolactonization and macrolactamization

Since naturally occurring macrocycles are often found to be lactones or lactams,[10] many examples of the application of lactonization and lactamization ring closing methods have been reported. As a recent example of a diversity-generating strategy based on macrolactonizations, the formation of a library of diverse macrodiolides (e.g. **9** and **10** in Figure 1.8) has been demonstrated by Panek and Porco.[30] The strategy takes advantage of directly accessible cyclization precursors (hydroxy esters) obtained through stereoselective addition of crotyl silanes to different electrophiles.[31] The hydroxy esters are then cyclodimerized (as illustrated in Figure 1.8a) by use of tin-catalyzed transesterifications performed under microwave heating. Initial biological evaluation of the library led to the identification of compound **10** (Figure 1.8b) as a κ opioid receptor antagonist that may have potential utility for the treatment of various neuropsychiatric conditions (e.g. depression).[30]

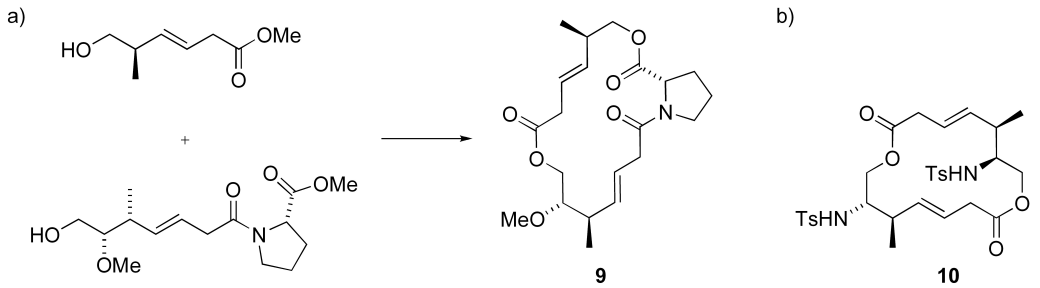


Figure 1.8: (a) The synthesis of **9** through cyclodimerization of two different hydroxy esters, and (b) the structure of another member **10** of a library of macrodiolides.

Analogously to the above described method, macrocyclic bislactams have recently been synthesized by zirconium-catalyzed cyclodimerization of alloc-

protected amino esters with the aim to facilitate transannular cyclizations leading to polycyclic frameworks.[32]

Another example of a method employing macrolactonization is the synthesis of complex polyketide-like macrocycles (e.g. **11** in Figure 1.9) reported by the group of Leighton.[33] These are formed through short syntheses of simple polyol fragments followed by cyclization according to the Yamaguchi macrolactonization protocol.[34] Only the 14-membered macrocycles were produced in the macrolactonization reaction.[33]

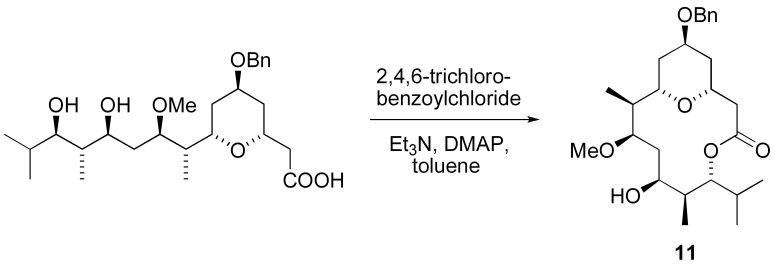


Figure 1.9: Yamaguchi macrolactonization of a simple polyol fragment to yield the complex polyketide-like macrocycle **11**.

Ring-closing metathesis

Ring-closing metathesis (RCM) has become one of the most popular macrocyclization methods in natural product synthesis due the high functional group compatibility, the possibility for further transformations, and the development of stable catalysts.[23] As a consequence hereof, the RCM reaction has also found its way to DOS. Recently, a diversity-oriented approach employing a cross-enyne metathesis and RCM cascade (Figure 1.10) has been presented by the group of Kotha.[35] Cascade precursors were built from three building blocks: glycine/α-aminoisobutyric acid, propargyl alcohol/bromide, and an unsaturated alcohol/bromide. Various macrocycles (e.g. **12**) were generated through combination of the precursors with 1,5-hexadiene in the tandem metathesis sequence. Linear side-products (e.g. **13**) not undergoing RCM were also formed.[35]

Click reactions

Sharpless *et al.* introduced the term 'click chemistry' referring to simple, selective, high-yielding reactions of easily accessible compounds.[36] Within this category, especially the Cu-catalyzed alkyne-azide cycloaddition[37] has been widely utilized in recent years.[38] Obviously, this kind of reactions are

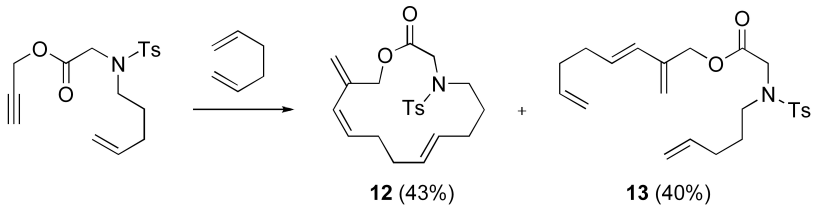


Figure 1.10: Cross-enyne metathesis and RCM cascade to form macrocycle **12** and side-product **13**.

suitable for DOS, and, recently, a skeletal diversity-generating method employing alkyne-azide cycloadditions for macrocyclic ring formation has been suggested by Marcaurelle and co-workers.[39] Different simple azido alkyne substrates were formed, which were used for both the Cu-catalyzed alkyne-azide cycloaddition forming a 1,4-triazole (e.g. **14** in Figure 1.11) and the recently introduced Ru-catalyzed alkyne-azide cycloaddition[40] forming a 1,5-triazole (e.g. **15**). The latter is the first example of an intramolecular Ru-catalyzed alkyne-azide cycloaddition.[39]

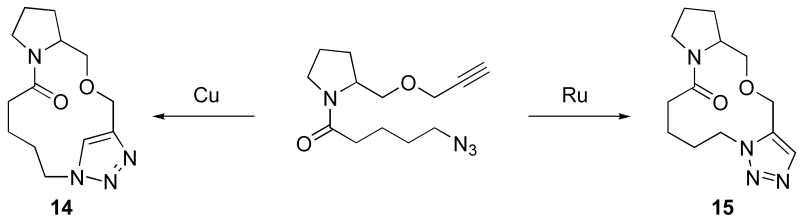


Figure 1.11: Catalyst controlled selective synthesis of macrocycles **14** and **15** from azido alkyne substrate.

1.4 Modern techniques for macrocycle synthesis

The large number of products synthesized in DOS and the required flash chromatography purifications render traditional solution phase synthesis impractical. Reactions that are selective, high-yielding, and rapidly creates more diversity are required to make solution-phase synthesis convenient. Furthermore, syntheses in which purification does not have to be done after every step are desired.[24] Modern techniques have been developed to overcome these problems and allow rapid access to huge libraries. These include solid-phase synthesis, fluorous synthesis, and preparation on a DNA template.

1.4.1 Solid-phase synthesis

There are many advantages to solid-phase synthesis when it comes to library creation. Most importantly, the use of synthesis automization is possible. Furthermore, the purification procedure is much more simple as compared to solution-phase synthesis, and conversions are often higher as it is often possible to use excess reagent. In case of macrocyclization, it is possible to use rigid or low loading resins, resembling very dilute solutions by having the functional groups far away from each other.[24]

Examples of libraries from solid-phase synthesis

An investigation of the ability of a variety of substrates to cyclize on solid-phase was presented by Schreiber and co-workers.[41] A pilot library of diverse 13- and 14-membered macrocycles (e.g. **16** in Figure 1.12) was synthesized from stereochemically and regiochemically diverse hydroxy acids. Figure 1.12 is a schematic view of how one of the hydroxy acids (protected with allyl and PMB), which were obtained from common starting materials in solution-phase, was attached to the resin, deprotected and esterified with another hydroxy acid (allyl protected). Removal of the protection groups followed by Yamaguchi lactonization (or attempt at it) and cleavage from the solid support furnished the macrocyclic products in 0-75% yield, reflecting a great influence of the steric environment on the cyclizations.[41]

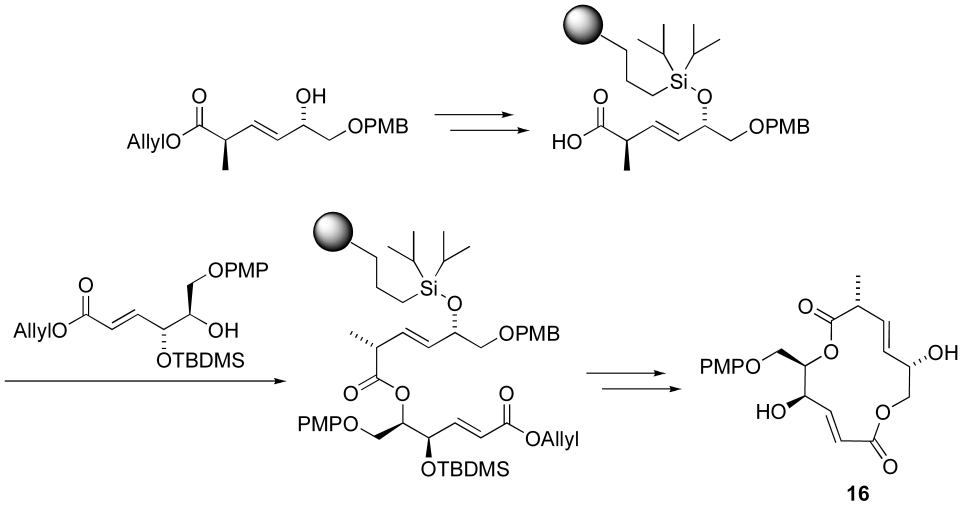
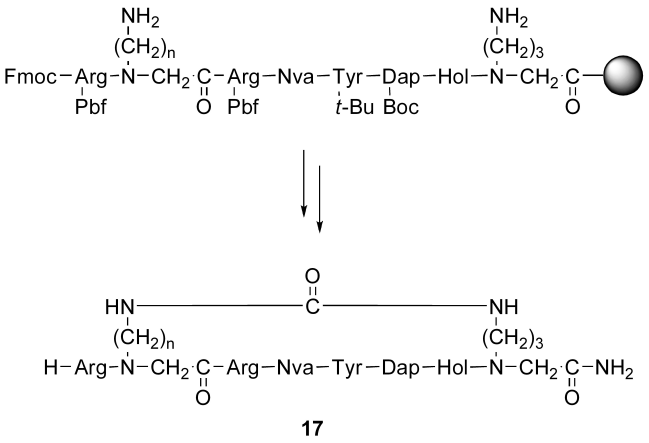


Figure 1.12: Synthesis of macrocycle **16** from hydroxy acid components.

More recently, a new methodology for the synthesis of cyclic peptides of

type **17** (Figure 1.13) was reported by Gilon and co-workers.[42] The cyclizations were accomplished by a bis(trichloromethyl) carbonate (BTC) mediated urea bridge formation between two amino moieties positioned on *N*-alkyl side chains of glycine derivatives. Different ring sizes were obtained through the use of different lengths of side chains. This approach offers an opportunity to increase the diversity by altering the amino acid sequence and the position of the side chains.[42]



17

Figure 1.13: Solid-phase synthesis of cyclic peptides **17** with varying ring sizes (n = 2, 3, 4, 6) from peptides bearing amino alkyl side chains.

Split-pool synthesis

Split-pool synthesis is a powerful tool within solid-phase synthesis providing quick access to huge libraries of compounds. An example of a split-pool synthesis of a library of more than 2.000 14-membered *para*-cyclophanes of type **18** (Figure 1.14), has been presented by Schreiber and co-workers.[43] As an alternative to the traditional strategies employing acyclic precursors for cyclization, the macrocycle forming step in this strategy is a skeletal transformation of a steroidal structure. A steroidal epoxide was synthesized in five steps and loaded onto macrobeads. These were then split and reacted with different reagents in two different pathways, one promoting epoxide opening by use of thiols and secondary amines, and one promoting epoxide opening by use of primary amines followed by alkylation of the amines. The compounds were then pooled and a Diels-Alder reaction with different ynones was performed giving a diene product, which was transformed into a macrocyclophane through a retro-Diels-Alder reaction.[43]

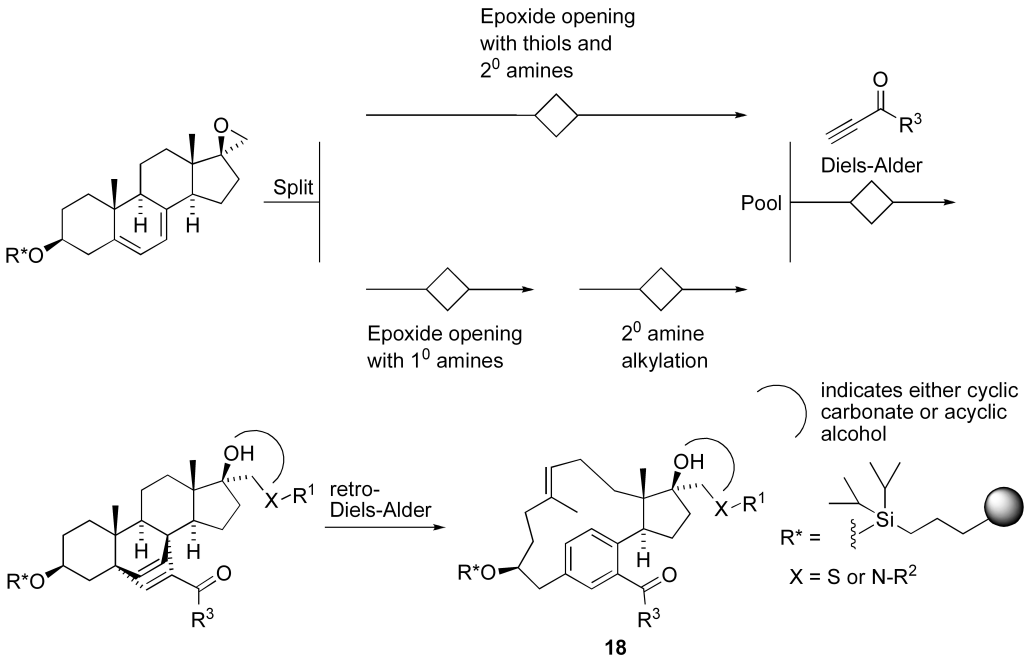


Figure 1.14: An overview of the split-pool synthesis of more than 2.000 14-membered *para*-cyclophanes **18**.

Cyclative release

Macrocycle synthesis on solid-phase has opened up opportunity for achieving simple purification in the ring-closing step by connecting this step to the resin-release step. This method ensures that only cyclic products are cleaved from the resin, whereas linear byproducts will remain attached.

As a recent example of the application of cyclative release, the synthesis of a combinatorial library of macrocyclic peptidomimetics of types **19** and **20** (Figure 1.15) has been reported by Marsault and co-workers.[44] Initially, a library of approximately 10.000 compounds was screened to find a lead compound, which is an antagonist to the human motilin receptor. A library of analogs for SAR analysis was then prepared by use of two complementary solid-phase parallel approaches employing RCM or macrolactamization as the cyclative release methods. By varying the three amino acids and the tether, a library of 53 macrocyclic compounds was synthesized and tested for binding affinity for the human motilin receptor.[44] An extension of the library

by use of new unnatural amino acids containing basic side chains has led to increased binding affinities.[45]

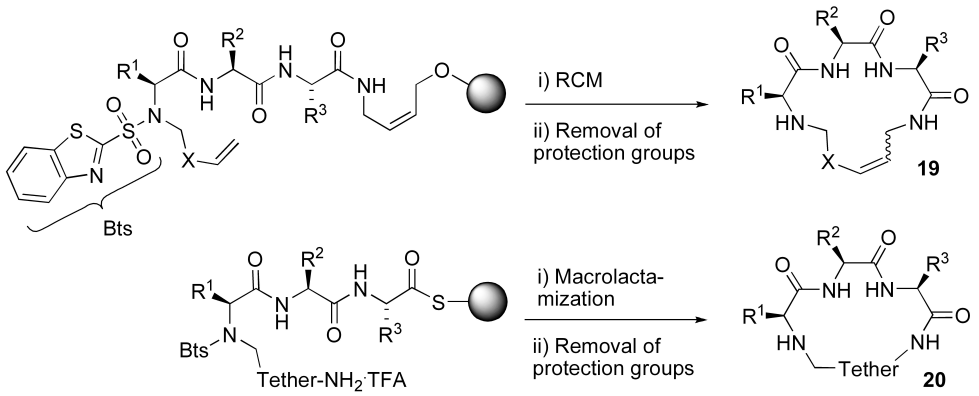


Figure 1.15: Cyclative release of peptidomimetics **19** and **20** by RCM and macrolactamization, respectively. Amino acids are shown as L-configured for clarity.

1.4.2 Fluorous synthesis

Fluorous synthesis utilizes functionalized perfluoroalkyl groups attached to substrates or reagents. Conceptually, fluorous tags are very similar to solid-phase tags. However, their solubility in organic solvents provides some distinct advantages over solid-phase tags such as the possibility to monitor reactions by use of traditional analytical techniques.[46] Excess reagent can be removed easily by fluorous-solid phase extraction.[47]

A diversity-oriented approach involving cyclative release of products (e.g. macrocycle **21** in Figure 1.16) from a fluorous-tagged linker has been reported by the group of Nelson.[48,49] This approach has led to a library of compounds with more than 80 distinct scaffolds including macrocycles formed by RCM reactions as well as other compounds obtained by metathesis cascade reactions.[48]

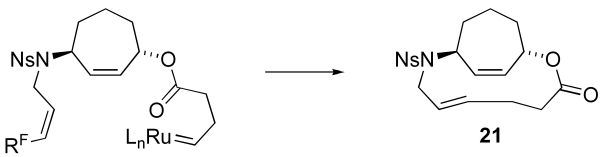


Figure 1.16: Synthesis of macrocycle **21** employing a fluorous-tagged linker (R^F).

1.4.3 Preparation on DNA template

Liu and co-workers have developed an approach for DNA-templated synthesis and selection of macrocyclic fumaramides of type **25** (Figure 1.17) employing three biotinylated DNA-linked building blocks.[50] Starting from a lysine-linked DNA oligonucleotide with three coding regions, the first reagent is hybridized to the first region, giving **22**. Attachment of the building block to the lysine, capping with a streptavidin-linked bead followed by subjection to basic conditions removed the DNA linker, and the process was repeated with another DNA-linked reagent giving **23**. Attachment of a third DNA-linked building block containing a Wittig ylide linker, capping with a streptavidin-linked bead followed by $NaIO_4$ mediated unmasking of an aldehyde linked to the lysine side chain gave the cyclization precursor **24**. Wittig cyclization with concomitant cleavage of the linker furnished the DNA-linked macrocyclic fumaramide **25**. Using this strategy, a library of 65 members was generated and subjected to in vitro selections for binding to carbonic anhydrase. The DNA templates of the binding macrocycles were subsequently amplified and decoded to confirm the identity of a control macrocycle having known target affinity.[50]

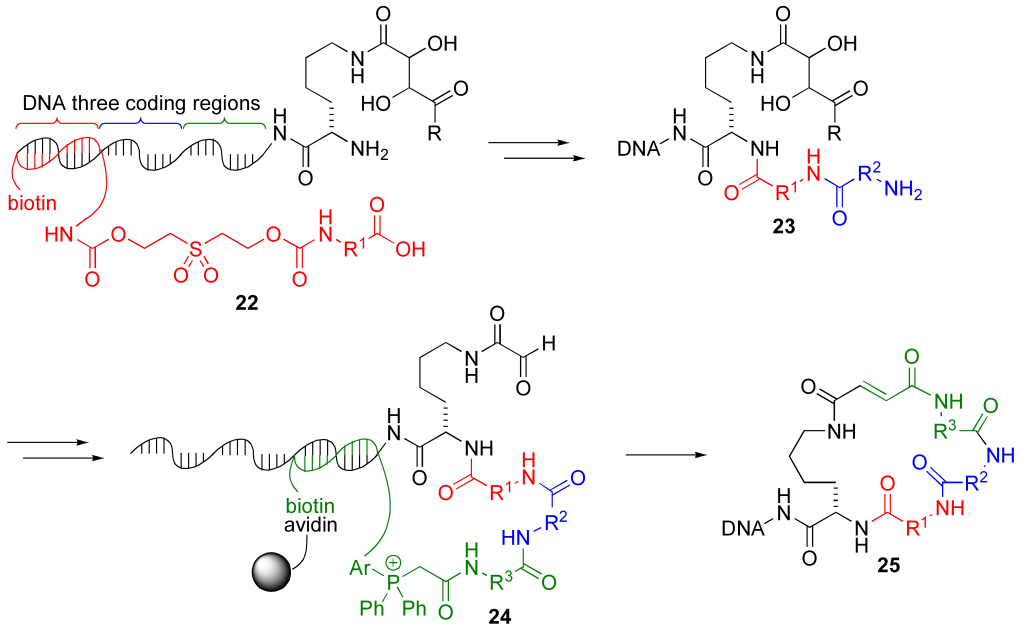


Figure 1.17: DNA duplex-driven synthesis of **25**. R = $NHCH_3$ or tryptamine; Ar = –(p-C_6H_4)–.

More recently, it was demonstrated that this strategy, after some opti-

mizations, could be extended to the synthesis of a massive library of more than 13.000 macrocycles.[51]

1.5 Concluding remarks

There is a growing interest in the application of synthetic macrocycles to chemical biology, potentially leading to drug discovery. The aim to occupy a vast part of chemical space has prompted the development of a range of methods for macrocycle synthesis. However, it is still unknown whether the (previously) unoccupied parts of chemical space provide increased chances of finding new compounds with biological activity. The answer to that question lies in future formation and screening of a large number of libraries.

Chapter 2

New macrocyclic compounds from diversity-oriented synthesis

A novel strategy for formation of a library of diverse macrocyclic compounds is presented. Diversity is created both through formation of different diol cyclization precursors in a few steps from easily accessible building blocks and through subsequent cyclizations by use of different methods.

2.1 Recent method development

Recently, a method for formation of macrocyclic compounds from diol precursurs was developed in the group of Clausen.[52] As seen in Figure 2.1, a diol **26** was cyclized by use of different reagents, thus creating a carbonate **27**, a sulfite **28**, a phosphotriester **29**, a sulfide **30**, and an amine **31**. In the latter two cases, the diol **26** was converted to a diiodide and a dialdehyde, respectively, prior to cyclization.[52]

2.2 The strategy

Encouraged by the above methods for formation of macrocyclic rings from diol precursors,[52] the generation of a library of diverse macrocycles based on this strategy is pursued. According to the planning strategies described in Chapter 1 (Section 1.1 and Subsection 1.2.1), the aim is to produce macrocycles in a few diversity-generating steps starting from two simple building blocks as outlined in Figure 2.2. The idea is to form four structurally isomeric diol precursors through combinations of the building blocks by esterifications.

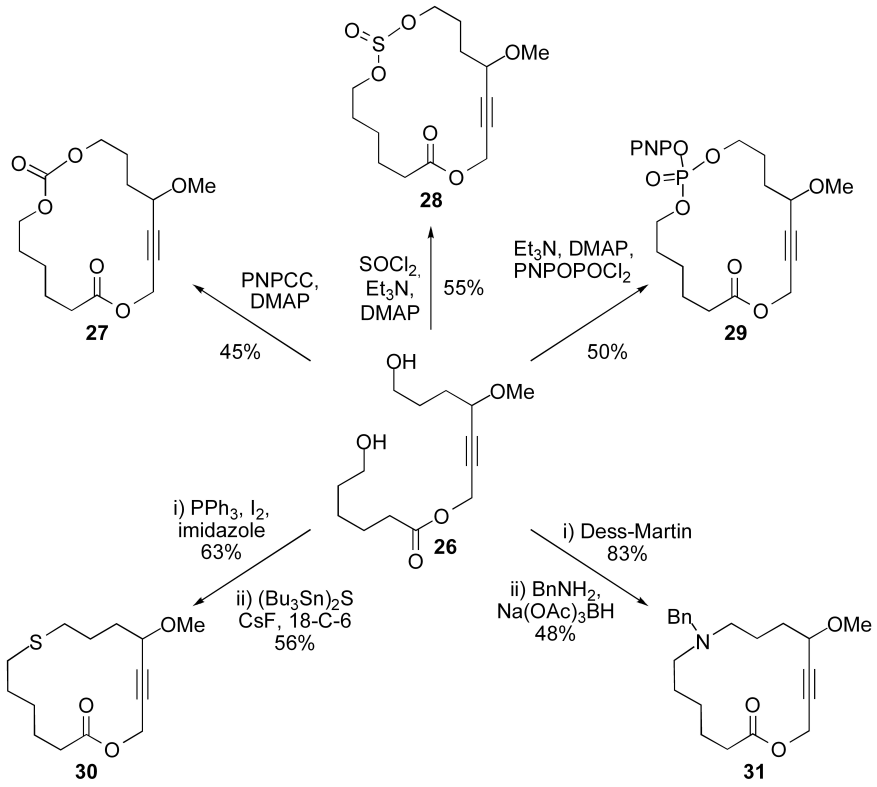


Figure 2.1: Recent method development.

These are then ready to be cyclized, as above, either in one step by reaction with bis-electrophilic reagents, or in two steps by forming the dialdehyde or diiodide derivatives and then reacting them with a nucleophilic reagent.

This strategy leads to skeletal diversity in the combination step as well as in the cyclization step. Specifically, in the combination step different sequences of the structural elements of the building blocks are obtained, and in the cyclization step different functionalities are introduced, leading to different ring sizes and conformations. Considering that the building blocks are appended to each other in different ways, the last step falls into the category of a substrate-based approach to skeletal diversity-generating reactions (Subsection 1.2.1).

2.2.1 Choice of building blocks

The parent structures, **32** and **33**, of the chosen building blocks for this project are shown in Figure 2.3. These can be readily obtained from commercially available starting materials and contain fragments inspired by nature,

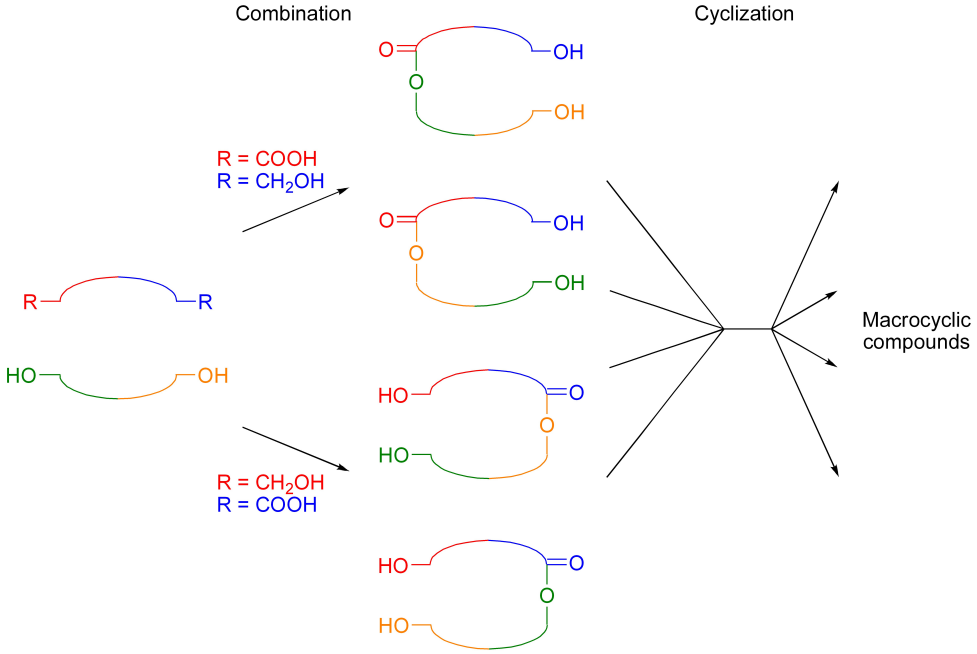


Figure 2.2: Schematic representation of the strategy.

as **32** contains a heterocycle (triazole) and **33** contains a hydroxy alkene (a fragment inspired by polyketides). The α,ω-diol nature of the building blocks is essential for this strategy, as it relies on the versatility of the hydroxy group, offering opportunity for conversions and functionalizations in a number of ways.

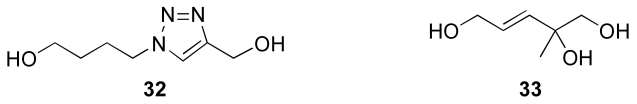


Figure 2.3: Parent structures of the chosen building blocks.

For building block **32**, the hydroxy groups will remain unconverted (but may however be protected) under the diol synthesis (illustrated as the lower building block in Figure 2.2), whereas for building block **33**, one of the hydroxy groups will be converted to the corresponding carboxylic acid (illustrated as the upper building block in Figure 2.2). It should be noted that this relationship might be reversed leading to a total of eight different diols.

Building block **33** contains an additional hydroxy group, which leaves opportunity for introduction of different appendages at a later stage of the

synthesis. **33** will be synthesized as a racemic mixture, and hence the macrocyclic compounds will too be racemic mixtures. This will increase the odds of finding a macrocyclic compound that displays biological activity. However, it will be possible, and also desirable in case of biological activity, to synthesize the two enantiomers selectively, since a fragment of building block **33** containing the chiral center can be synthesized by asymmetric allylic alkylation of 2-methyl-2-vinyloxirane (Figure 2.4).[53]

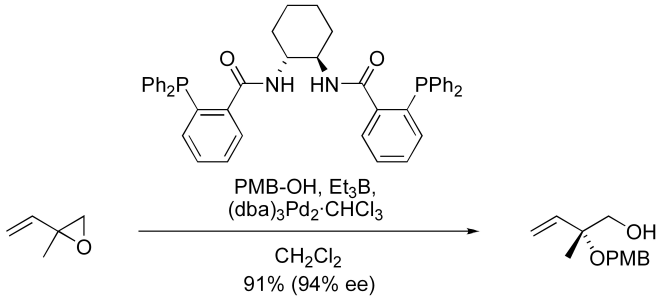


Figure 2.4: Asymmetric allylic alkylation yielding a fragment of building block **33**.

2.3 Results and discussion

The synthesis of the building blocks is described below, followed by diol precursor synthesis and subsequent cyclizations (and attempts hereof). Preliminary investigations have previously been carried out by the group of Clausen.[54]

2.3.1 Synthesis of the building blocks

The synthesis of the triazole-containing building block is shown in Figure 2.5. Substitution of 4-chlorobutyl benzoate with sodium azide, followed by a copper(I) catalyzed alkyne-azide cycloaddition reaction[37] of the resulting azide **34** with TBDMS protected propargyl alcohol afforded the protected triazole building block **35**. Reductive cleavage of the benzoyl group gave one of the desired alcohol derivatives **36** (ready for esterification) in a high yield.

An initial attempt at the synthesis of the other desired alcohol derivative involved the use of a triphenylsilyl (TPS) ether as protection group giving **37**. The TPS ether is normally more stable to cleavage by TBAF than the TBDMS ether.[55] Surprisingly, the expected selective removal of the TBDMS group failed by use of TBAF at -78 °C as the TPS ether was found to be

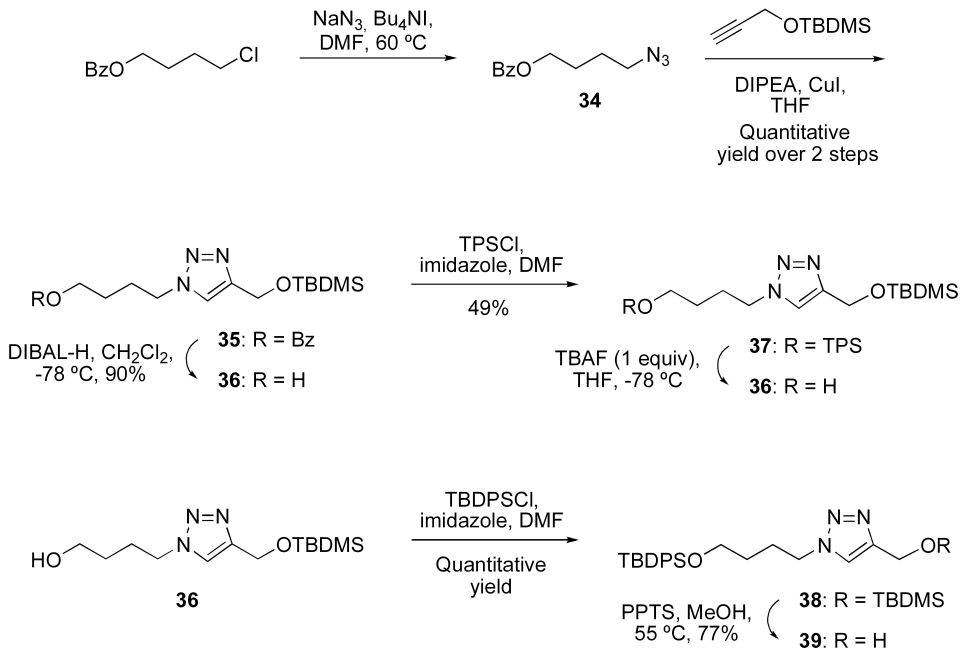


Figure 2.5: Synthesis of the triazole building block.

more prone to cleavage than the TBDMS ether for this substrate, thus giving **36**. The same result was obtained by use of PPTS at 0 °C, although not surprising, as the TBDMS ether is more stable to acid than the TPS ether.[55] However, the product **39** was achieved in a good yield by TBDPS protection of **36** and subsequent selective removal of the TBDMS group by acidic solvolysis.[56]

The synthesis of the other building block is shown in Figure 2.6. Grignard reaction[57] of TBDMS protected hydroxy acetone with vinyl magnesium chloride followed by a cross-metathesis reaction[58] with methyl acrylate gave the (*E*)-enol building block **41** in a good yield. The Hoveyda-Grubbs' second generation catalyst **48**[59] (Figure 2.7) was more efficient in this transformation than the Grubbs' second generation catalyst **49**.[60] Interestingly, despite the reaction being somewhat slower with 0.5% catalyst loading as compared to 5%, the overall conversion was found to be higher with the lower loading. Methyl acrylate was added in large excess (20 equivalents) to disfavor homodimerization of **40** since both reactants are slowly homodimerizing alkenes (Type II alkenes for catalyst **49**).[61] The excellent *E*-selectivity of the reaction arises from the quaternary allylic nature of **40**.[61]

PMB protection of **41** with *p*-methoxybenzyl trichloroacetimidate (PMB-TCA)[62] under mild conditions[63] gave **42**, which could be hydrolyzed under

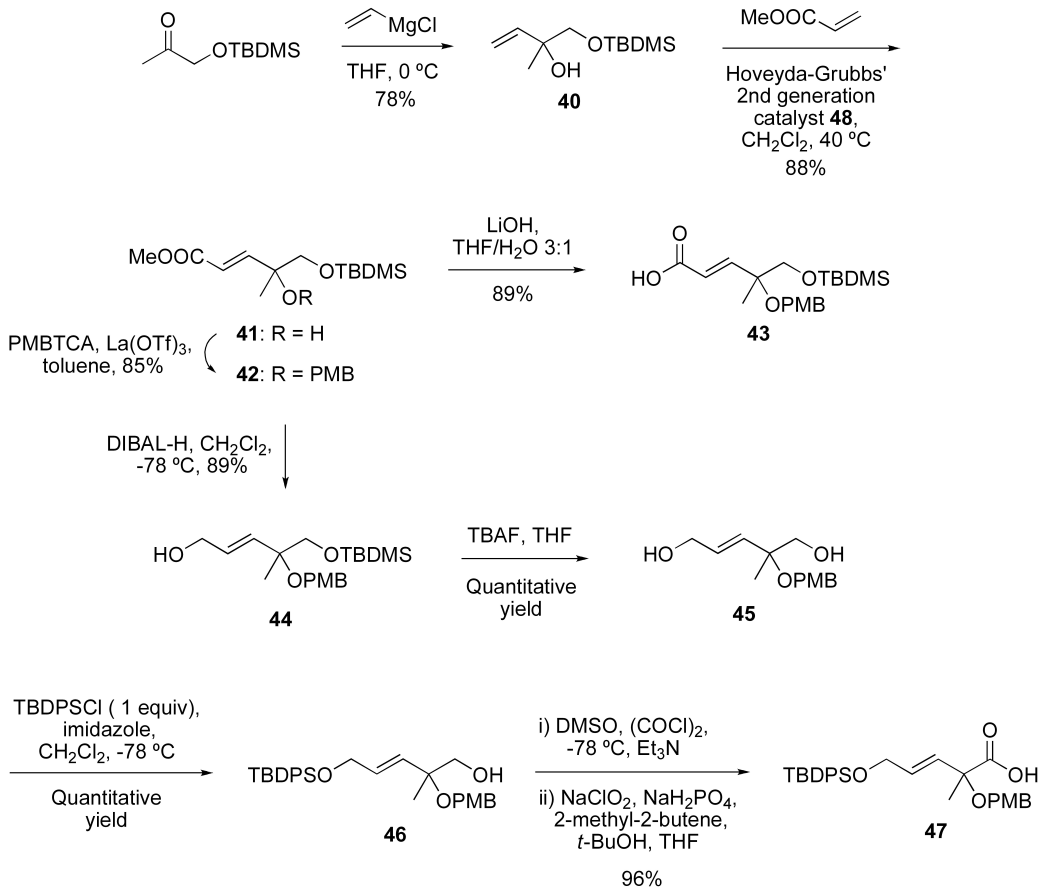


Figure 2.6: Synthesis of the (*E*)-enol building block.

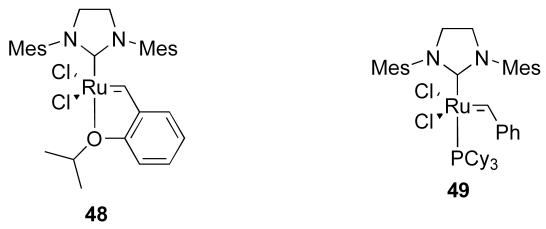


Figure 2.7: Hoveyda-Grubbs' second generation catalyst **48** and Grubbs' second generation catalyst **49**. Mes = 2,4,6-trimethylphenyl; Cy = cyclohexyl.

basic conditions to yield one of the desired carboxylic acid derivatives **43** in a high yield. PMBTCA was prepared in a quantitative yield from anisalcohol and trichloroacetonitrile according to a literature procedure.[64] The alcohol **44** was obtained from **42** by reductive cleavage of the methyl ester. Deprotection

with TBAF went smoothly, giving the diol **45** in an excellent yield. Most satisfyingly, the allylic hydroxy group could be selectively TBDPS protected at -78 °C in dichloromethane. Swern[65] and sodium chlorite[66] oxidations gave the other desired carboxylic acid **47** in a high yield. Preliminary attempts to selectively cleave the TBDMS group from the TPS protected analog of **44** proved unsuccessful for the same reason as specified above for the triazole building block.

2.3.2 Synthesis of the diols

The alcohols **36** and **39** were combined with the carboxylic acids **43** and **47** by carbodiimide promoted esterifications[67] (Figure 2.8) yielding the four esters **50**, **52**, **54**, and **56**, which were deprotected smoothly with TBAF to give the desired diol precursors.

2.3.3 Synthesis of macrocyclic sulfites

The diols **51**, **53**, **55** and **57** were treated with thionyl chloride, triethylamine and DMAP according to the recently developed method.[52] This involves slow addition of a solution of thionyl chloride in dichloromethane to a dilute solution of the diol (12 mM), triethylamine and DMAP in dichloromethane. The 17-membered macrocyclic sulfites **58**, **60**, **62** and **64** (Figure 2.9) were obtained in yields ranging from 43% to 79% reflecting a difference in the steric environment of the cyclization precursors. This is further emphasized by the fact that the diastereomeric ratio of **58**, formed from the most sterically hindered diol precursor, differs from the diastereomeric ratios of the other sulfites in being 2:1 as compared to 1:1 (or 3:2). Not surprisingly, cyclizations of the two least sterically hindered diol precursors **55** and **57** result in higher yields than cyclizations of the more hindered substrates **51** and **53**.

Subsequent cleavage of the PMB ethers with DDQ to obtain the sulfites **59a**, **61**, **63** and **65** resulted in yields ranging from 30% to 67%. The low yield for the deprotection of **58** is caused by lability of the product to column chromatography. This was proven by the isolation of a 5-membered cyclic sulfite byproduct **59b** formed upon nucleophilic attack by the tertiary hydroxy group on the macrocyclic sulfite. The identification of the product **59a** and the byproduct **59b** as single diastereomers confirms that only one of the diastereomers of the deprotected sulfite is susceptible to the intramolecular transesterification of the sulfite.

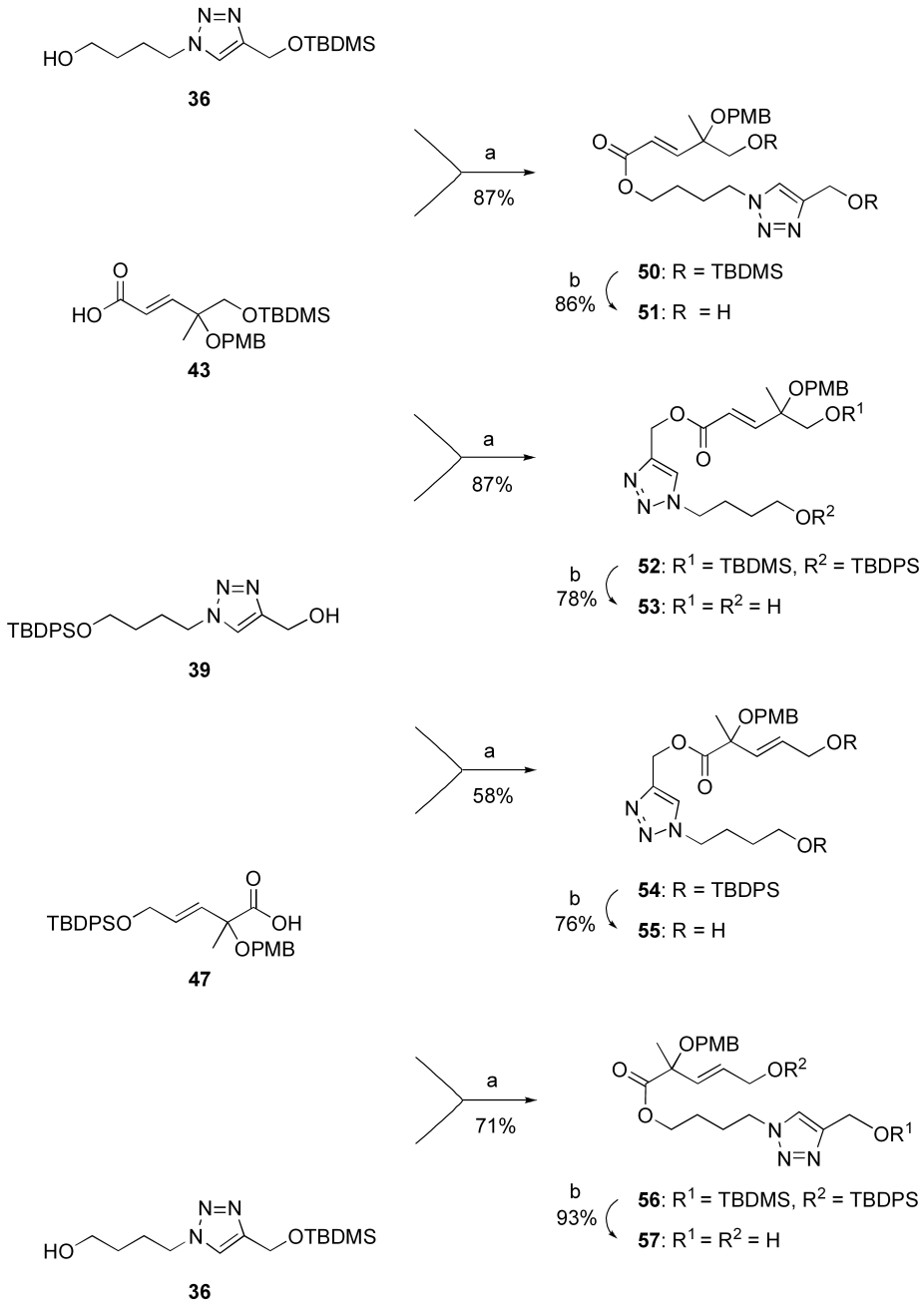


Figure 2.8: Synthesis of the diol precursors. Reagents and conditions: (a) EDC·HCl, DMAP, CH_2Cl_2; (b) TBAF, THF.

2.3.4 Synthesis of macrocyclic malonates

The above cyclization method was extended to the formation of malonates. Diol precursors **51** and **53** were treated with malonyl chloride under the above

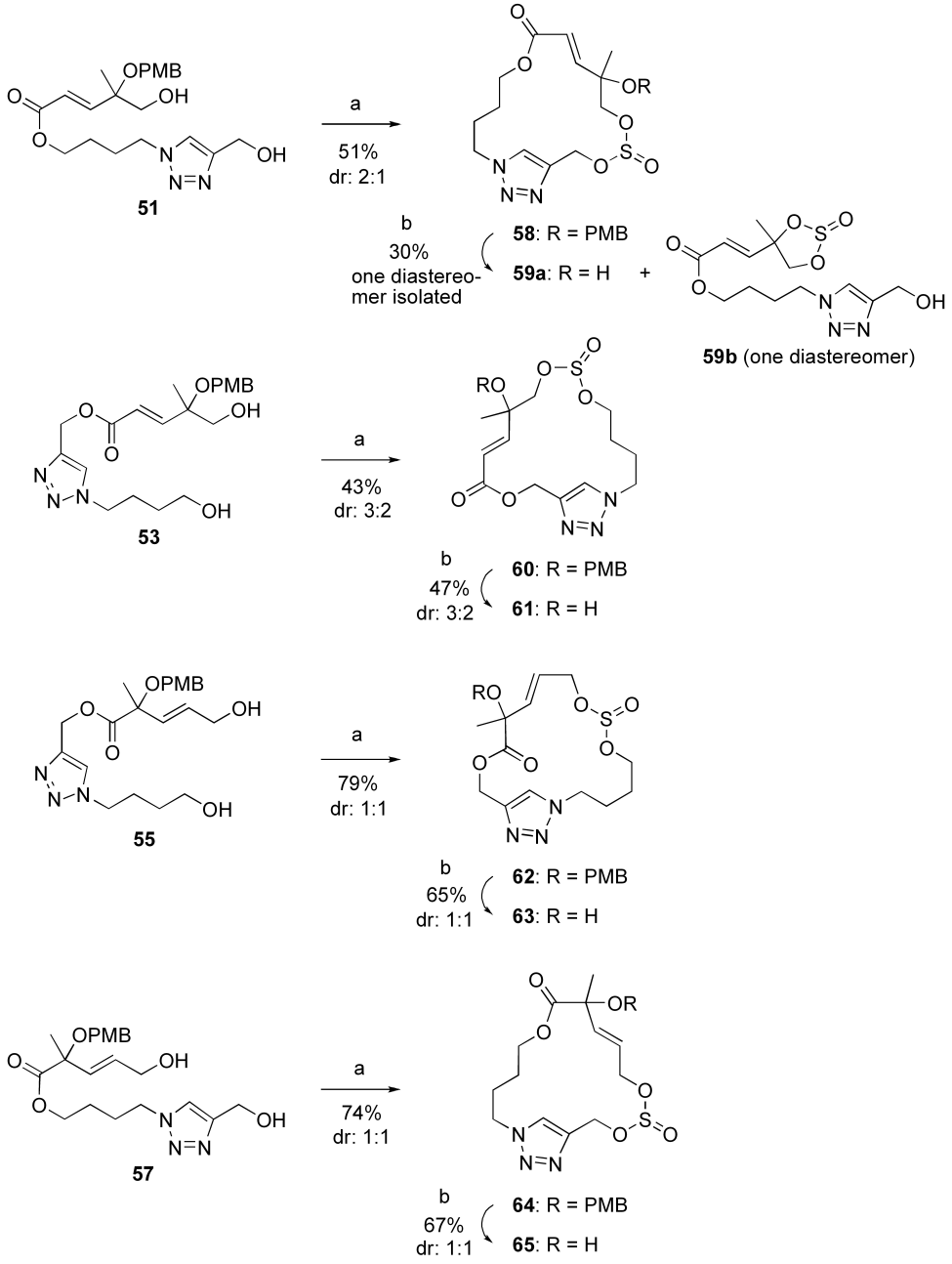


Figure 2.9: Synthesis of macrocyclic sulfites. Reagents and conditions: (a) $SOCl_2$, Et_3N, DMAP, CH_2Cl_2; (b) DDQ, CH_2Cl_2/H_2O 18:1.

conditions, giving the 19-membered malonates **66** and **68** (Figure 2.10) in 37 and 34% yield, respectively. Thus, the yields for formation of malonates are slightly lower than for the formation of sulfites, possibly related to the

difference in ring sizes formed and/or the relative reactivity of the reagents.

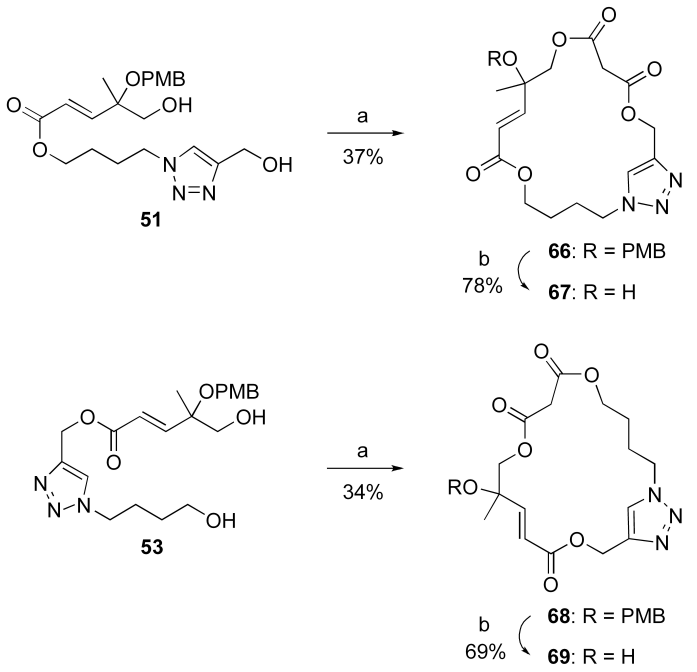


Figure 2.10: Synthesis of macrocyclic malonates. Reagents and conditions: (a) malonyl chloride, Et_3N, DMAP, CH_2Cl_2; (b) DDQ, CH_2Cl_2/H_2O 18:1.

The malonates were deprotected analogously to the sulfites, giving **67** and **69**. The products were obtained in higher yields than their sulfite analogs, presumably because the malonates are more stable than the sulfites.

2.3.5 Synthesis of macrocyclic phthalates

The method was furhter extended to the synthesis of phthalates. A phthalate **70** (20-membered), an isophthalate **71** (21-membered) and a terephthalate **72** (22-membered) (Figure 2.11) were synthesized from diol **51**. The yields were lower than for the formation of malonates. Since the phthalates have larger ring sizes than the malonates, this supports that the yield of this macrocyclization method is related to the ring size formed.

Due to the low yields of the phthalates and the amount of the diol precursor thus required for upscaling, it was chosen not to deprotect these compounds. However, they are still interesting for investigation of biological properties.

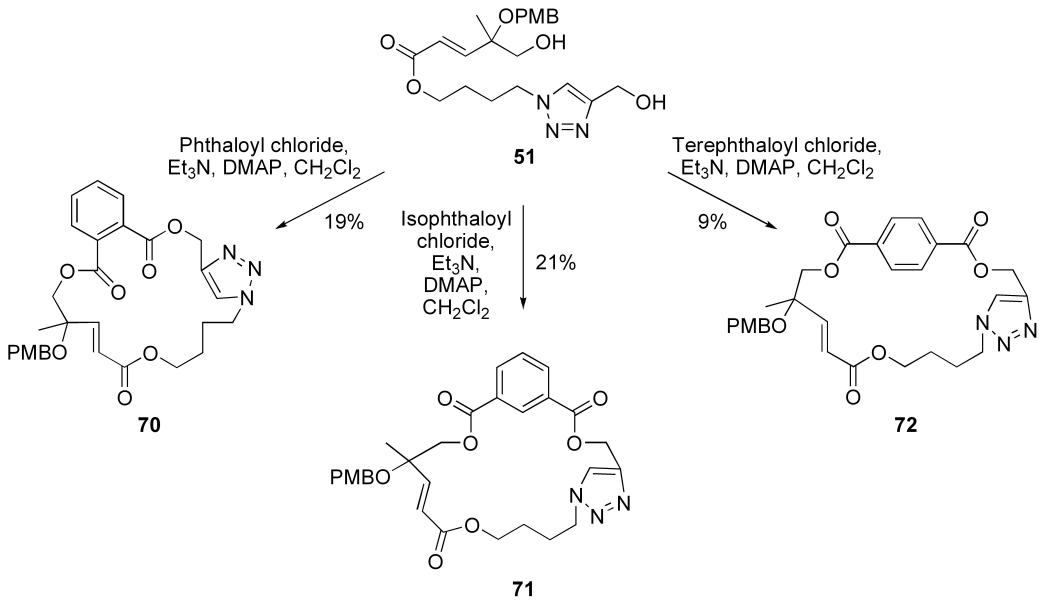


Figure 2.11: Synthesis of macrocyclic phthalates from diol **51**.

2.3.6 Synthesis of macrocyclic oxalate

An 18-membered oxalate **73** (Figure 2.12) was synthesized from diol **53** according to the above method, albeit in a low yield. As the conversion seen on TLC indicated a yield that is significantly higher than the isolated 9%, the product is presumably unstable to column chromatography.

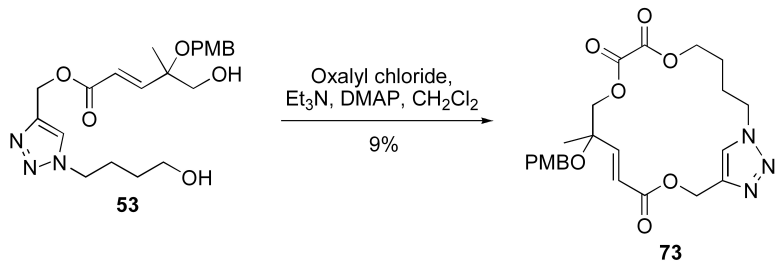


Figure 2.12: Synthesis of macrocyclic oxalate from diol **53**.

For the reasons specified above for the phthalates, combined with the instability to column chromatography, the oxalate was not deprotected.

2.3.7 Attempts at the synthesis of macrocyclic diether

It was attempted to synthesize a 19-membered macrocyclic diether **74** from diol **51** and dibromopropane (Figure 2.13). However, neither the use of potassium carbonate (Figure 2.13a) nor sodium hydride (Figure 2.13b) was successful. In the former case, no reaction was seen - not even after stirring at 60 °C for 2 days. In the latter case, ester cleavage was seen.

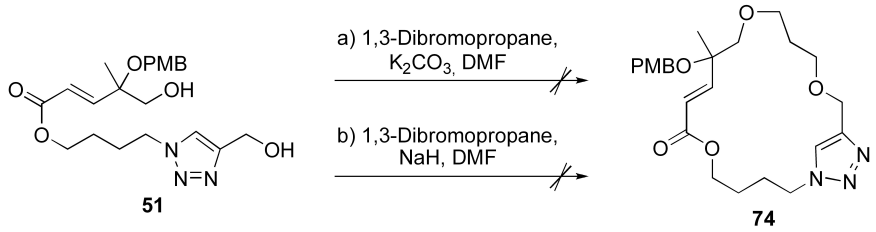


Figure 2.13: Attempts at the synthesis of diether **74** from diol **51**.

2.3.8 Synthesis of macrocyclic amines

The previously reported method, converting a diol to a dialdehyde followed by a double-reductive amination,[52] was applied to diol **51** (Figure 2.14). Before that publication, the use of double-reductive amination of dialdehydes with a monoamine to prepare macrocyclic compounds had never been reported.[68] The dialdehyde cyclization precursor **75** was prepared by oxidation of **51** in an excellent yield. For this reaction, IBX[69] was found to be superior to the Dess-Martin periodinane[70] as oxidizing agent. IBX was prepared by oxidation of 2-iodobenzoic acid according to a literature procedure.[71]

3,4-dimethoxybenzylamine ($DMBNH_2$) was chosen as the amine, since it has been reported that removal of the DMB group from a tertiary amine can be accomplished under mild conditions by the use of DDQ.[72] Unfortunately, double-reductive amination of **75** resulted in only 9% yield of the 15-membered product **76** (entry 1, Table 2.1). The formation of several byproducts, probably of an oligomeric nature, was indicated by TLC.

Several experiments were conducted in order to optimize the yield (entries 2-9, Table 2.1). Substituting $Na(OAc)_3BH$[73] with the more reactive reducing agents $NaBH_4$[74] (entry 2) or $NaCNBH_3$[75] (entry 3) did not lead to any formation of the amine **76**; only the formation of byproducts was indicated by TLC as described above. The use of a longer imine formation time before addition of the reducing agent (entry 4) was also unsuccessful.

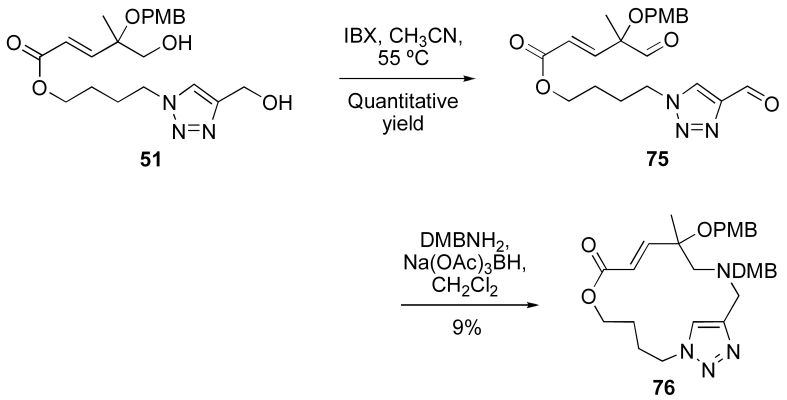


Figure 2.14: Conversion of diol **51** to dialdehyde **75** followed by double-reductive amination giving amine **76**.

Substituting $DMBNH_2$ with ammonium acetate (entry 5, Table 2.1) seemed attractive, as it is a smaller reagent that decreases the steric crowding at the reaction site along with eliminating the need for a subsequent deprotection. Unfortunately, this did not result in formation of the desired product, but reduction of the dialdehyde to the monoaldehyde **77** and the diol **51** (Figure 2.15).

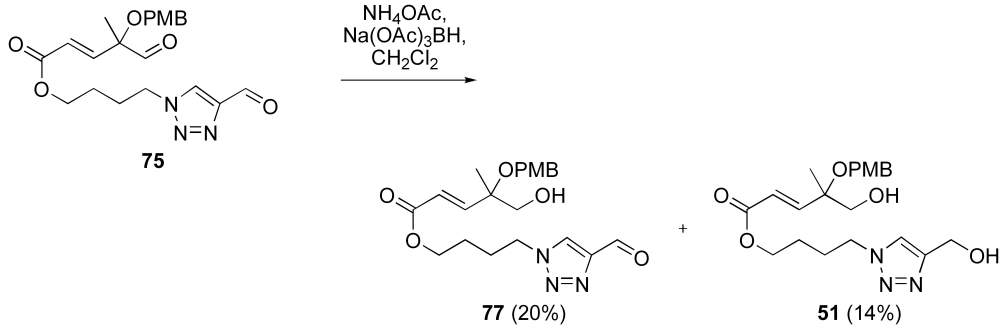


Figure 2.15: Reaction of dialdehyde **75** with ammonium acetate yielding monoaldehyde **77** and diol **51**.

The identification of product **77** reveals that the α,α,α-trisubstituted carbonyl group is reduced faster than the other carbonyl group. An attempt to catalyze imine formation by addition of 1% of acetic acid to the solvent (entry 6, Table 2.1) also resulted in aldehyde reduction instead of product formation.

The use of magnesium ions as a template[76] for imine formation (entry 7, Table 2.1) did not improve the yield of **76**. Altering the concentration of

Entry	Amine	Reducing agent	Other conditions	Yield of amine
1	$DMBNH_2$	$Na(OAc)_3BH$	-	9%
2	$DMBNH_2$	$NaBH_4$	-	0%
3	$DMBNH_2$	$NaCNBH_3$	-	0%
4	$DMBNH_2$	$Na(OAc)_3BH$	17h imine formation	0%
5	Ammonium acetate	$Na(OAc)_3BH$	-	0%*
6	$DMBNH_2$	$Na(OAc)_3BH$	$AcOH/CH_2Cl_2$ 1:99	0%*
7	$DMBNH_2$	$Na(OAc)_3BH$	DMF/CH_2Cl_2 1:22, $MgCl_2$	<10%
8	$DMBNH_2$	$Na(OAc)_3BH$	0.002 M	<10%
9	$DMBNH_2$	$Na(OAc)_3BH$	0.045 M	<10%
10	Benzylamine	$Na(OAc)_3BH$	-	0%
11	*n*-Propyl-amine	$Na(OAc)_3BH$	-	0%
12	1,3-Diamino-propane	$Na(OAc)_3BH$	$CaCl_2$	0%
13	1,3-Diamino-propane	$Na(OAc)_3BH$	-	0%*

Table 2.1: Different reaction conditions tried for the synthesis of a macrocyclic amine from dialdehyde **75**. The reaction was performed in a 12 mM solution of **75** in CH_2Cl_2 and 15-25 minutes were allowed for imine formation before addition of the reducing agent unless otherwise stated. * Isolation of the reduced product(s) **77** (and **51**).

the dialdehyde **75** either to a more dilute (entry 8) or a more concentrated solution (entry 9) resulted in a decreased yield of the product.

The possibility of using other primary amines was also investigated. However, attempts at the double-reductive amination of **75** with the previously used benzylamine[52] (entry 10, Table 2.1) and the smaller *n*-propylamine (entry 11) were unsuccessful. Furthermore, attempts at using a diamine, 1,3-diaminopropane with or without calcium ions as a template (entry 12-13), were not successful. The reduced starting material **77** was isolated in the latter case.

The reason for the low yield of formation of **76** and the failure of the attempts at optimization described above was likely to be found in the steric environment of the aldehyde groups of **75**, especially in one of them being an α,α,α-trisubstituted carbonyl group. Thus, it was decided to investigate the cyclizations of the two less sterically hindered dialdehydes **78** and **80** (Figure

2.16), obtained in excellent yields from **55** and **57**. Most satisfyingly, the products **79** and **81** of these cyclizations were obtained in highly improved yields, 46% and 60%, respectively. Thus, these results confirm that **75** is too sterically hindered to undergo double-reductive amination in a satisfactory yield.

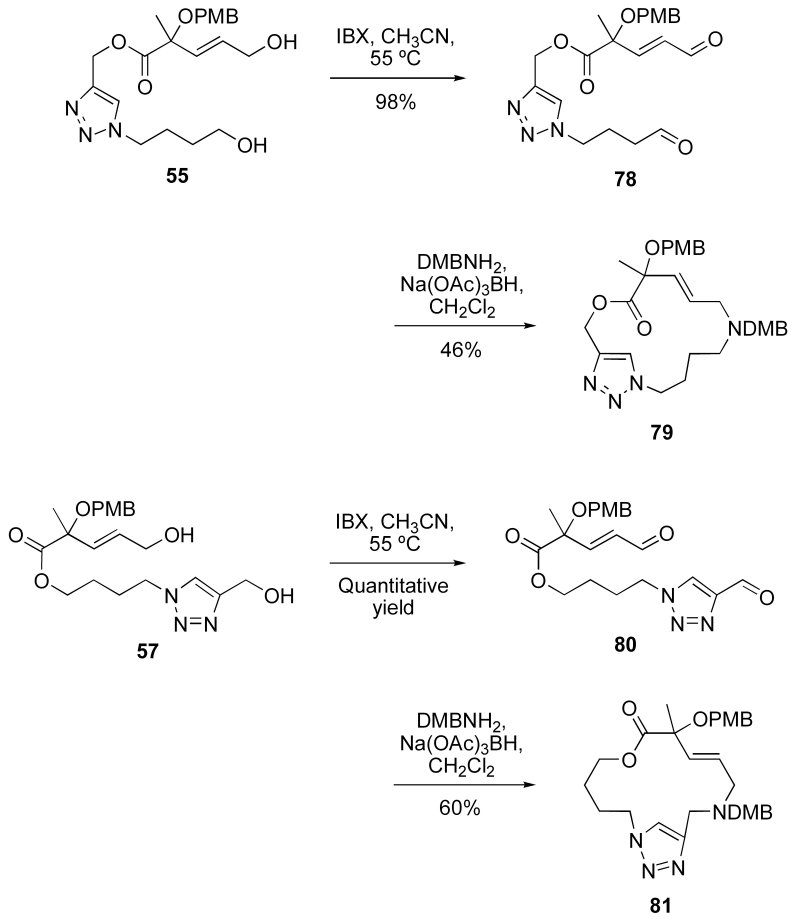


Figure 2.16: Conversion of diols **55** and **57** to dialdehydes **78** and **80** followed by double-reductive amination giving amines **79** and **81**.

The deprotection of the amines turned out to be a very slow reaction, especially for the removal of the DMB group. Hence, the PMB group of the amines **79** and **81** could be selectively cleaved by use of 3 equivalents of DDQ over 21 hours, yielding the amines **82** and **83** (Figure 2.17).

Several attempts at the full deprotection of the amines **81** and **79** to **84** and **85** (Figure 2.18) were carried out with DDQ and CAN (see Table 2.2). Since the CH_2Cl_2/H_2O 18:1 solvent system has been reported to be

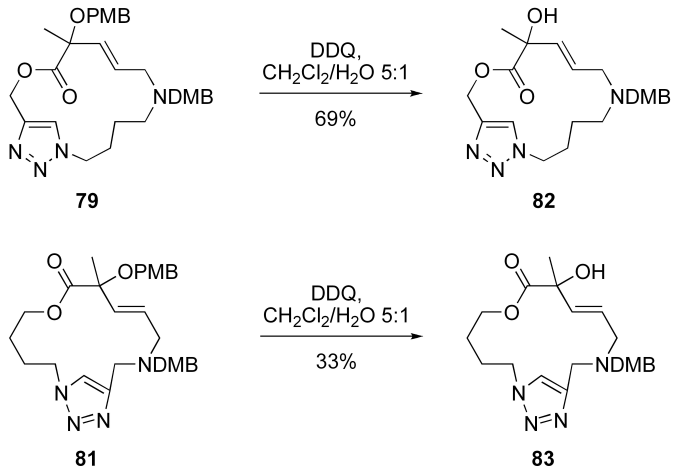


Figure 2.17: Selective removal of the PMB group from amines **79** and **81** yielding amines **82** and **83**.

the optimal solvent system for DDQ deprotection,[77] the first unsuccessful attempt was carried out analogously to the deprotection of the sulfites and malonates, albeit with more equivalents of DDQ (entry 1). Other attempts were carried out by use of a more concentrated CH_2Cl_2/H_2O 5:1 solvent system (entries 2-3) according to a literature procedure for removal of a DMB group from a tertiary amine.[78] However, also in this case, only the monoprotected amines were isolated.

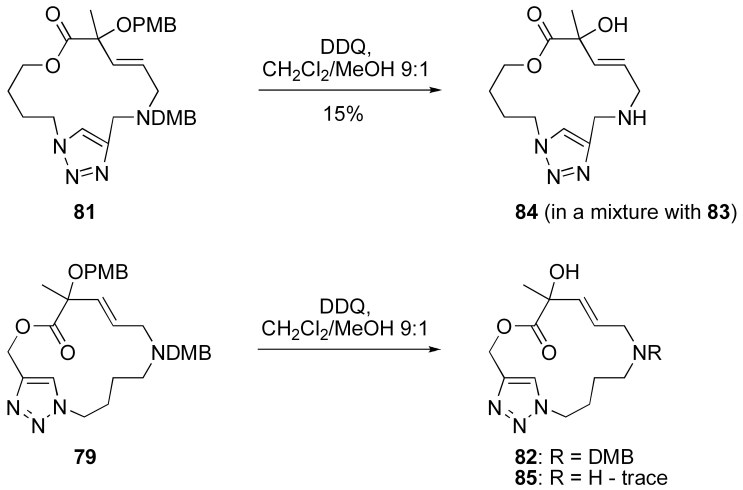


Figure 2.18: Full deprotection of amine **81** yielding amine **84** in a mixture with amine **83** and attempt at the full deprotection of amine **79** giving the monoprotected amine **82**.

Entry	Amine	Oxidizing agent	Equiv	Solvent	Other conditions	Yield of product
1	**81**	DDQ	5	CH_2Cl_2/H_2O 18:1	10 mM	0%
2	**81**	DDQ	5	CH_2Cl_2/H_2O 5:1	33 mM	0%
3	**79**	DDQ	5	CH_2Cl_2/H_2O 5:1	33 mM	0%
4	**81**	CAN	5	CH_3CN/H_2O 5:1	10 mM	0%*
5	**81**	DDQ	3.3	CH_2Cl_2/Phosphate buffer (pH 7) 5:1	33 mM	0%
6	**79**	DDQ	9.9	CH_2Cl_2/Phosphate buffer (pH 7) 5:1	33 mM	0%
7	**79**	DDQ	5	CH_2Cl_2/H_2O 5:1	33 mM, 40 °C	0%
8	**79**	DDQ	9.9	CH_2Cl_2/Phosphate buffer (pH 7) 5:1	33 mM, 40 °C	0%
9	**81**	DDQ	20	CH_2Cl_2/MeOH 9:1	17 mM, 7 days	15%
10	**79**	DDQ	20	CH_2Cl_2/MeOH 9:1	17 mM, 7 days	trace

Table 2.2: Different reaction conditions tried for the formation of the deprotected amines **84** and **85** from **81** and **79**, respectively. The reaction time was less than 24 hours unless otherwise stated. * The monodeprotected amine **83** was not formed in this case.

An attempt to use CAN for the deprotection of **81** (entry 4, Table 2.2) resulted in consumption of the starting material but no formation of either the monodeprotected amine **83** or the desired product **84**.

Attempts at substituting the water phase of the CH_2Cl_2/H_2O 5:1 solvent system with a phosphate buffer (entries 5-6, Table 2.2) were carried out in order to keep the solvent neutral under the reaction, thus keeping the DMB group as electron rich as possible. However, no improvement was seen. Performing the experiment at an elevated temperature (entries 7-8) either with a water or buffer phase was also unsuccessful.

Substituting the usual biphasic CH_2Cl_2/H_2O solvent system with a miscible solvent system (CH_2Cl_2/MeOH 9:1) (entry 9, Table 2.2) led to some conversion, although the use of as much as 20 equivalents of DDQ over 7 days gave a modest NMR yield of 15%. Attempts at the isolation of **84** (verified by LCMS) from a mixture of the amines **83** and **84** by flash column chromatography were not successful, presumably due to the two compounds having the same R_f value. Unfortunately, the full deprotection of **79** to **85** (entry 10) only gave trace of product by use of these conditions.

It is evident from literature that this reaction is highly substrate dependent, since it has been reported that deprotection of DMB protected amines can be inefficient for some substrates,[79] whereas for others even the removal of the less electron-rich PMB group from a tertiary amine is possible.[80]

2.3.9 Attempts at the synthesis of macrocyclic sulfides

Next, it was intended to synthesize 15-membered macrocyclic sulfides from diiodides as previously reported[52] by use of bis(tributyltin) sulfide in the presence of CsF and 18-crown-6.[81,82] Bis(tributyltin) sulfide was prepared from tributyltin chloride and sodium sulfide according to a literature procedure.[81]

Initially, an attempt to convert diol **51** into a diiodide was carried out. However, reacting **51** with iodine, triphenylphosphine and imidazole only gave a monoiodide **86** (Figure 2.19). This is presumably due to the difficult substitution of the activated neopentylic hydroxy group. The monoiodide **86** was obtained in a 32% NMR yield in a mixture with triphenylphosphine oxide, due to a difficult separation of these two compounds.

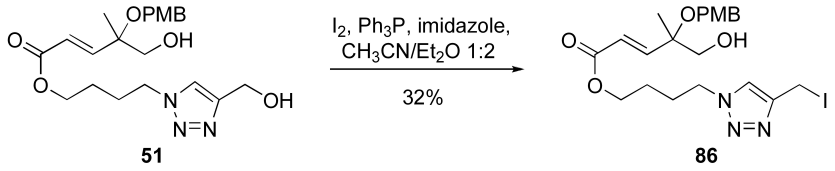


Figure 2.19: Conversion of diol **51** into monoiodide **86**.

As expected, subjection of the two less hindered diols **55** and **57** to the above reaction conditions led to formation of the diiodides **87** and **88** (Figure 2.20). However, the intended synthesis of the sulfides **89** and **90** from diiodides **87** and **88** (Figure 2.21) was not successful. The reason for the unsuccessful result is likely to be found in the diiodides not being stable enough for the reaction, since decomposition of the starting material was indicated by TLC and has been seen by NMR analysis of stored material.

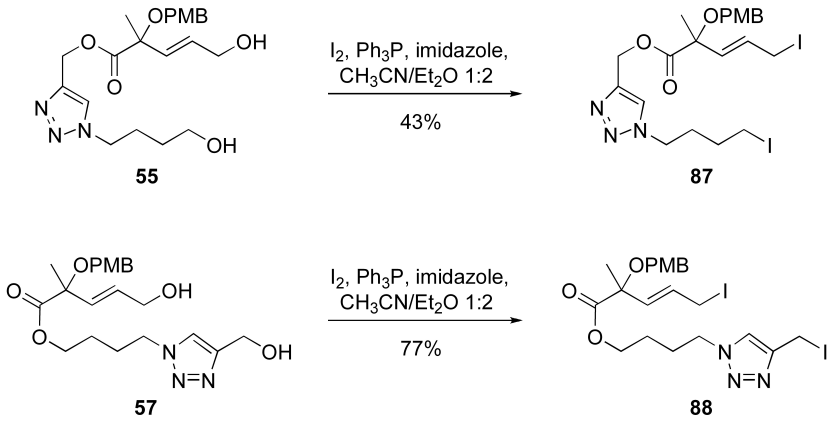


Figure 2.20: Conversion of diols **55** and **57** into diiodides **87** and **88**.

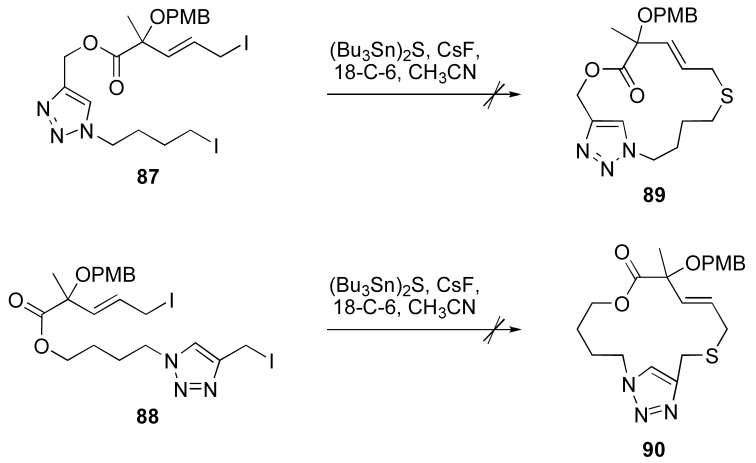


Figure 2.21: Attempt at the synthesis of sulfides **89** and **90** from diiodides **87** and **88**.

The more reactive 1,3-benzenedithiol was then employed in an attempt at forming the 19-membered disulfide **91** (Figure 2.22a) from diiodide **88**. A solution of **88** in dichloromethane was added dropwise to a solution of 1,3-benzenedithiol and potassium carbonate in dichloromethane, followed by triethylamine. The starting material was consumed but no cyclic product was isolated.

A previously reported macrocyclization method involving slow addition (12 hours) of separate solutions of a dithiol and a dibromide in DMF to a dilute suspension of cesium carbonate in DMF[83] was also applied to these substrates (Figure 2.22b). Unfortunately, the result was the same as above.

The formation of a disulfide by the above method[83] has been reported to

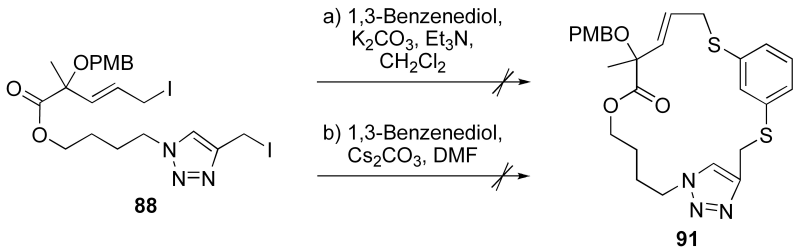


Figure 2.22: Attempts at the synthesis of disulfide **91** from diiodide **88**.

be low-yielding in case of the synthesis of a dithia-18-crown-6 derivative.[84] Thus, in the case of diiodide **88**, the missing formation of a cyclic product could be due to the reaction being difficult for this substrate and/or due to the diiodide not being stable enough for the reaction.

Chapter 3

Conclusion

The project has resulted in the formation of a library of diverse macrocyclic compounds with different ring sizes and functionalities. The macrocycles were synthesized in a few steps from easily accessible building blocks in accordance with the planning strategies for DOS.

A novel strategy within DOS of macrocycles is introduced, utilizing the versatility of the primary alcohol. Specifically, two α,ω-diols were combined in four different ways by esterifications leading to the formation of four structurally isomeric diol precursors, which could be cyclized in a number of ways along with introducing different functionalities.

The diols were cyclized directly to form sulfites (17-membered) and malonates (19-membered) followed by removal of a PMB group from a tertiary hydroxy group, giving reasonable yields for both steps. However, the yield for one of the sulfite deprotections was low due to one of the diastereomers being transesterified into a 5-membered sulfite. Syntheses of a phthalate (20-membered), an isophthalate (21-membered), a terephthalate (22-membered), and an oxalate (18-membered) were also accomplished, however in low yields. Unfortunately, attempts at the synthesis of a diether (19-membered) were unsuccessful, due to the reagents either not having the required reactivity or causing ester cleavage.

Dialdehydes and diiodides were formed from some of the diols with the aim to form macrocycles by reaction with nucleophilic reagents. Not surprisingly, an attempt at the synthesis of a diiodide from one of the diols bearing a neopentylic hydroxy group only led to the formation of a monoiodide.

Double-reductive amination of the dialdehydes with $DMBNH_2$ led to the formation of amines (15-membered). The yield of cyclization was low for a dialdehyde that contained an α,α,α-trisubstituted carbonyl group, whereas the yields were much higher for two less sterically hindered dialdehydes. Subsequent removal of the PMB and DMB groups from the latter two amines

turned out to be difficult, as only the PMB group was removed under conditions employing more equivalents of DDQ and longer reaction times than usual. The use of a very large excess of DDQ over 7 days led to 15% conversion to the fully deprotected product. However, attempts at separating the product from the monodeprotected amine were not successful as the two amines presumably have the same R_f value.

Unfortunately, attempts at forming sulfides (15-membered) and disulfides (19-membered) from the diiodides were not successful, presumably due to instability of the diiodides.

The library of diverse macrocyclic compounds formed in this project is currently being screened for biological activity. Furthermore, investigations of the structural properties are currently being undertaken. Hopefully, the synthetic strategy described herein will encourage others to create libraries of new diverse macrocyclic compounds.

Chapter 4

Experimental section

Starting materials, reagents, and solvents were purchased from Sigma-Aldrich Chemical Co. and used without further purification. Reactions involving air or moisture sensitive reagents were carried out under N_2. CH_2Cl_2, DMF, CH_3CN and DMSO were dried over 4 Å molecular sieves. THF, Et_2O and toluene were distilled from Na under N_2. Et_3N was distilled from CaH_2 under N_2. TLC was performed on Merck aluminum sheets precoated with silica gel 60 F_{254}. Compounds were visualized by charring after dipping in a solution of *p*-anisaldehyde (10 mL of H_2SO_4 and 10 mL of *p*-anisaldehyde in 200 mL of 95% EtOH), or cerium sulfate (6.25 g of $(NH_4)_6Mo_7O_{24}$ and 1.5 g of $Ce(SO_4)_2$ in 250 mL of 10% aqueous H_2SO_4). Flash column chromatography was performed using Merck silica gel 60 (particle size 0.040-0.063 mm). NMR spectra were recorded using a Varian Mercury 300 MHz spectrometer or a Varian Unity Inova 500 MHz spectrometer. Chemical shifts were measured in ppm and coupling constants in Hz, and the field is indicated in each case. The solvent peaks from $CDCl_3$ (7.26 ppm in ^{1}H NMR and 77.16 ppm in ^{13}C NMR) or CD_3OD (3.31 ppm in ^{1}H NMR) were used as standards. In case of diastereomeric mixtures, the following abbreviations are used; maj: major diastereomer, min: minor diastereomer, both: both diastereomers, one: one diastereomer. Elemental analyses were obtained from H. Kolbe, Mikroanalytisches Laboratorium, Mülheim/Ruhr, Germany. IR analysis was carried out on a Perkin-Elmer 1600 series FTIR spectrometer or on a Bruker Alpha FTIR spectrometer. Melting points were measured with a Buch Holm melting point apparatus and are uncorrected. High-resolution LC-DAD-MS was performed on an Agilent 1100 system equipped with a photodiode array detector (DAD) and coupled to an LCT orthogonal time-of-flight mass spectrometer (Waters-Micromass) with a *Z*-spray electrospray ionization (ESI) source and a LockSpray probe (M + H 556.2771) and controlled by MassLynx 4.0 software.

4-(4-((*tert*-Butyldimethylsilyloxy)methyl)-1*H*-1,2,3-triazol-1-yl)butyl benzoate 35

4-Chlorobutyl benzoate (10.02 g, 47.09 mmol) and Bu_4NI (1.74 g, 4.71 mmol) were dissolved in anhydrous DMF (94 mL). NaN_3 (3.83 g, 58.86 mmol) was added cautiously. The solution was slowly heated to 60 °C and stirred for 23 hours. The mixture was transferred to a separatory funnel and diluted with Et_2O (600 mL). After washing with water (3×320 mL), the resulting organic phase was concentrated *in vacuo* to afford **34** as a yellow oil, which was used without further purification. The crude was dissolved in THF (422 mL) and DIPEA (12.09 mL, 70.64 mmol) was added followed by CuI (8.97 g, 47.09 mmol) and *tert*-butyldimethylsilyl propargyl ether (9.55 mL, 47.09 mmol). After stirring at 20 °C for 18 hours, the yellow mixture was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo* giving a green oil. The residue was dissolved in EtOAc (500 mL) and washed with water (2×330 mL) and brine (330 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford an oil which was purified by flash column chromatography (MeOH/CH_2Cl_2 3:97) to give the triazole **35** (18.34 g, quantitative yield) as a yellow oil. R_f 0.60 (EtOAc/heptane 1:1); IR (neat, AgCl) ν 3428 (w), 3138 (m), 3069 (m), 2956 (s), 1719 (s), 1602 (m), 1585 (m), 1451 (s), 1389 (m), 1361 (m), 1271 (s), 1219 (m), 1176 (m), 1096 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04-8.01 (2H, m), 7.60-7.52 (2H, m), 7.47-7.42 (2H, m), 4.88 (2H, s), 4.46 (2H, t, *J* 7.1 Hz), 4.36 (2H, t, *J* 6.3 Hz), 2.15-2.05 (2H, m), 1.87-1.77 (2H, m), 0.91 (9H, s), 0.10 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 149.0, 133.2, 130.1, 129.6 (2C), 128.5 (2C), 121.5, 64.0, 58.1, 49.9, 27.3, 26.0 (3C), 25.9, 18.4, -5.2 (2C).

4-(4-((*tert*-Butyldimethylsilyloxy)methyl)-1*H*-1,2,3-triazol-1-yl)butan-1-ol 36

A solution of the triazole **35** (1.98 g, 5.08 mmol) in anhydrous CH_2Cl_2 (49 mL) was cooled to -78 °C. DIBAL-H (1.0 M in hexane, 11.2 mL, 11.2 mmol) was added, and the mixture was stirred at -78 °C for 3 hours. The reaction was quenched with MeOH (2.0 mL) and allowed to reach 20 °C. A sat. aq. solution of Rochelle's salt (60 mL), water (40 mL) and Et_2O (250 mL) were added, and the viscous mixture was stirred vigorously for 15 minutes. The mixture was transferred to a separatory funnel and the organic layer was isolated. The aqueous layer was extracted with EtOAc (3×80 mL) and the pooled organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. The product was purified by flash column chromatography (EtOAc/heptane 1:1 → EtOAc) to afford the alcohol **36** (1.31 g, 90%) as a colorless oil. R_f 0.10 (EtOAc/heptane 1:1); IR (neat, AgCl) ν

3372 (m), 2929 (s), 1734 (w), 1636 (w), 1559 (w), 1473 (m), 1257 (m), 1006 (s), 840 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (1H, s), 4.85 (2H, s), 4.41 (2H, t, J 7.1 Hz), 3.69 (2H, t, J 6.2 Hz), 2.07-1.98 (2H, m), 1.81 (1H, br s, OH), 1.63-1.54 (2H, m), 0.91 (9H, s), 0.10 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 121.6, 61.9, 58.0, 50.2, 29.4, 27.1, 26.0 (3C), 18.5, -5.2 (2C); Anal. calcd. for $C_{13}H_{27}N_3O_2Si$: C, 54.70; H, 9.53; N, 14.72. Found: C, 54.63; H, 9.50; N, 14.81.

4-((*tert*-Butyldimethylsilyloxy)methyl)-1-(4-(triphenylsilyloxy)butyl)-1*H*-1,2,3-triazole 37

The alcohol **36** (1.66 g, 5.82 mmol) was dissolved in anhydrous DMF (10 mL). Imidazole (0.79 g, 11.64 mmol) and TPSCl (2.57 g, 8.73 mmol) were added. After stirring at 20 °C for 18 hours, the mixture was diluted with EtOAc (20 mL) and then washed with water (10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography ($MeOH/CH_2Cl_2$ 1:199) to afford **37** (1.54 g, 49%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.62-7.59 (6H, m), 7.48-7.36 (10H, m), 4.84 (2H, s), 4.31 (2H, t, J 7.2 Hz), 3.83 (2H, t, J 6.0 Hz), 2.05-1.95 (2H, m), 1.64-1.55 (2H, m), 0.91 (9H, s), 0.10 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 135.4 (6C), 134.1 (3C), 130.3 (3C), 128.1 (6C), 121.5, 63.0, 58.1, 50.1, 29.3, 27.1, 26.0 (3C), 18.5, -5.1 (2C).

4-((*tert*-Butyldimethylsilyloxy)methyl)-1-(4-(*tert*-butyldiphenylsilyloxy)butyl)-1*H*-1,2,3-triazole 38

The alcohol **36** (5.95 g, 20.85 mmol) was dissolved in anhydrous DMF (41.7 mL). Imidazole (2.84 g, 41.70 mmol) and TBDPSCl (8.13 mL, 31.28 mmol) were added. After stirring for 1 hour at 20 °C, the mixture was diluted with EtOAc (140 mL) and then washed with water (70 mL) and brine (70 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/heptane 1:1) to give **38** (10.92 g, quantitative yield) as a colorless oil. R_f 0.85 (EtOAc/hep-tane 3:1); IR (neat) ν 3135 (w), 3071 (w), 3050 (w), 2998 (w), 2953 (m), 2930 (s), 2886 (m), 2857 (s), 1589 (w), 1471 (m), 1463 (m), 1428 (m), 1389 (m), 1361 (w), 1334 (w), 1308 (w), 1255 (m), 1218 (w), 1188 (w), 1134 (m), 1105 (s), 1088 (s), 1045 (m), 1022 (m), 1007 (m), 972 (w), 938 (w), 910 (w), 836 (m), 777 (m), 736 (m), 687 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66-7.63 (4H, m), 7.43-7.35 (7H, m), 4.85 (2H, s), 4.34 (2H, t, J 7.2 Hz), 3.68 (2H, t, J 6.0 Hz), 2.06-1.96 (2H, m), 1.61-1.52 (2H, m), 1.04 (9H, s), 0.91 (9H, s), 0.10 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 135.7 (4C), 133.8 (2C), 129.8 (2C), 127.8 (4C), 121.4, 63.1, 58.1, 50.2, 29.4, 27.2, 27.0 (3C), 26.0 (3C), 19.3, 18.5, -5.1 (2C).

(1-(4-(*tert*-Butyldiphenylsilyloxy)butyl)-1*H*-1,2,3-triazol-4-yl)methanol 39

The disilylprotected compound **38** (10.92 g, 20.85 mmol) was dissolved in MeOH (350 mL). PPTS (262 mg, 1.04 mmol) was added, and the solution was heated to 55 °C. After stirring for 23 hours, the solvent was removed *in vacuo*. The residue was redissolved in EtOAc (420 mL) and washed with brine (420 mL) and water (420 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/heptane 3:7 → EtOAc) to give the alcohol **39** (6.54 g, 77%) as white crystals. R_f 0.39 (EtOAc/heptane 3:1); m.p. 111-112 °C; IR (neat) ν 3232 (s), 3126 (m), 2927 (s), 2854 (m), 1472 (w), 1427 (m), 1359 (w), 1225 (w), 1145 (w), 1109 (s), 1081 (s), 1020 (m), 980 (m), 817 (w), 708 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65-7.62 (4H, m), 7.47 (1H, s), 7.43-7.35 (6H, m), 4.79 (2H, d, *J* 6.1 Hz), 4.35 (2H, t, *J* 7.2 Hz), 3.68 (2H, t, *J* 6.0 Hz), 2.23 (1H, t, *J* 6.1 Hz, OH), 2.07-1.97 (2H, m), 1.63-1.52 (2H, m), 1.04 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 135.6 (4C), 133.7 (2C), 129.8 (2C), 127.8 (4C), 121.7, 63.0, 56.3, 50.3, 29.4, 27.0, 27.0 (3C), 19.3; anal. calcd. for $C_{23}H_{31}N_3O_2Si$: C, 67.44; H, 7.63; N, 10.26. Found: C, 67.52; H, 7.59; N, 10.22.

(+/-)-1-(*tert*-Butyldimethylsilyloxy)-2-methylbut-3-en-2-ol 40

1-(*tert*-Butyldimethylsilyloxy)propan-2-one (12 mL, 62.18 mmol) was dissolved in anhydrous THF (114 mL). The mixture was stirred at 0 °C, and vinyl magnesium chloride (1.6 M in THF, 47 mL, 74.62 mmol) was added dropwise over 20 minutes. The cooling bath was removed and after two hours, the reaction mixture was diluted with Et_2O (480 mL) and washed with sat. aq. NH_4Cl (290 mL) and water (290 mL). The combined aqueous phases were extracted with Et_2O (200 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give **40** as a colorless oil (10.43 g, 78%), which was used without further purification. R_f 0.63 (EtOAc/heptane 1:1); IR (neat, AgCl) ν 3447 (br), 3088 (w), 2931 (s), 1718 (w), 1653 (w), 1472 (m), 1362 (m), 1257 (m), 1100 (s), 1006 (m), 922 (m), 838 (s), 778 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (1H, dd, *J* 17.4 Hz, 10.8 Hz), 5.29 (1H, dd, *J* 17.4 Hz, 1.4 Hz), 5.11 (1H, dd, *J* 10.8 Hz, 1.4 Hz), 3.47 (1H, d, *J* 9.5 Hz), 3.42 (1H, d, *J* 9.5 Hz), 1.23 (3H, s), 0.90 (9H, s), 0.06 (3H, s), 0.06 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 113.6, 73.1, 70.4, 26.0 (3C), 23.9, 18.5, -5.2, -5.3.

(+/-)-(*E*)-Methyl 5-(*tert*-butyldimethylsilyloxy)-4-hydroxy-4-methylpent-2-enoate 41

Alcohol **40** (8.40 g, 38.82 mmol) was dissolved in anhydrous CH_2Cl_2 (400 mL) and methyl acrylate (69.45 mL, 776.4 mmol) was added. Hoveyda-Grubbs' 2nd generation catalyst (0.122 g, 0.195 mmol) was added, and the mixture was heated to reflux. After stirring for 48 hours, the mixture was concentrated *in vacuo* to give a green semisolid, which was recrystallized from EtOAc/heptane, and a crystalline byproduct was filtered off. The filtrate was concentrated *in vacuo* to give a green oil. The crude product was purified by flash column chromatography (EtOAc/heptane 1:7) to afford the methyl ester **41** (9.31 g, 88%) as a pale yellow oil. R_f 0.30 (EtOAc/heptane 1:4); IR (neat, AgCl) ν 3482 (br), 2954 (s), 2858 (s), 1728 (s), 1662 (m), 1472 (m), 1437 (m), 1363 (m), 1259 (s), 1100 (s), 981 (m), 838 (s), 778 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (1H, d, *J* 15.7 Hz), 6.10 (1H, d, *J* 15.7 Hz), 3.74 (3H, s), 3.53 (1H, d, *J* 9.6 Hz), 3.48 (1H, d, *J* 9.6 Hz), 1.26 (3H, s), 0.88 (9H, s), 0.06 (3H, s), 0.04 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 152.1, 119.9, 73.1, 69.8, 51.7, 25.9 (3C), 23.6, 18.4, -5.3, -5.4.

(+/-)-(*E*)-Methyl 5-(*tert*-butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-4-methylpent-2-enoate 42

The methyl ester **41** (4.16 g, 15.16 mmol) and PMBTCA[64] (8.14 g, 30.32 mmol) were dissolved in anhydrous toluene (125 mL), and $La(OTf)_3$ (622 mg, 1.06 mmol) was added. After stirring at 20 °C for 16 hours, the mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to give a yellowish oil which was purified by flash column chromatography (EtOAc/toluene/heptane 1:50:50) to give the PMB-protected methyl ester **42** (5.07 g, 85%) as a colorless oil. R_f 0.73 (toluene/heptane 1:4); IR (neat, AgCl) ν 2952 (s), 2856 (s), 2061 (w), 1883 (w), 1726 (s), 1658 (m), 1613 (m), 1587 (m), 1515 (s), 1465 (m), 1382 (m), 1250 (s), 1113 (s), 939 (m), 840 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* 8.6 Hz), 6.99 (1H, d, *J* 16.0 Hz), 6.88 (2H, d, *J* 8.6 Hz), 6.06 (1H, d, *J* 16.0 Hz), 4.44 (1H, d, *J* 10.7 Hz), 4.38 (1H, d, *J* 10.7 Hz), 3.81 (3H, s), 3.77 (3H, s), 3.63 (2H, s), 1.41 (3H, s), 0.89 (9H, s), 0.05 (3H, s), 0.04 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 159.1, 151.2, 131.1, 129.1 (2C), 121.6, 113.9 (2C), 78.3, 69.0, 65.3, 55.4, 51.8, 25.9 (3C), 20.3, 18.3, -5.3 (2C).

(+/-)-(*E*)-5-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-4-methylpent-2-enoic acid 43

The methyl ester **42** (3.47 g, 8.79 mmol) was dissolved in THF (132 mL) and cooled to 0 °C. A solution of LiOH (631 mg, 26.37 mmol) in H_2O (44 mL) was added, and the resulting mixture was stirred at 20 °C. After 46 hours, the reaction was quenched with sat. aq. NaH_2PO_4 (100 mL), and EtOAc (100 mL) was added. The organic phase was isolated, and the aque-

ous phase was extracted with EtOAc (3×100 mL). The pooled organic phases were washed with water (200 mL) and brine (200 mL). Subsequently, they were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/heptane/AcOH 9:90:1) to afford the carboxylic acid **43** (2.97 g, 89%) as a white solid. R_f 0.60 (EtOAc/heptane/AcOH 70:30:1); m.p. 68-71 °C; IR (neat) ν 2927 (br), 1880 (w), 1698 (s), 1652 (m), 1614 (m), 1587 (m), 1515 (s), 1463 (m), 1373 (m), 1254 (s), 939 (m), 845 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* 8.6 Hz), 7.09 (1H, d, *J* 16.0 Hz), 6.87 (2H, d, *J* 8.6 Hz), 6.06 (1H, d, *J* 16.0 Hz), 4.44 (1H, d, *J* 10.7 Hz), 4.38 (1H, d, *J* 10.7 Hz), 3.80 (3H, s), 3.63 (2H, s), 1.42 (3H, s), 0.88 (9H, s), 0.04 (3H, s), 0.03 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 159.1, 153.8, 131.0, 129.1 (2C), 121.4, 113.9 (2C), 78.3, 68.9, 65.4, 55.4, 25.9 (3C), 20.3, 18.3, -5.3 (2C); anal. calcd. for $C_{20}H_{32}O_5Si$: C, 63.12; H, 8.48. Found: C, 63.20; H, 8.36.

(+/-)-(*E*)-5-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-4-methylpent-2-en-1-ol 44

The methyl ester **42** (703 mg, 1.78 mmol) was dissolved in anhydrous CH_2Cl_2 (16 mL) and cooled to -78 °C. DIBAL-H (1.0 M in hexanes, 3.92 mL, 3.92 mmol) was added, and the mixture was stirred at -78 °C for 3 hours. The reaction was quenched with MeOH (1.0 mL) and the cold bath was removed. At 20 °C, a sat. aq. solution of Rochelle's salt (20 mL), water (10 mL) and Et_2O (100 mL) were added, and the viscous mixture was stirred vigorously for 15 minutes. The organic phase was isolated, and the aqueous phase was extracted with EtOAc (3×50 mL). The pooled organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. The oil was purified by flash column chromatography (EtOAc/heptane 1:2) to afford the alcohol **44** (0.583 g, 89%) as a colorless oil. R_f 0.87 (MeOH/EtOAc 1:99); IR (neat, AgCl) ν 3418 (br), 2930 (s), 1740 (m), 1613 (m), 1587 (m), 1514 (s), 1464 (m), 1379 (m), 1250 (s), 1172 (m), 1110 (s) cm^{-1}: ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* 8.5 Hz), 6.86 (2H, d, *J* 8.5 Hz), 5.88 (1H, dt, *J* 16.2 Hz, 5.3 Hz), 5.74 (1H, d, *J* 16.2 Hz), 4.39 (2H, s), 4.19 (2H, dd, *J* 5.3 Hz, 1.0 Hz), 3.79 (3H, s), 3.59 (1H, d, *J* 9.9 Hz), 3.55 (1H, d, *J* 9.9 Hz), 1.36 (3H, s), 0.89 (9H, s), 0.04 (3H, s), 0.03 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 134.5, 131.8, 130.7, 129.0 (2C), 113.8 (2C), 78.0, 69.6, 64.7, 63.6, 55.4, 26.0 (3C), 20.3, 18.4, -5.2, -5.2; anal. calcd. for $C_{20}H_{34}O_4Si$: C, 65.53; H, 9.35. Found: C, 65.45; H, 9.31.

(+/-)-(*E*)-4-(4-Methoxybenzyloxy)-4-methylpent-2-en-1,5-diol 45

The alcohol **44** (8.80 g, 24.01 mmol) was dissolved in anhydrous THF (59 mL) and TBAF (1.0 M in THF, 36.01 mL, 36.01 mmol) was added drop-

wise. After stirring for 19 hours, the mixture was diluted with EtOAc (150 mL) and washed with sat. aq. NH_4Cl (120 mL) and water (2×120 mL). The combined aqueous phases were extracted with EtOAc (2×120 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/heptane 1:1 → MeOH/EtOAc 1:99) giving the diol **45** (6.06 g, quantitative yield) as a colorless oil, which crystallizes upon storage at 5 °C to give a white solid. R_f 0.54 (MeOH/EtOAc 1:99); m.p. 44-45 °C; IR (neat, AgCl) ν 3379 (br), 2935 (s), 1613 (m), 1586 (m), 1514 (s), 1465 (m), 1381 (m), 1302 (m), 1248 (s), 1173 (m), 1112 (m), 1036 (s), 981 (m), 913 (w), 891 (w), 822 (m), 733 (m) cm^{-1}: ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (2H, d, J 8.6 Hz), 6.87 (2H, d, J 8.6 Hz), 5.91 (1H, dt, J 16.1 Hz, 5.2 Hz), 5.78 (1H, d, J 16.1 Hz), 4.33 (2H, s), 4.19 (2H, d, J 5.2 Hz), 3.80 (3H, s), 3.50 (2H, s), 2.08 (2H, br s), 1.38 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 132.9, 131.8, 131.1, 129.2 (2C), 113.9 (2C), 77.9, 69.7, 64.6, 63.0, 55.4, 19.3.

(+/-)-(*E*)-5-(*tert*-Butyldiphenylsilyloxy)-2-(4-methoxybenzyloxy)-2-methylpent-3-en-1-ol 46

The diol **45** (1.41 g, 5.60 mmol) was dissolved in anhydrous CH_2Cl_2 (65 mL) and imidazole (539 mg, 8.41 mmol) was added. The mixture was cooled to -78 °C, and a solution of TBDPSCl (1.46 mL, 5.60 mmol) in anhydrous CH_2Cl_2 (10 mL) was added over 5 minutes. After 3 hours, the mixture was diluted with CH_2Cl_2 (60 mL) and washed with brine (40 mL) and water (40 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (EtOAc/heptane 1:2) affording the TBDPS-protected alcohol **46** (2.75 g, quantitative yield) as a colorless oil. R_f 0.30 (EtOAc/heptane 1:2); IR (neat, AgCl) ν 3457 (br), 2932 (s), 1613 (m), 1588 (m), 1514 (s), 1473 (m), 1428 (m), 1380 (m), 1302 (m), 1249 (s), 1173 (m), 1112 (s), 978 (m), 823 (m), 741 (m), 702 (m) cm^{-1}: ^1H NMR (300 MHz, $CDCl_3$) δ 7.70-7.66 (4H, m), 7.45-7.33 (6H, m), 7.23 (2H, d, J 8.5 Hz), 6.86 (2H, d, J 8.5 Hz), 5.81-5.80 (2H, m), 4.29-4.28 (4H, m), 3.80 (3H, s), 3.52 (1H, d, J 10.9 Hz), 3.41 (1H, d, J 10.9 Hz), 1.98 (1H, br s), 1.36 (3H, s), 1.07 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 135.6 (4C), 133.7, 133.7, 131.9, 131.5, 131.2, 129.8 (2C), 129.3 (2C), 127.8 (4C), 113.9 (2C), 77.9, 69.8, 64.7, 64.1, 55.4, 27.0 (3C), 19.4, 19.3; anal. calcd. for $C_{30}H_{38}O_4Si$: C, 73.43; H, 7.81. Found: C, 73.27; H, 7.75.

(+/-)-(*E*)-5-(*tert*-Butyldiphenylsilyloxy)-2-(4-methoxybenzyloxy)-2-methylpent-3-enoic acid 47

Anhydrous CH_2Cl_2 (220 mL) and DMSO (5.79 mL, 81.66 mmol) were mixed

and cooled to -78 °C. Oxalyl chloride (3.45 mL, 40.83 mmol) was added dropwise, followed by dropwise addition of a solution of the alcohol **46** (10.02 g, 20.42 mmol) in anhydrous CH_2Cl_2 (110 mL). After 30 minutes, anhydrous Et_3N (28.50 mL, 204.15 mmol) was added. After further 15 minutes, the mixture was allowed to reach 20 °C and then diluted with CH_2Cl_2 (600 mL) and washed with sat. aq. NH_4Cl (400 mL) and water (400 mL) The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude aldehyde, which was used without further purification. The crude aldehyde was dissolved in THF (120 mL). *t*-BuOH (240 mL) and 2-methyl-2-butene (86 mL, 811.23 mmol) were added followed by a solution of $NaClO_2$ (23.26 g, 257.14 mmol) and NaH_2PO_4 (30.85 g, 257.14 mmol) in water (160 mL). After $1\frac{1}{2}$ hours, the mixture was diluted with sat. aq. NaH_2PO_4 (500 mL) and stirred for 15 minutes. Subsequently, the mixture was extracted with EtOAc (3×500 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/heptane/AcOH 66:33:1) to afford the carboxylic acid **47** (9.89 g, 96%) as a colorless oil. R_f 0.25 (MeOH/toluene 5:95); IR (neat) ν 3071 (m), 3049 (m), 2997 (m), 2956 (m), 2931 (m), 2893 (m), 2857 (m), 1712 (m), 1613 (m), 1588 (w), 1513 (m), 1462 (m), 1428 (m), 1380 (m), 1302 (m), 1247 (s), 1202 (m), 1174 (m), 1107 (s), 1028 (m), 998 (m), 971 (m), 939 (m), 909 (m), 821 (m), 735 (m), 700 (s) cm^{-1}: ^1H NMR (300 MHz, $CDCl_3$) δ 7.68-7.65 (4H, m), 7.42-7.34 (6H, m), 7.25 (2H, d, *J* 8.7 Hz), 6.89 (2H, d, *J* 8.7 Hz), 6.01 (1H, dt, *J* 15.7 Hz, 3.4 Hz), 5.92 (1H, m), 4.43 (1H, d, *J* 10.5 Hz), 4.38 (1H, d, *J* 10.5 Hz), 4.29 (2H, dd, *J* 3.4 Hz, 1.1 Hz), 3.82 (3H, s), 1.65 (3H, s), 1.07 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 159.5, 135.6 (4C), 133.5, 133.2 (2C), 129.9 (2C), 129.8, 129.6 (2C), 128.1, 127.9 (4C), 114.0 (2C), 80.2, 66.5, 63.6, 55.4, 26.9 (3C), 22.1, 19.4; anal. calcd. for $C_{30}H_{36}O_5Si$: C, 71.39; H, 7.19. Found: C, 70.67; H, 7.17.

Representative procedure for the preparation of esters 50, 52, 54, and 56

(+/-)-(*E*)-4-(4-((*tert*-Butyldimethylsilyloxy)methyl)-1*H*-1,2,3-triazol-1-yl)butyl 5-(*tert*-butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-4-methylpent-2-enoate 50

The carboxylic acid **43** (0.624 g, 1.640 mmol) and the alcohol **36** (0.515 g, 1.804 mmol) were dissolved in anhydrous CH_2Cl_2 (25 mL) and DMAP (0.040 g, 0.328 mmol) and EDC·HCl (0.472 g, 2.460 mmol) were added. The reaction was stirred for 18 hours at 20 °C and then concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/heptane 1:2) to afford the ester **50** (0.930 g, 87%) as a colorless oil. R_f 0.31 (MeOH/toluene 5:95); IR (neat, AgCl) ν 2927 (s), 1734 (s), 1653 (m), 1613 (m), 1516 (m),

1472 (m), 1374 (m), 1249 (s), 1104 (s), 939 (w), 839 (m), 779 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (1H, s), 7.25 (2H, d, J 8.4 Hz), 6.97 (1H, d, J 16.0 Hz), 6.86 (2H, d, J 8.4 Hz), 6.02 (1H, d, J 16.0 Hz), 4.84 (2H, s), 4.42 (1H, d, J 11.1 Hz), 4.38 (2H, t, J 7.4 Hz), 4.37 (1H, d, J 11.1 Hz), 4.18 (2H, t, J 6.3 Hz), 3.79 (3H, s), 3.61 (2H, s), 2.05-1.95 (2H, m), 1.76-1.65 (2H, m), 1.40 (3H, s), 0.91 (9H, s), 0.87 (9H, s), 0.09 (6H, s), 0.02 (3H, s), 0.01 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 159.1, 151.5, 148.9, 131.1, 129.0 (2C), 121.6, 121.5, 113.9 (2C), 78.3, 68.9, 65.3, 63.5, 58.1, 55.4, 49.9, 27.2, 26.0 (3C), 25.9 (3C), 25.9, 20.2, 18.5, 18.3, -5.1 (2C), -5.3 (2C).

(+/-)-(*E*)-(1-(4-(*tert*-Butyldiphenylsilyloxy)butyl)-1*H*-1,2,3-triazol-4-yl)methyl 5-(*tert*-butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-4-methylpent-2-enoate 52

Colorless oil, 87% yield. R_f 0.40 (MeOH/toluene 5:95); IR (neat) ν 3139 (w), 3071 (w), 3048 (w), 2998 (w), 2954 (s), 2930 (s), 2894 (m), 2857 (s), 1720 (s), 1656 (w), 1613 (w), 1588 (w), 1514 (m), 1463 (m), 1442 (m), 1428 (m), 1387 (m), 1361 (w), 1301 (m), 1249 (s), 1169 (m), 1105 (s), 1033 (m), 1007 (m), 938 (w), 910 (w), 836 (s), 823 (m), 777 (m), 731 (m), 701 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65-7.62 (4H, m), 7.56 (1H, s), 7.45-7.36 (6H, m), 7.23 (2H, d, J 8.5 Hz), 7.00 (1H, d, J 16.1 Hz), 6.85 (2H, d, J 8.5 Hz), 6.05 (1H, d, J 16.1 Hz), 5.30 (2H, s), 4.46-4.32 (4H, m), 3.79 (3H, s), 3.68 (2H, t, J 6.0 Hz), 3.60 (2H, s), 2.07-1.97 (2H, m), 1.61-1.52 (2H, m), 1.38 (3H, s), 1.04 (9H, s), 0.86 (9H, s), 0.01 (3H, s), 0.00 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 164.4, 157.3, 148.2, 141.0 (4C), 139.0 (2C), 136.4, 135.2 (2C), 134.4 (2C), 133.2 (4C), 129.1, 126.7, 119.2 (2C), 83.6, 74.3, 70.6, 68.4, 63.2, 60.7, 55.7, 34.7, 32.4, 32.3 (3C), 31.3 (3C), 25.6, 24.7, 23.7, 0.0, 0.0.

(+/-)-(*E*)-(1-(4-(*tert*-Butyldiphenylsilyloxy)butyl)-1*H*-1,2,3-triazol-4-yl)methyl 5-(*tert*-butyldiphenylsilyloxy)-2-(4-methoxybenzyloxy)-2-methylpent-3-enoate 54

Colorless oil, 58% yield. R_f 0.40 (MeOH/toluene 5:95); IR (neat) ν 3136 (w), 3071 (w), 3048 (w), 3013 (w), 2998 (w), 2955 (m), 2931 (m), 2892 (m), 2857 (m), 1736 (m), 1613 (w), 1588 (w), 1514 (m), 1471 (m), 1462 (m), 1427 (m), 1387 (m), 1362 (w), 1302 (w), 1248 (m), 1174 (m), 1105 (s), 1047 (m), 1032 (m), 998 (m), 968 (m), 939 (w), 910 (w), 822 (m), 735 (m), 700 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67-7.62 (8H, m), 7.48 (1H, s), 7.44-7.32 (12H, m), 7.26 (2H, d, J 8.7 Hz), 6.84 (2H, d, J 8.7 Hz), 6.03 (1H, dt, J 15.7 Hz, 1.6 Hz), 5.91 (1H, dt, J 15.7 Hz, 4.0 Hz), 5.31 (2H, s), 4.42 (1H, d, J 10.6 Hz), 4.36 (1H, d, J 10.6 Hz), 4.28 (2H, t, J 7.3 Hz), 4.24 (2H, dd, J 4.0 Hz, 1.6 Hz), 3.78 (3H, s), 3.66 (2H, t, J 6.0 Hz), 2.01-1.91 (2H, m), 1.56 (3H, s), 1.55-1.48 (2H, m), 1.05 (9H, s), 1.04 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 159.2, 142.7, 135.6 (4C), 135.6 (4C), 133.7 (2C), 133.6 (2C), 131.6, 130.7, 129.8 (4C), 129.4, 129.4 (2C), 127.8 (4C), 127.8 (4C), 123.7, 113.8

(2C), 80.1, 66.9, 63.8, 63.0, 58.6, 55.4, 50.3, 29.4, 27.0, 27.0 (3C), 26.9 (3C), 24.2, 19.4, 19.3.

(+/-)-(*E*))-4-(4-((*tert*-Butyldimethylsilyloxy)methyl)-1*H*-1,2,3-triazol-1-yl)butyl 5-(*tert*-butyldiphenylsilyloxy)-2-(4-methoxybenzyloxy)-2-methylpent-3-enoate 56

Colorless oil, 71% yield. R_f 0.31 (MeOH/toluene 5:95); IR (neat) ν 3136 (w), 3071 (w), 3048 (w), 2997 (w), 2954 (m), 2931 (s), 2893 (m), 2856 (m), 1734 (m), 1613 (m), 1588 (w), 1514 (m), 1462 (m), 1428 (m), 1381 (m), 1362 (m), 1301 (m), 1247 (s), 1174 (m), 1105 (s), 1043 (m), 970 (m), 939 (w), 836 (m), 777 (m), 740 (m), 701 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68-7.64 (4H, m), 7.42-7.33 (7H, m), 7.28 (2H, d, *J* 8.6 Hz), 6.85 (2H, d, *J* 8.6 Hz), 6.04 (1H, dt, *J* 15.7 Hz, 1.5 Hz), 5.92 (1H, dt, *J* 15.7 Hz, 3.8 Hz), 4.83 (2H, s), 4.44 (1H, d, *J* 10.8 Hz), 4.38 (1H, d, *J* 10.8 Hz), 4.31 (2H, t, *J* 7.0 Hz), 4.26 (2H, dd, *J* 3.9 Hz, 1.5 Hz), 4.18 (2H, t, *J* 6.4 Hz), 3.79 (3H, s), 2.01-1.90 (2H, m), 1.73-1.60 (2H, m), 1.58 (3H, s), 1.06 (9H, s), 0.91 (9H, s), 0.09 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 159.2, 148.8, 135.6 (4C), 133.6 (2C), 131.5, 130.8, 129.9 (2C), 129.6, 129.2 (2C), 127.8 (4C), 121.5, 113.8 (2C), 80.2, 66.8, 64.3, 63.8, 58.1, 55.4, 49.7, 27.1, 26.9 (3C), 26.0 (3C), 25.7, 24.0, 19.4, 18.5, -5.1 (2C).

Representative procedure for the preparation of diols 51, 53, 55, and 57

(+/-)-(*E*)-4-(4-(Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)butyl 5-hydroxy-4-(4-methoxybenzyloxy)-4-methylpent-2-enoate 51

The ester **50** (2.034 g, 3.14 mmol) was dissolved in anhydrous THF (27.7 mL) and TBAF (1.0 M in THF, 9.42 mL, 9.42 mmol) was added dropwise. The mixture was stirred for $4\frac{1}{2}$ hours and then diluted with EtOAc (140 mL), washed with sat. aq. NH_4Cl (80 mL) and water (2×80 mL). The combined aqueous phases were extracted with EtOAc (2×80 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (MeOH/EtOAc 1:99 → 5:95) to afford the diol **51** (1.133 g, 86%) as a colorless oil. R_f 0.10 (MeOH/EtOAc 1:99); IR (neat) ν 3374 (br), 3142 (m), 2938 (m), 2873 (m), 2839 (m), 1712 (s), 1654 (m), 1612 (m), 1513 (m), 1462 (m), 1443 (m), 1383 (m), 1301 (m), 1247 (s), 1171 (m), 1110 (m), 1031 (s), 895 (w), 821 (m), 778 (w), 754 (w), 726 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (1H, s), 7.25 (2H, d, *J* 8.8 Hz), 6.97 (1H, d, *J* 16.1 Hz), 6.88 (2H, d, *J* 8.8 Hz), 6.04 (1H, d, *J* 16.1 Hz), 4.77 (2H, s), 4.40 (2H, t, *J* 7.1 Hz), 4.39 (1H, d, *J* 10.6 Hz), 4.32 (1H, d, *J* 10.6 Hz), 4.17 (2H, t, *J* 6.3 Hz), 3.80 (3H, s), 3.60 (1H, d, *J* 11.5 Hz), 3.55 (1H, d, *J* 11.5 Hz), 2.07-1.97 (2H, m), 1.75-1.66 (2H, m), 1.42 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 159.3, 150.0, 147.9, 130.4,

129.3 (2C), 122.5, 121.8, 114.0 (2C), 78.1, 68.9, 65.3, 63.7, 56.7, 55.4, 49.9, 27.1, 25.7, 19.3; anal. calcd. for $C_{21}H_{29}N_3O_6$: C, 60.13; H, 6.97; N, 10.02. Found: C, 60.02; H, 7.06; N, 9.88.

(+/-)-(*E*)-(1-(4-Hydroxybutyl)-1*H*-1,2,3-triazol-4-yl)methyl 5-hydroxy-4-(4-methoxybenzyloxy)-4-methylpent-2-enoate 53

White solid, 78% yield. R_f 0.15 (MeOH/EtOAc 1:99); m.p. 70-71 °C; IR (neat) ν 3332 (br), 3120 (m), 3072 (w), 3034 (w), 2935 (m), 2870 (m), 2838 (m), 1716 (s), 1655 (m), 1612 (m), 1586 (w), 1513 (m), 1462 (m), 1442 (m), 1381 (m), 1316 (m), 1301 (m), 1249 (m), 1218 (m), 1171 (s), 1108 (m), 1046 (s), 1007 (m), 973 (m), 942 (w), 900 (w), 871 (m), 827 (m), 815 (m), 781 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (1H, s), 7.24 (2H, d, *J* 8.7 Hz), 7.00 (1H, d, *J* 16.1 Hz), 6.87 (2H, d, *J* 8.7 Hz), 6.07 (1H, d, *J* 16.1 Hz), 5.30 (2H, s), 4.41 (2H, t, *J* 7.1 Hz), 4.37 (1H, d, *J* 10.4 Hz), 4.31 (1H, d, *J* 10.4 Hz), 3.80 (3H, s), 3.67 (2H, t, *J* 6.2 Hz), 3.57 (1H, d, *J* 11.5 Hz), 3.52 (1H, d, *J* 11.5 Hz), 2.07-1.97 (2H, m), 1.62-1.53 (2H, m), 1.41 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 159.3, 150.4, 142.7, 130.4, 129.2 (2C), 124.1, 122.2, 114.0 (2C), 78.1, 68.8, 65.2, 61.9, 57.8, 55.4, 50.3, 29.3, 27.0, 19.3; anal. calcd. for $C_{21}H_{29}N_3O_6$: C, 60.13; H, 6.97; N, 10.02. Found: C, 60.04; H, 7.08; N, 9.94.

(+/-)-(*E*)-(1-(4-Hydroxybutyl)-1*H*-1,2,3-triazol-4-yl)methyl 5-hydroxy-2-(4-methoxybenzyloxy)-2-methylpent-3-enoate 55

Colorless oil, 76% yield. R_f 0.15 (MeOH/EtOAc 1:99); IR (neat) ν 3362 (br), 3143 (m), 3042 (w), 2937 (m), 2870 (m), 2839 (m), 1732 (s), 1612 (m), 1586 (w), 1513 (s), 1456 (m), 1443 (m), 1381 (m), 1302 (m), 1245 (s), 1175 (m), 1107 (s), 1084 (m), 1051 (m), 1027 (s), 968 (m), 821 (m), 784 (w), 755 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (1H, s), 7.27 (2H, d, *J* 8.8 Hz), 6.85 (2H, d, *J* 8.8 Hz), 5.96 (1H, dt, *J* 15.8 Hz, 4.4 Hz), 5.87 (1H, d, *J* 15.8 Hz), 5.35 (1H, d, *J* 12.7 Hz), 5.29 (1H, d, *J* 12.7 Hz), 4.44 (1H, d, *J* 10.4 Hz), 4.39 (2H, t, *J* 7.0 Hz), 4.37 (1H, d, *J* 10.4 Hz), 4.15 (2H, dd, *J* 4.4 Hz, 0.9 Hz), 3.79 (3H, s), 3.63 (2H, t, *J* 6.2 Hz), 2.08-1.93 (2H, m), 1.60 (3H, s), 1.57-1.48 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 159.2, 142.5, 131.9, 130.6, 130.5, 129.4 (2C), 123.9, 113.8 (2C), 80.0, 66.8, 62.5, 61.7, 58.4, 55.4, 50.3, 29.3, 26.9, 23.1; anal. calcd. for $C_{21}H_{29}N_3O_6$: C, 60.13; H, 6.97; N, 10.02. Found: C, 60.45; H, 7.06; N, 10.08.

(+/-)-(*E*)-4-(4-(Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)butyl 5-hydroxy-2-(4-methoxybenzyloxy)-2-methylpent-3-enoate 57

Colorless oil, 93% yield. R_f 0.10 (MeOH/EtOAc 1:99); IR(neat) ν 3360 (br), 3144 (m), 2961 (m), 2936 (m), 2872 (m), 2839 (m), 1730 (s), 1668 (w), 1613 (m), 1586 (w), 1553 (w), 1513 (s), 1457 (m), 1382 (m), 1301 (m), 1246 (s), 1175 (m), 1112 (m), 1084 (m), 1031 (s), 979 (m), 880 (w), 821 (m), 778 (m), 756 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, s), 7.28 (2H, d, *J* 8.7

Hz), 6.85 (2H, d, *J* 8.7 Hz), 6.00 (1H, dt, *J* 15.8 Hz, 4.5 Hz), 5.90 (1H, d, *J* 15.8 Hz), 4.73 (2H, s), 4.45 (1H, d, *J* 10.6 Hz), 4.38 (1H, d, *J* 10.6 Hz), 4.34 (2H, t, *J* 7.0 Hz), 4.20-4.16 (4H, m), 3.78 (3H, s), 3.30 (2H, br s), 1.98 (2H, tt, *J* 7.3 Hz, 7.3 Hz), 1.71-1.62 (2H, m), 1.59 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 159.1, 147.9, 131.9, 130.5, 130.5, 129.2 (2C), 122.2, 113.8 (2C), 80.0, 66.6, 64.3, 62.3, 56.1, 55.4, 49.8, 27.0, 25.5, 22.9; anal. calcd. for $C_{21}H_{29}N_3O_6$: C, 60.13; H, 6.97; N, 10.02. Found: C, 59.71; H, 7.19; N, 9.94.

Representative procedure for the preparation of macrocyclic sulfites 58, 60, 62, and 64

Sulfite 58

The diol **51** (107 mg, 0.26 mmol) was dissolved in anhydrous CH_2Cl_2 (21 mL). Anhydrous Et_3N (0.11 mL, 0.77 mmol) and DMAP (6 mg, 0.05 mmol) were added. A solution of $SOCl_2$ in anhydrous CH_2Cl_2 (0.36 M, 1 mL, 0.36 mmol) was added over 10 minutes at 20 °C, under vigorous stirring. After stirring for 1 hour, the reaction mixture was concentrated *in vacuo*. The residue was redissolved in EtOAc, filtered through Celite and concentrated *in vacuo*. Purification by flash column chromatography (MeOH/CH_2Cl_2 1:99) gave the sulfite **58** (60 mg, 51%) as white crystals. R_f 0.60 (MeOH/EtOAc 1:99); m.p. 91-93 °C; dr: 2:1, de: 33% (NMR); IR (neat) ν 3133 (w), 2963 (m), 2933 (m), 2879 (m), 2841 (m), 1716 (s), 1657 (m), 1613 (m), 1587 (w), 1515 (m), 1457 (m), 1390 (m), 1361 (w), 1317 (m), 1304 (m), 1286 (m), 1247 (m), 1194 (m), 1168 (s), 1111 (m), 1028 (s), 1001 (m), 939 (m), 899 (m), 828 (m), 777 (m), 729 (m), 706 (m), 690 (m), 669 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (maj, s), 7.56 (min, s), 7.24 (min, d, *J* 8.6 Hz), 7.21 (maj, d, *J* 8.6 Hz), 6.87 (min, d, *J* 8.7 Hz), 6.86 (maj, d, *J* 8.7 Hz), 6.82 (both, d, *J* 16.1 Hz), 6.05 (min, d, *J* 16.1 Hz), 6.03 (maj, d, *J* 16.1 Hz), 5.55 (maj, d, *J* 13.3 Hz), 5.49 (min, d, *J* 13.0 Hz), 4.96 (min, d, *J* 13.0 Hz), 4.95 (maj, d, *J* 13.3 Hz), 4.48-4.33 (m), 4.30-4.24 (m), 4.19-4.11 (m), 4.14 (min, d, *J* 10.1 Hz), 4.13 (maj, *J* 11.0 Hz), 3.92 (maj, d, *J* 11.0 Hz), 3.87 (min, d, *J* 10.1 Hz), 3.79 (both, s), 2.09-2.02 (m), 1.76-1.66 (m), 1.45 (min, s), 1.43 (maj, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6 (min), 165.5 (maj), 159.3 (min), 159.2 (maj), 149.2 (min), 148.6 (maj), 143.8 (maj), 143.4 (min), 130.2 (maj), 130.2 (min), 129.1 (2C, min), 128.9 (2C, maj), 123.0 (min), 122.9 (maj), 122.8 (maj), 122.5 (min), 114.0 (2C, min), 113.9 (2C, maj), 76.3 (maj), 76.2 (min), 69.3 (maj), 67.7 (min), 65.3 (maj), 65.2 (min), 63.5 (both), 56.6 (min), 56.0 (maj), 55.4 (both), 49.5 (both), 26.8 (both), 25.0 (min), 24.9 (maj), 20.2 (min), 19.6 (maj); HRMS (ESI): *m/z* calcd. for $C_{21}H_{27}N_3O_7S$ $[M+H]^+$ 466.1643, found 466.1637.

Sulfite 60

White crystals, 43% yield; R_f 0.60 (MeOH/EtOAc 1:99); m.p. 130-131 °C;

dr: 3:2, de: 20% (NMR); IR(neat) ν 3133 (w), 3075 (w), 3034 (w), 2963 (m), 2875 (m), 2841 (w), 1714 (s), 1643 (w), 1612 (m), 1585 (w), 1514 (m), 1462 (m), 1446 (m), 1384 (m), 1304 (m), 1250 (s), 1225 (m), 1203 (m), 1174 (m), 1141 (m), 1115 (m), 1056 (m), 1031 (m), 1001 (m), 977 (m), 897 (m), 884 (m), 854 (m), 824, 806, 773, 733, 711 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (both, s), 7.22 (both, d, J 8.6 Hz), 6.87 (both, d, J 8.6 Hz), 6.85 (both, d, J 16.1 Hz), 6.04 (min, d, J 16.1 Hz), 6.03 (maj, d, J 16.1 Hz), 5.39-5.38 (m), 4.53-4.37 (m), 4.40 (both, d, J 10.6 Hz), 4.34 (both, d, J 10.6 Hz), 3.94 (min, d, J 10.3 Hz), 3.91 (maj, d, J 9.6 Hz), 3.79 (both, s), 3.78 (min, d, J 10.3 Hz), 3.74 (maj, d, J 9.6 Hz), 3.65-3.48 (m), 1.97-1.86 (m), 1.54-1.46 (m), 1.44 (both, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0 (maj), 165.9 (min), 159.3 (maj), 159.3 (min), 150.3 (maj), 150.0 (min), 144.2 (both), 130.2 (min), 130.2 (maj), 129.1 (2C, maj), 129.0 (2C, min), 123.9 (maj), 123.8 (min), 122.8 (maj), 122.7 (min), 114.0 (2C, maj), 114.0 (2C, min), 76.4 (min), 76.3 (maj), 68.3 (min), 67.4 (maj), 65.3 (maj), 65.2 (min), 62.7 (maj), 62.1 (min), 57.7 (both), 55.4 (both), 50.1 (both), 27.1 (min), 27.0 (maj), 26.3 (min), 26.3 (maj), 19.6 (maj), 19.4 (min).

Sulfite 62

White crystals, 79% yield; R_f 0.60 (MeOH/EtOAc 1:99); m.p. 130-131 °C; dr: 1:1 (NMR); IR (neat) ν 3127 (w), 3071 (w), 3044 (w), 3001 (w), 2954 (m), 2930 (m), 2877 (w), 2858 (w), 2836 (w), 1730 (s), 1680 (w), 1613 (m), 1586 (w), 1512 (m), 1454 (m), 1390 (m), 1331 (w), 1303 (m), 1274 (w), 1246 (m), 1233 (m), 1199 (m), 1172 (m), 1133 (m), 1106 (m), 1053 (m), 1036 (m), 1011 (m), 994 (m), 971 (m), 951 (m), 919 (m), 898 (m), 820 (m), 780 (m), 754 (m), 732 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (both, s), 7.33 (both, d, J 8.7 Hz), 6.88 (both, d, J 8.7 Hz), 5.76-5.73 (m), 5.49 (one, d, J 12.5 Hz), 5.46 (one, d, J 12.5 Hz), 5.32 (one, d, J 12.5 Hz), 5.30 (one, d, J 12.5 Hz), 4.54-4.31 (m), 4.28-4.26 (m), 4.12-4.02 (m), 3.80 (both, s), 3.77-3.67 (m), 2.04-1.92 (m), 1.63 (one, s), 1.63 (one, s), 1.59-1.47 (m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4 (both), 159.3 (both), 143.0 (both), 134.9 (one), 134.4 (one), 130.3 (one), 130.3 (one), 129.4 (2C, both), 125.8 (one), 125.6 (one), 124.3 (one), 124.2 (one), 113.9 (2C, both), 80.0 (one), 79.9 (one), 67.0 (both), 62.3 (one), 62.1 (one), 62.0 (one), 61.7 (one), 58.2 (both), 55.4 (both), 50.0 (both), 27.0 (one), 27.0 (one), 26.4 (one), 26.4 (one), 22.2 (one), 22.1 (one); anal. calcd. for $C_{21}H_{27}N_3O_7S$: C, 54.18; H, 5.85; N, 9.03. Found: C, 54.28; H, 5.77; N, 8.95.

Sulfite 64

White crystals, 74% yield; R_f 0.60 (MeOH/EtOAc 1:99); m.p. 92 °C; dr: 1:1 (NMR); IR(neat) ν 3145 (w), 3046 (w), 2994 (m), 2960 (m), 2941 (m), 2922 (m), 2877 (m), 2837 (m), 1735 (s), 1614 (m), 1587 (w), 1512 (m), 1458 (m), 1440 (m), 1387 (m), 1303 (m), 1243 (m), 1201 (m), 1189 (m), 1172 (m),

1145 (m), 1107 (s), 1038 (m), 1006 (m), 981 (m), 941 (m), 924 (m), 904 (s), 839 (m), 813 (m), 804 (m), 786 (m), 757 (m), 739 (m), 717 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (one, s), 7.64 (one, s), 7.28 (one, d, J 8.6 Hz), 7.27 (one, d, J 8.6 Hz), 6.86 (both, d, J 8.6 Hz), 5.86-5.84 (m), 5.60 (one, d, J 13.4 Hz), 5.55 (one, d, J 13.4 Hz), 4.96 (one, d, J 13.4 Hz), 4.93 (one, d, J 13.4 Hz), 4.51-4.22 (m), 3.79 (both, s), 1.99-1.84 (m), 1.76-1.64 (m), 1.59 (one, s), 1.58 (one, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3 (both), 159.3 (both), 143.4 (one), 143.3 (one), 134.7 (one), 134.7 (one), 130.2 (one), 130.2 (one), 129.3 (2C, both), 125.4 (one), 125.3 (one), 124.1 (one), 124.1 (one), 113.9 (2C, both), 79.9 (one), 79.9 (one), 66.8 (both), 64.1 (one), 64.1 (one), 62.7 (one), 62.6 (one), 55.4 (both), 55.3 (one), 55.1 (one), 49.5 (both), 27.5 (one), 27.5 (one), 25.5 (both), 22.3 (both).

Representative procedure for the preparation of deprotected sulfites 59a, 59b, 61, 63, and 65

Sulfites 59a and 59b

The sulfite **58** (259 mg, 0.56 mmol) was dissolved in CH_2Cl_2 (52.8 mL) and water (2.9 mL). DDQ (152 mg, 0.67 mmol) was added, and the mixture was stirred at 20 °C for 6 hours. Then the mixture was diluted with EtOAc (260 mL) and washed with 40% aqueous $NaHSO_3$ (260 mL) and water (2×260 mL). The aqueous phase was extracted with EtOAc (260 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified twice by flash column chromatography (EtOAc/toluene 1:1) to give the deprotected sulfite **59a** (58 mg, 30%, one diastereomer) as white crystals and the sulfite **59b** (one diastereomer). **59a**: R_f 0.42 (MeOH/EtOAc 1:99); m.p. 121-123 °C; IR(neat) ν 3362 (m), 3134 (m), 2961 (m), 2929 (m), 2876 (m), 1716 (s), 1658 (m), 1467 (m), 1455 (m), 1408 (w), 1392 (w), 1378 (w), 1362 (w), 1304 (m), 1284 (m), 1248 (m), 1194 (m), 1177 (m), 1133 (m), 1105 (m), 1059 (m), 1049 (m), 1033 (m), 1004 (m), 989 (m), 947 (m), 886 (m), 815 (m), 766 (m), 731 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (1H, s), 6.78 (1H, d, J 15.8 Hz), 6.05 (1H, d, J 15.8 Hz), 5.66 (1H, d, J 13.2 Hz), 4.87 (1H, d, J 13.2 Hz), 4.50 (1H, ddd, J 13.9 Hz, 7.0 Hz, 5.1 Hz), 4.38 (1H, ddd, J 13.9 Hz, 7.0 Hz, 5.1 Hz), 4.22 (2H, t, J 5.5 Hz), 4.03 (1H, d, J 10.3 Hz), 3.86 (1H, d, J 10.3 Hz), 2.99 (1H, br s), 2.17-2.01 (2H, m), 1.77-1.65 (2H, m), 1.33 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 150.8, 143.1, 123.8, 120.9, 71.9, 71.3, 63.3, 55.3, 49.7, 26.6, 25.2, 23.7; HRMS (ESI): *m/z* calcd. for $C_{13}H_{19}N_3O_6S$ $[M+H]^+$ 346.1067, found 346.1048; anal. calcd. for $C_{13}H_{19}N_3O_6S$: C, 45.21; H, 5.55; N, 12.17. Found: C, 45.30; H, 5.51; N, 12.08. **59b**: R_f 0.12 (MeOH/EtOAc 1:99); ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (1H, s), 6.81 (1H, d, J 15.5 Hz), 6.04 (1H, d, J 15.5 Hz), 4.81 (2H, s), 4.56 (1H, d, J 8.9 Hz), 4.42 (1H, d, J 8.9

Hz), 4.43-4.39 (2H, m), 4.18 (2H, t, *J* 6.3 Hz), 2.05-1.97 (2H, m), 1.78 (3H, s), 1.74-1.67 (2H, m); HRMS (ESI): *m/z* calcd. for $C_{13}H_{19}N_3O_6S$ $[M+H]^+$ 346.1067, found 346.1094.

Sulfite 61

White crystals, 47% yield; R_f 0.42 (MeOH/EtOAc 1:99); m.p. 115-118 °C; dr: 3:2, de: 20% (NMR); IR(neat) ν 3152 (w), 3065 (w), 2965 (m), 2944 (m), 2917 (w), 2872 (w), 2842 (w), 1747 (m), 1725 (m), 1711 (s), 1657 (m), 1611 (w), 1514 (m), 1466 (w), 1449 (m), 1413 (w), 1382 (m), 1324 (m), 1300 (m), 1283 (m), 1264 (m), 1249 (m), 1220 (m), 1179 (m), 1149 (m), 1134 (m), 1027 (m), 1003 (m), 975 (m), 928 (m), 892 (m), 846 (w), 821 (m), 802 (w), 787 (m), 757 (m), 741 (m), 700 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (maj, s), 7.63 (min, s), 6.84 (maj, d, *J* 15.6 Hz), 6.82 (min, d, *J* 15.6 Hz), 6.07 (both, d, *J* 15.6 Hz), 5.46 (maj, d, *J* 12.2 Hz), 5.41 (min, d, *J* 12.3 Hz), 5.32 (min, d, *J* 12.3 Hz), 5.27 (maj, d, *J* 12.2 Hz), 4.52-4.37 (m), 3.91 (min, d, *J* 10.1 Hz), 3.87 (maj, d, *J* 10.0 Hz), 3.77 (maj, d, *J* 10.0 Hz), 3.72 (min, d, *J* 10.1 Hz), 3.68 (min, dt, *J* 7.2 Hz, 7.2 Hz), 3.64 (maj, dt, *J* 7.1 Hz, 7.1 Hz), 3.51 (maj, dt, *J* 7.6 Hz, 7.6 Hz), 3.47 (min, dt, *J* 7.6 Hz, 7.6 Hz), 2.69 (both, br s), 2.02-1.78 (m), 1.52-1.41 (m), 1.33 (min, s), 1.32 (maj, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2 (maj), 166.2 (min), 151.8 (maj), 151.8 (min), 144.3 (maj), 144.2 (min), 123.9 (min), 123.8 (maj), 120.8 (both), 72.2 (min), 72.1 (maj), 70.7 (maj), 69.0 (min), 62.6 (min), 62.0 (maj), 57.5 (min), 57.5 (maj), 50.1 (maj), 50.1 (min), 27.1 (both), 26.2 (both), 23.6 (both); HRMS (ESI): *m/z* calcd. for $C_{13}H_{19}N_3O_6S$ $[M+H]^+$ 346.1067, found 346.1068; anal. calcd. for $C_{13}H_{19}N_3O_6S$: C, 45.21; H, 5.55; N, 12.17. Found: C, 45.06; H, 5.48; N, 12.07.

Sulfite 63

White crystals, 65% yield; R_f 0.36 (MeOH/EtOAc 1:99); m.p. 129-130 °C; dr: 1:1 (NMR); IR (neat) ν 3503 (br), 3142 (w), 2970 (m), 2941 (m), 2889 (w), 2871 (w), 1713 (s), 1470 (w), 1447 (m), 1364 (m), 1342 (w), 1264 (m), 1228 (m), 1197 (s) 1150 (m), 1135 (m), 1069 (m), 1053 (m), 983 (m), 970 (m), 946 (m), 920 (m), 871 (m), 839 (w), 821 (w), 805 (w), 777 (m), 731 (m), 678 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (both, s), 5.88-5.82 (one, m), 5.81 (one, d, *J* 15.4 Hz), 5.75 (one, d, *J* 15.4 Hz), 5.70 (both, d, *J* 12.5 Hz), 5.16 (one, d, *J* 12.5 Hz), 5.15 (one, d, *J* 12.5 Hz), 4.58-4.42 (m), 4.39-4.23 (m), 4.07-4.01 (m), 3.74-3.65 (m), 3.28 (both, br s), 2.07-1.97 (m), 1.96-1.85 (m), 1.66-1.54 (m), 1.53 (both, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9 (one), 174.8 (one), 142.7 (one), 142.7 (one), 136.3 (one), 135.2 (one), 124.1 (both), 124.1 (one), 123.9 (one), 74.3 (both), 62.2 (one), 62.0 (one), 61.9 (one), 61.8 (one), 58.9 (one), 58.8 (one), 50.0 (one), 50.0 (one), 26.9 (one), 26.9 (one), 26.4 (one), 26.3 (one), 25.2 (both); HRMS (ESI): *m/z* calcd. for $C_{13}H_{19}N_3O_6S$ $[M+H]^+$ 346.1067, found 346.1073; anal. calcd. for

$C_{13}H_{19}N_3O_6S$: C, 45.21; H, 5.55; N, 12.17. Found: C, 44.59; H, 5.78; N, 12.07.

Sulfite 65

White crystals, 67% yield; R_f 0.36 (MeOH/EtOAc 1:99); m.p. 93-95 °C; dr: 1:1 (NMR); IR (neat) ν 3500 (m), 3151 (w), 2966 (m), 2872 (w), 1719 (s), 1676 (w), 1454 (m), 1443 (m), 1373 (m) 1278 (m), 1198 (m), 1171 (s), 1134 (m), 1075 (w), 1049 (m), 1027 (m), 978 (m), 940 (m), 925 (m), 889 (m), 854 (m), 835 (m), 788 (m), 767 (m), 736 (m), 710 (m), 670 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (one, s), 7.61 (one, s), 5.94-5.74 (m), 5.63 (one, dd, *J* 13.6 Hz, 0.4 Hz), 5.54 (one, dd, *J* 13.6 Hz, 0.4 Hz), 4.97 (one, dd, *J* 13.6 Hz, 0.4 Hz), 4.91 (one, dd, *J* 13.6 Hz, 0.4 Hz), 4.61-4.18 (m), 4.05-3.98 (m), 3.36 (both, br s), 1.99-1.62 (m), 1.46 (one, s), 1.45 (one, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1 (one), 175.0 (one), 143.7 (one), 143.7 (one), 135.4 (one), 135.3 (one), 124.1 (one), 124.0 (one), 123.8 (one), 123.6 (one), 74.1 (one), 74.1 (one), 64.6 (one), 64.6 (one), 63.0 (one), 62.2 (one), 55.7 (one), 54.6 (one), 49.5 (one), 49.5 (one), 27.4 (one), 27.3 (one), 26.0 (one), 25.9 (one), 25.8 (one), 25.8 (one); HRMS (ESI): *m/z* calcd. for $C_{13}H_{19}N_3O_6S$ $[M+H]^+$ 346.1067, found 346.1063; anal. calcd. for $C_{13}H_{19}N_3O_6S$: C, 45.21; H, 5.55; N, 12.17. Found: C, 45.56; H, 5.76; N, 11.85.

Representative procedure for the preparation of macrocyclic malonates 66 and 68

Malonate 66

The diol **51** (55 mg, 0.13 mmol) was dissolved in anhydrous CH_2Cl_2 (9.74 mL) and anhydrous Et_3N (0.05 mL, 0.36 mmol) and DMAP (3 mg, 0.03 mmol) were added. A solution of malonyl chloride in anhydrous CH_2Cl_2 (0.18 M, 1 mL, 0.18 mmol) was added over 10 minutes at 20 °C, under vigorous stirring. After stirring for $1\frac{1}{2}$ hours, the reaction mixture was concentrated *in vacuo*. The residue was redissolved in EtOAc, filtered through Celite and concentrated *in vacuo*. Purification by flash column chromatography ($MeOH/CH_2Cl_2$ 1:99) gave the malonate **66** (23 mg, 37%) as a colorless oil. R_f 0.54 (MeOH/EtOAc 1:99); IR (neat) ν 3146 (w), 2956 (m), 2872 (w), 2838 (w), 1751 (s), 1733 (s), 1715 (s), 1656 (w), 1613 (m), 1586 (w), 1514 (m), 1463 (m), 1443 (m), 1409 (w), 1385 (m), 1364 (m), 1300 (m), 1247 (s), 1172 (m), 1146 (m), 1130 (m), 1030 (m), 993 (m), 911 (m), 822 (m), 727 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (1H, s), 7.24 (2H, d, *J* 8.7 Hz), 6.91 (1H, d, *J* 16.0 Hz), 6.87 (2H, d, *J* 8.7 Hz), 6.04 (1H, d, *J* 16.0 Hz), 5.36 (1H, d, *J* 12.7 Hz), 5.21 (1H, d, *J* 12.7 Hz), 4.46 (2H, t, *J* 6.4 Hz), 4.42 (1H, d, *J* 10.5 Hz), 4.36 (1H, d, *J* 10.5 Hz), 4.29 (1H, d, *J* 11.1 Hz), 4.22 (1H, d, *J* 11.1 Hz), 4.28-4.13 (2H, m), 3.80 (3H, s), 3.48 (1H, d, *J* 16.3 Hz), 3.42 (1H, d, *J* 16.3 Hz), 2.05-1.89 (2H, m), 1.67-1.59 (2H, m), 1.45 (3H, s);

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 165.9, 165.9, 159.3, 149.3, 143.0, 130.3, 129.0 (2C), 124.0, 122.4, 114.0 (2C), 76.1, 69.5, 65.2, 63.0, 59.1, 55.4, 49.5, 41.2, 27.0, 25.5, 20.6.

Malonate 68

White crystals, 34% yield; m.p. 113-115 °C; R_f 0.54 (MeOH/EtOAc 1:99); IR(neat) ν 3153 (w), 3064 (w), 3039 (w), 2998 (w), 2944 (m), 2916 (w), 2872 (m), 2842 (w), 1747 (s), 1726 (s), 1712 (s), 1657 (m), 1611 (m), 1587 (w), 1514 (m), 1465 (w), 1449 (m), 1413 (w), 1383 (m), 1324 (m), 1300 (m), 1283 (m), 1265 (m), 1249 (m), 1220 (m), 1179 (s), 1149 (m), 1135 (m), 1122 (m), 1059 (m), 1027 (s) 976 (m), 928 (m), 847 (m), 821 (m), 803 (m), 788 (m), 757 (m), 742 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (1H, s), 7.24 (2H, d, *J* 8.5 Hz), 6.94 (1H, d, *J* 16.0 Hz), 6.87 (2H, d, *J* 8.5 Hz), 6.08 (1H, d, *J* 16.0 Hz), 5.38 (1H, d, *J* 12.8 Hz), 5.35 (1H, d, *J* 12.8 Hz), 4.48-4.43 (2H, m), 4.42 (1H, d, *J* 10.7 Hz), 4.37 (1H, d, *J* 10.7 Hz), 4.27 (1H, d, *J* 11.2 Hz), 4.15 (1H, d, *J* 11.2 Hz), 4.00-3.90 (2H, m), 3.80 (3H, s), 3.34 (1H, d, *J* 15.9 Hz), 3.30 (1H, d, *J* 15.9 Hz), 1.96-1.91 (2H, m), 1.54-1.47 (2H, m), 1.44 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 166.1, 165.7, 159.3, 149.4, 148.6, 130.3, 129.0 (2C), 124.2, 122.5, 113.9 (2C), 76.3, 69.5, 65.2, 64.2, 58.1, 55.4, 49.6, 41.3, 26.1, 25.3, 20.2.

Representative procedure for the preparation of deprotected macrocyclic malonates 67 and 69

Malonate 67

The malonate **66** (100 mg, 0.21 mmol) was dissolved in CH_2Cl_2 (19.5 mL) and water (1.1 mL). DDQ (56 mg, 0.25 mmol) was added, and the mixture was stirred at 20 °C for $5\frac{1}{2}$ hours. Then the mixture was diluted with EtOAc (100 mL) and washed with 40% aqueous $NaHSO_3$ (120 mL) and water (2×80 mL). The aqueous phase was extracted with EtOAc (120 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified twice by flash column chromatography (EtOAc/toluene 1:1) to give the deprotected malonate **67** (59 mg, 78%) as a colorless oil. R_f 0.38 (MeOH/EtOAc 1:99); IR (neat) ν 3468 (br), 3148 (w), 2958 (m), 1713 (s), 1658 (m), 1444 (m), 1373 (m), 1328 (m), 1264 (s), 1182 (m), 1136 (s), 1046 (m), 1024 (m), 979 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (1H, s), 6.92 (1H, d, *J* 15.7 Hz), 6.04 (1H, d, *J* 15.7 Hz), 5.44 (1H, d, *J* 12.6 Hz), 5.17 (1H, d, *J* 12.6 Hz), 4.48 (1H, d, *J* 10.9 Hz), 4.46 (2H, t, *J* 6.4 Hz), 4.42 (1H, m), 4.03 (1H, d, *J* 10.9 Hz), 4.02 (1H, m), 3.48 (1H, d, *J* 17.5 Hz), 3.45 (1H, d, *J* 17.5 Hz), 2.13 (1H, m), 2.04 (1H, m), 1.73 (1H, m), 1.57 (1H, m), 1.36 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 166.1, 165.7, 151.5, 142.5, 124.6, 120.2, 72.2, 71.1, 63.2, 59.1, 49.5, 41.1, 26.9, 25.1, 23.6; HRMS (ESI): *m/z* calcd. for $C_{16}H_{21}N_3O_7$ $[M+H]^+$

368.1452, found 368.1449; anal. calcd. for $C_{16}H_{21}N_3O_7$: C, 52.31; H, 5.76; N, 11.44. Found: C, 52.23; H, 5.71; N, 11.40.

Malonate (69)

White crystals, 69% yield; m.p. 105-106 °C; R_f 0.38 (MeOH/EtOAc 1:99); IR (neat) ν 3308 (br), 3156 (w), 2986 (w), 2968 (m), 2941 (w), 2873 (w), 1727 (s), 1711 (s), 1650 (w), 1462 (w), 1447 (w), 1422 (w), 1376 (w), 1351 (m), 1324 (m), 1295 (m), 1259 (m), 1239 (m), 1224 (m), 1169 (m), 1075 (m), 1065 (m), 1030 (m), 1007 (m), 981 (m), 841 (m), 782 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (1H, s), 6.96 (1H, d, J 15.7 Hz), 6.10 (1H, d, J 15.7 Hz), 5.39 (1H, d, J 12.6 Hz), 5.33 (1H, d, J 12.6 Hz), 4.49-4.40 (2H, m), 4.24 (1H, d, J 11.2 Hz), 4.17 (1H, d, J 11.2 Hz), 3.92 (2H, t, J 7.3 Hz), 3.35 (1H, d, J 16.4 Hz), 3.32 (1H, d, J 16.4 Hz), 1.96-1.90 (2H, m), 1.52-1.45 (2H, m), 1.35 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 166.1, 165.9, 151.4, 143.8, 124.2, 120.4, 72.3, 71.4, 64.3, 57.8, 49.7, 41.2, 25.9, 25.4, 24.1; HRMS (ESI): m/z calcd. for $C_{16}H_{21}N_3O_7$ $[M+H]^+$ 368.1452, found 368,1450; anal. calcd. for $C_{16}H_{21}N_3O_7$: C, 52.31; H, 5.76; N, 11.44. Found: C, 52.18; H, 5.74; N, 11.29.

Representative procedure for the preparation of macrocyclic phthalates 70, 71, and 72

Macrocyclic phthalates **70**, **71**, and **72** were prepared from diol **51** analogously to the representative procedure for the preparation of macrocyclic malonates **66** and **68**, by substitution of malonyl chloride with phthaloyl chloride, isophthaloyl chloride, and terephthaloyl chloride, respectively.

Phthalate 70: Colorless oil, 19% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (1H, m), 7.75 (1H, s), 7.55-7.51 (3H, m), 7.28 (2H, d, J 8.8 Hz), 6.97 (1H, d, J 16.0 Hz), 6.89 (2H, d, J 8.8 Hz), 6.07 (1H, d, J 16.0 Hz), 5.49 (1H, d, J 12.7 Hz), 5.43 (1H, d, J 12.7 Hz), 4.58 (1H, d, J 11.4 Hz), 4.48-4.43 (4H, m), 4.43 (1H, d, J 11.4 Hz), 4.20-4.15 (2H, m), 3.81 (3H, s), 2.02-1.92 (2H, m), 1.65-1.57 (2H, m), 1.51 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 166.4, 166.2, 159.3, 149.7, 143.1, 133.4, 132.0, 130.9, 130.6, 130.1, 129.8, 129.0 (2C), 128.2, 124.2, 122.1, 114.0 (2C), 76.1, 69.6, 65.3, 63.0, 58.9, 55.5, 49.4, 26.9, 25.2, 21.4; HRMS (ESI): m/z calcd. for $C_{29}H_{31}N_3O_8$ $[M+H]^+$ 550.2184, found 550.2191.

Isophthalate 71: Amorphous solid, 21% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (1H, t, J 1.7 Hz), 8.25 (2H, dd, J 7.8 Hz, 1.7 Hz), 7.79 (1H, s), 7.56 (1H, t, J 7.8 Hz), 7.26 (2H, d, J 8.4 Hz), 7.02 (1H, d, J 15.9 Hz), 6.86 (2H, d, J 8.4 Hz), 6.13 (1H, d, J 15.9 Hz), 5.55 (1H, d, J 12.9 Hz), 5.49 (1H, d, J 12.9 Hz), 4.51 (1H, d, J 11.3 Hz), 4.50 (1H, d, J 10.8 Hz), 4.51-4.46 (2H, m), 4.43 (1H, d, J 10.8 Hz), 4.30 (1H, d, J 11.3 Hz), 4.17-4.09 (2H, m), 3.78 (3H, s), 1.99-1.90 (2H, m), 1.59-1.54 (2H, m), 1.52 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 165.7, 165.2, 159.2, 149.7, 142.9, 134.7, 134.3, 130.6,

130.5, 130.4, 130.1, 129.0, 128.9 (2C), 124.6, 122.4, 114.0 (2C), 76.4, 69.0, 65.1, 63.4, 59.0, 55.4, 49.7, 26.8, 25.5, 20.6; HRMS (ESI): *m/z* calcd. for $C_{29}H_{31}N_3O_8$ $[M+H]^+$ 550.2184, found 550.2173.

Terephthalate 72: White solid, 9% yield; m.p. 162-163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (2H, d, *J* 8.4 Hz), 7.96 (2H, d, *J* 8.4 Hz), 7.56 (1H, s), 7.23 (2H, d, *J* 8.4 Hz), 6.87 (2H, d, *J* 8.4 Hz), 6.85 (1H, d, *J* 15.8 Hz), 5.97 (1H, d, *J* 15.8 Hz), 5.63 (1H, d, *J* 12.5 Hz), 5.57 (1H, d, *J* 12.5 Hz), 4.64 (1H, d, *J* 11.4 Hz), 4.57-4.37 (2H, m), 4.48 (1H, d, *J* 10.8 Hz), 4.38 (1H, d, *J* 10.8 Hz), 4.23 (1H, d, *J* 11.4 Hz), 4.01-3.83 (2H, m), 3.80 (3H, s), 1.88-1.78 (2H, m), 1.50 (3H, s), 1.43-1.27 (2H, m); HRMS (ESI): *m/z* calcd. for $C_{29}H_{31}N_3O_8$ $[M+H]^+$ 550.2184, found 550.2187.

Representative procedure for the preparation of macrocyclic oxalate 73

Macrocyclic oxalate **73** was prepared from diol **53** analogously to the representative procedure for the preparation of macrocyclic malonates **66** and **68**, by substitution of malonyl chloride with oxalyl chloride.

Oxalate 73: 9% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (1H, s), 7.23 (2H, d, *J* 8.7 Hz), 6.91 (1H, d, *J* 15.9 Hz), 6.87 (2H, d, *J* 8.7 Hz), 6.07 (1H, d, *J* 15.9 Hz), 5.41 (1H, d, *J* 12.6 Hz), 5.36 (1H, d, *J* 12.6 Hz), 4.52 (1H, d, *J* 11.1 Hz), 4.51-4.47 (2H, m), 4.44 (1H, d, *J* 10.8 Hz), 4.36 (1H, d, *J* 10.8 Hz), 4.24-4.17 (2H, m), 4.18 (1H, d, *J* 11.1 Hz), 3.80 (3H, s), 2.01-1.92 (2H, m), 1.47 (3H, s), 1.46-1.40 (2H, m); HRMS (ESI): *m/z* calcd. for $C_{23}H_{27}N_3O_8$ $[M+H]^+$ 474.1871, found 474.1877.

Representative procedure for the preparation of dialdehydes 75, 78, and 80

(+/-)-(*E*))-4-(4-Formyl-1*H*-1,2,3-triazol-1-yl)butyl 2-(4-methoxybenzyloxy)-2-methyl-5-oxopent-3-enoate 80

The diol **57** (51 mg, 0.12 mmol) was dissolved in CH_3CN (2.1 mL). IBX[71] (202 mg, 0.72 mmol) was added, and the suspension was heated to 55 °C. After stirring at 55 °C for $3\frac{1}{2}$ hours, the suspension was concentrated *in vacuo*. The residue was redissolved in Et_2O, filtered and concentrated *in vacuo* giving the dialdehyde **80** (50 mg, quantitative yield) as a colorless oil. R_f 0.46 ($MeOH/CH_2Cl_2$ 5:95); IR (neat) ν 3133 (w), 2960 (m), 2937 (m), 2872 (m), 2837 (m), 1733 (s), 1688 (s), 1612 (m), 1531 (m), 1513 (s), 1463 (m), 1443 (m), 1384 (m), 1301 (m), 1245 (s), 1174 (m), 1110 (s), 1092 (s), 1028 (s), 979 (m), 822 (m), 782 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.13 (1H, s), 9.62 (1H, d, *J* 7.7 Hz), 8.02 (1H, s), 7.27 (2H, d, *J* 8.5 Hz), 6.99 (1H, d, *J* 15.9 Hz), 6.87 (2H, d, *J* 8.5 Hz), 6.43 (1H, dd, *J* 15.9 Hz, 7.7 Hz), 4.44 (2H, s), 4.43 (2H, t, *J* 7.1 Hz), 4.23 (2H, t, *J* 6.3 Hz), 3.80 (3H, s), 2.07-1.97 (2H,

m), 1.77-1.70 (2H, m), 1.67 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.2, 185.1, 171.3, 159.4, 155.1, 147.9, 132.3, 129.6, 129.1 (2C), 125.3, 113.9 (2C), 80.3, 67.4, 64.9, 55.4, 50.2, 26.9, 25.5, 23.6.

(+/-)-(*E*))-(1-(4-Oxobutyl)-1*H*-1,2,3-triazol-4-yl)methyl 2-(4-methoxybenzyloxy)-2-methyl-5-oxopent-3-enoate 78

Colorless oil, 98% yield; R_f 0.35 (MeOH/CH_2Cl_2 5:95); IR (neat) ν 3143 (w), 2957 (m), 2938 (m), 2837 (m), 2733 (w), 1723 (s), 1688 (s), 1613 (m), 1514 (s), 1461 (m), 1443 (m), 1386 (m), 1302 (m), 1247 (s), 1175 (m), 1106 (s), 1048 (m), 1028 (m), 979 (m), 913 (m), 821 (m), 729 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (1H, s), 9.58 (1H, d, *J* 7.8 Hz), 7.58 (1H, s), 7.25 (2H, d, *J* 8.6 Hz), 6.99 (1H, d, *J* 15.9 Hz), 6.86 (2H, d, *J* 8.6 Hz), 6.38 (1H, dd, *J* 15.9 Hz, 7.8 Hz), 5.37 (1H, d, *J* 13.2 Hz), 5.32 (1H, d, *J* 13.2 Hz), 4.44-4.37 (4H, m), 3.80 (3H, s), 2.52 (2H, t, *J* 6.8 Hz), 2.24-2.15 (2H, m), 1.66 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.3, 193.2, 171.3, 159.4, 155.1, 142.3, 132.2, 129.6, 129.4 (2C), 124.1, 113.9 (2C), 80.2, 67.5, 58.9, 55.4, 49.4, 40.2, 23.8, 22.7.

(+/-)-(*E*)-4-(4-Formyl-1*H*-1,2,3-triazol-1-yl)butyl 4-(4-methoxybenzyloxy)-4-methyl-5-oxopent-2-enoate 75

Colorless oil, quantitative yield; R_f 0.55 (MeOH/EtOAc 1:99); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.15 (1H, s), 9.51 (1H, s), 8.11 (1H, s), 7.29 (2H, d, *J* 8.8 Hz), 6.90 (2H, d, *J* 8.8 Hz), 6.87 (1H, d, *J* 15.9 Hz), 6.20 (1H, d, *J* 15.9 Hz), 4.51-4.45 (4H, m), 4.20 (2H, t, *J* 6.3 Hz), 3.81 (3H, s), 2.11-2.01 (2H, m), 1.77-1.68 (2H, m), 1.52 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 185.3, 165.6, 159.6, 148.0, 145.0, 129.6, 129.4 (2C), 125.2, 123.7, 114.1 (2C), 83.3, 66.8, 63.6, 55.4, 50.4, 27.0, 25.7, 19.6.

Representative procedure for the preparation of macrocyclic amines 76, 79, and 81

Amine 81

The dialdehyde **80** (43 mg, 0.10 mmol) was dissolved in anhydrous CH_2Cl_2 (6.9 mL). The mixture was cooled to 0 °C, and a solution of veratrylamine in anhydrous CH_2Cl_2 (0.11 M, 1 mL, 0.11 mmol) was added. After stirring at 0 °C for 25 minutes, $Na(OAc)_3BH$ (65 mg, 0.31 mmol) was added. After stirring at 0 °C for further 15 minutes, powdered 3 Å molecular sieves (40 mg) were added. The suspension was then stirred at 0 °C for 3 hours, whereafter it was quenched with Et_2O (10 mL) and then water (20 mL). After filtration, the mixture was transferred to a separatory funnel with Et_2O (40 mL) and CH_2Cl_2 (20 mL). The organic phase was isolated and washed with a mixture of sat. aq. $NaHCO_3$ (40 mL) and water (20 mL). The aqueous phase was extracted with CH_2Cl_2 (2×30 mL) and Et_2O (30 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification

by flash column chromatography (EtOAc/heptane 3:1) gave the azalide **81** (34 mg, 60%) as an amorphous solid. R_f 0.30 (MeOH/CH_2Cl_2 5:95); IR (neat) ν 3134 (w), 3034 (m), 2996 (m), 2934 (m), 2872 (m), 2834 (m), 1730 (s), 1612 (m), 1589 (m), 1512 (s), 1453 (m), 1418 (m), 1367 (m), 1329 (m), 1301 (m), 1244 (s), 1175 (m), 1108 (s), 1025 (s), 980 (m), 943 (m), 893 (m), 853 (m), 810 (m), 764 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, s), 7.27 (2H, d, *J* 8.8 Hz), 6.96 (1H, s), 6.89 (1H, d, *J* 8.2 Hz), 6.85 (2H, d, *J* 8.8 Hz), 6.79 (1H, d, *J* 8.2 Hz), 5.77 (1H, d, *J* 15.7 Hz), 5.64 (1H, dt, *J* 15.7 Hz, 4.9 Hz), 4.43 (1H, d, *J* 10.6 Hz), 4.41-4.36 (2H, m), 4.31 (1H, d, *J* 10.6 Hz), 4.26-4.11 (2H, m), 3.86 (3H, s), 3.84 (3H, s), 3.81 (2H, s), 3.79 (3H, s), 3.74 (1H, d, *J* 13.3 Hz), 3.68 (1H, d, *J* 13.3 Hz), 3.21 (2H, d, *J* 4.9 Hz), 2.10-2.01 (2H, m), 1.68-1.62 (2H, m), 1.53 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 159.2, 149.0, 148.2, 147.4, 131.7, 131.6, 131.0, 130.7, 129.3 (2C), 122.0, 121.1, 113.8 (2C), 112.1, 110.9, 80.3, 66.7, 63.4, 60.6, 56.1, 56.0, 56.0, 55.4, 50.1, 49.4, 26.6, 26.5, 22.4; HRMS (ESI): *m/z* calcd. for $C_{30}H_{38}N_4O_6$ $[M+H]^+$ 551.2864, found 551.2859.

Amine (79)

White solid, 46% yield; R_f 0.17 (MeOH/CH_2Cl_2 5:95); m.p. 141-143 °C; IR(neat) ν 3129 (w), 2994 (w), 2966 (w), 2937 (m), 2915 (w), 2875 (w), 2837 (w), 2797 (m), 1718 (s), 1614 (m), 1589 (w), 1516 (s), 1452 (m), 1420 (w), 1389 (w), 1375 (w), 1328 (w), 1252 (s), 1237 (m), 1184 (m), 1160 (m), 1122 (s), 1058 (w), 1024 (m), 966 (w), 929 (w), 879 (w), 856 (w), 826 (m), 805 (m), 761 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (1H, s), 7.32 (2H, d, *J* 8.7 Hz), 6.87 (2H, d, *J* 8.7 Hz), 6.83 (1H, s), 6.76 (2H, s), 5.66 (1H, dt, *J* 15.7 Hz, 6.0 Hz), 5.49 (1H, d, *J* 12.1 Hz), 5.44 (1H, d, *J* 15.7 Hz), 5.31 (1H, d, *J* 12.1 Hz), 4.49 (1H, d, *J* 10.6 Hz), 4.41 (1H, d, *J* 10.6 Hz), 4.39-4.28 (2H, m), 3.85 (3H, s), 3.84 (3H, s), 3.80 (3H, s), 3.47 (1H, d, *J* 13.9 Hz), 3.42 (1H, d, *J* 13.9 Hz), 2.89 (2H, d, *J* 6.0 Hz), 2.15-2.09 (2H, m), 1.90-1.79 (2H, m), 1.58 (3H, s), 1.27-1.15 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 159.2, 149.0, 148.1, 142.9, 132.3, 132.3, 131.9, 130.6, 129.3 (2C), 124.7, 120.9, 113.8 (2C), 111.8, 110.8, 80.4, 66.7, 59.3, 58.0, 56.0, 56.0, 55.4, 54.8, 52.7, 50.1, 27.7, 22.7, 20.9; HRMS (ESI): *m/z* calcd. for $C_{30}H_{38}N_4O_6$ $[M+H]^+$ 551.2864, found 551.2862.

Amine (76)

9% yield; R_f 0.30 (MeOH/EtOAc 1:99); ^1H NMR (500 MHz, CD_3OD) δ 7.57 (1H, s), 7.18 (2H, d, *J* 8.6 Hz), 7.05 (1H, m), 6.90-6.83 (2H, m), 6.78 (2H, d, *J* 8.6 Hz), 6.65 (1H, d, *J* 16.1 Hz), 5.85 (1H, d, *J* 16.1 Hz), 4.41 (1H, d, *J* 11.0 Hz), 4.35 (1H, m), 4.28 (1H, d, *J* 11.0 Hz), 4.27 (1H, m), 4.23 (1H, m), 4.16 (1H, d, *J* 13.6 Hz), 4.08 (1H, m), 3.82 (3H, s), 3.74 (6H, s), 3.65 (1H, d, *J* 14.3 Hz), 3.57 (1H, d, *J* 13.6 Hz), 3.43 (1H, d, *J* 14.3 Hz), 3.05 (1H, d, *J* 14.2 Hz), 2.85 (1H, d, *J* 14.2 Hz), 2.10-1.97 (2H, m), 1.84-1.74 (2H, m), 1.35

(3H, s); HRMS (ESI): *m/z* calcd. for $C_{30}H_{38}N_4O_6$ $[M+H]^+$ 551.2864, found 551.2845.

Attempt at the synthesis of a macrocyclic amine with ammonium acetate

The dialdehyde **75** (42 mg, 0.101 mmol) was dissolved in anhydrous CH_2Cl_2 (7.8 mL). The mixture was cooled to 0 °C and a solution of ammonium acetate in anhydrous CH_2Cl_2 (0.104 mM, 1 mL, 0.104 mmol) was added. After stirring at 0 °C for 10 minutes, powdered 3 Å molecular sieves (39 mg) were added. After stirring for further 5 minutes at 0 °C, $Na(OAc)_3BH$ (64 mg, 0.303 mmol) was added. The suspension was then stirred for 22 hours, whereafter it was quenched with Et_2O (10 mL) and then water (20 mL). After filtration, the mixture was transferred to a separatory funnel with Et_2O (40 mL) and CH_2Cl_2 (20 mL). The organic phase was isolated and washed with a mixture of sat. aq. $NaHCO_3$ (40 mL) and water (20 mL). The aqueous phase was extracted with CH_2Cl_2 (2×30 mL) and Et_2O (30 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/heptane 1:1 → MeOH/EtOAc 3:97) to give the hydroxy aldehyde **77** (8 mg, 20%) and the diol **51** (6 mg, 14%) as colorless oils.

(+/-)-(*E*)-4-(4-formyl-1*H*-1,2,3-triazol-1-yl)butyl 5-hydroxy-4-(4-methoxybenzyloxy)-4-methylpent-2-enoate 77:

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.14 (1H, s), 8.12 (1H, s), 7.25 (2H, d, *J* 8.7 Hz), 6.98 (1H, d, *J* 16.1 Hz), 6.88 (2H, d, *J* 8.7 Hz), 6.05 (1H, d, *J* 16.1 Hz), 4.49 (2H, t, *J* 7.1 Hz), 4.39 (1H, d, *J* 10.7 Hz), 4.33 (1H, d, *J* 10.7 Hz), 4.21 (2H, t, *J* 6.3 Hz), 3.81 (3H, s), 3.60 (1H, d, *J* 11.5 Hz), 3.55 (1H, d, *J* 11.5 Hz), 2.12-2.02 (2H, m), 1.78-1.68 (2H, m), 1.43 (3H, s).

Representative procedure for the preparation of monodeprotected macrocyclic amines 82 and 83

Amine 82

The amine **79** (15 mg, 0.027 mmol) was dissolved in CH_2Cl_2 (0.70 mL) and water (0.14 mL). DDQ (18 mg, 0.08 mmol) was added, and the reaction mixture was stirred at 20 °C for 21 hours. Subsequently, the mixture was concentrated *in vacuo*, and the residue was purified by flash column chromatography (EtOAc/toluene 4:1 + 0.5% Et_3N) to give the monodeprotected amine **82** (8 mg, 69%) as a colorless film. R_f 0.07 (MeOH/CH_2Cl_2 5:95); ^{1}H NMR (300 MHz, CD_3OD) δ 7.94 (1H, s), 6.95 (1H, d, *J* 1.6 Hz), 6.89 (1H, d, *J* 8.2 Hz), 6.83 (1H, dd, *J* 8.2 Hz, 1.6 Hz), 5.71 (1H, ddd, *J* 15.4 Hz, 8.5 Hz, 4.4 Hz), 5.60 (1H, d, *J* 12.3 Hz), 5.44 (1H, d, *J* 15.4 Hz), 5.11 (1H, d, *J* 12.3 Hz), 4.46-4.41 (2H, m), 3.83 (3H, s), 3.81 (3H, s), 3.58 (1H, d, *J* 13.0

Hz), 3.51 (1H, d, *J* 13.0 Hz), 3.07 (1H, ddd, *J* 14.7 Hz, 4.4 Hz, 1.6 Hz), 2.85 (1H, dd, *J* 14.7 Hz, 8.5 Hz), 2.15 (2H, t, *J* 8.1 Hz), 1.90 (1H, m), 1.75 (1H, m), 1.43 (3H, s), 1.33 (1H, m), 1.07 (1H, m); HRMS (ESI): *m/z* calcd. for $C_{22}H_{30}N_4O_5$ $[M+H]^+$ 431.2289, found 431.2289.

Amine 83

33% yield; R_f 0.10 ($MeOH/CH_2Cl_2$ 5:95); ^1H NMR (500 MHz, CD_3OD) δ 7.87 (1H, s), 7.07 (1H, s), 6.94 (1H, d, *J* 8.2 Hz), 6.91 (1H, d, *J* 8.2 Hz), 5.65 (1H, d, *J* 15.6 Hz), 5.57 (1H, ddd, *J* 15.6 Hz, 6.2 Hz, 4.8 Hz), 4.47 (1H, m), 4.39 (1H, m), 4.27 (1H, m), 4.03 (1H, m), 3.85 (3H, s), 3.82 (3H, s), 3.78 (2H, d, *J* 6.9 Hz), 3.74 (2H, s), 3.25 (1H, m), 3.18 (1H, dd, *J* 15.5 Hz, 6.2 Hz), 2.04 (2H, m), 1.66 (1H, m), 1.57 (1H, m), 1.36 (3H, s); HRMS (ESI): *m/z* calcd. for $C_{22}H_{30}N_4O_5$ $[M+H]^+$ 431.2289, found 431.2281.

(+/-)-(*E*)-4-(4-(Iodomethyl)-1*H*-1,2,3-triazol-1-yl)butyl 5-hydroxy-4-(4-methoxybenzyloxy)-4-methylpent-2-enoate 86

Ph_3P (110 mg, 0.42 mmol) and imidazole (31 mg, 0.46 mmol) were added to a stirred solvent mixture of anhydrous CH_3CN/Et_2O 1:2 (10 mL). The mixture was cooled to 0 °C, and I_2 (107 mg, 0.42 mmol) was added in one portion. After stirring for 35 minutes at 0 °C, a solution of the diol **51** in anhydrous CH_3CN/Et_2O 1:3 (0.17 M, 1.25 mL, 0.21 mmol) was added dropwise to the mixture. The mixture was stirred at 0 °C for 5 hours, whereafter it was diluted with Et_2O (30 mL). The white precipitate was filtered off and washed with Et_2O (12 mL). The Et_2O phase was washed with a mixture of sat. aq. $Na_2S_2O_3$ (7 mL) and water (10 mL), and then with water (10 mL). The combined aqueous phases were extracted with Et_2O (15 mL) and the combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc/heptane 1:1) gave a mixture of the monoiodide **86** and Ph_3PO as a yellowish-white solid (122 mg). NMR yield of **86**: 36 mg, 32%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.71-7.63 (Ph_3PO), 7.58-7.43 (1H + Ph_3PO), 7.25 (2H, d, *J* 8.7 Hz), 6.98 (1H, d, *J* 16.1 Hz), 6.89 (2H, d, *J* 8.7 Hz), 6.05 (1H, d, *J* 16.1 Hz), 4.47 (2H, s), 4.39 (1H, d, *J* 10.7 Hz), 4.38 (2H, t, *J* 7.1 Hz), 4.33 (1H, d, *J* 10.7 Hz), 4.19 (2H, t, *J* 6.3 Hz), 3.81 (3H, s), 3.58 (2H, dd, *J* 6.7 Hz, 1.9 Hz), 2.07-1.97 (2H, m), 1.76-1.67 (2H, m), 1.66 (3H, s); HRMS (ESI) *m/z* calcd. for $C_{21}H_{28}IN_3O_5$ $[M+H]^+$ 530.1146, found 530.1112.

Representative procedure for the preparation of diiodides 87 and 88

(+/-)-(*E*)-(1-(4-Iodobutyl)-1*H*-1,2,3-triazol-4-yl)methyl 5-iodo-2-(4-methoxybenzyloxy)-2-methylpent-3-enoate 87

Ph_3P (66 mg, 0.25 mmol) and imidazole (19 mg, 0.27 mmol) were added

to a stirred solvent mixture of anhydrous CH_3CN/Et_2O 1:2 (6.0 mL). The mixture was cooled to 0 °C, and I_2 (64 mg, 0.25 mmol) was added in one portion. After stirring for 35 minutes at 0 °C, a solution of the diol **55** in anhydrous CH_3CN/Et_2O 1:3 (0.12 M, 0.8 mL, 0.097 mmol) was added dropwise to the mixture. The mixture was stirred at 0 °C for $2\frac{1}{2}$ hours, and then it was diluted with Et_2O (15 mL). The white precipitate was filtered off and washed with Et_2O (6 mL). The Et_2O phase was washed with a mixture of sat. aq. $Na_2S_2O_3$ (4 mL) and water (5 mL), and then with water (5 mL). The combined aqueous phases were extracted with Et_2O (8 mL) and the combined organic phases were washed with brine (5 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc/heptane 1:1) gave the diiodide **87** (27 mg, 43%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (1H, s), 7.28 (2H, d, *J* 8.4 Hz), 6.86 (2H, d, *J* 8.4 Hz), 6.09 (1H, dt, *J* 15.7 Hz, 7.9 Hz), 5.92 (1H, d, *J* 15.7 Hz), 5.33 (2H, s), 4.39-4.35 (4H, m), 3.87 (2H, d, *J* 7.9 Hz), 3.80 (3H, s), 3.17 (2H, t, *J* 6.8 Hz), 2.03 (2H, tt, *J* 7.6 Hz, 7.6 Hz), 1.85-1.76 (2H, m), 1.56 (3H, s).

(+/-)-(*E*)-4-(4-(Iodomethyl)-1*H*-1,2,3-triazol-1-yl)butyl 5-iodo-2-(4-methoxybenzyloxy)-2-methylpent-3-enoate 88

Yellow oil, 77% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (1H, s), 7.30 (2H, d, *J* 8.7 Hz), 6.87 (2H, d, *J* 8.7 Hz), 6.11 (1H, dt, *J* 15.5 Hz, 7.9 Hz), 5.92 (1H, d, *J* 15.5 Hz), 4.44 (2H, s), 4.41 (2H, d, *J* 3.0 Hz), 4.34 (2H, t, *J* 7.1 Hz), 4.20 (2H, t, *J* 6.2 Hz), 3.89 (2H, dd, *J* 7.9 Hz, 0.7 Hz), 3.80 (3H, s), 2.03-1.93 (2H, m), 1.75-1.65 (2H, m), 1.57 (3H, s).

Part II

Toward Materials from Silver(I) Acetylides

Chapter 5

Toward a spacer for carbon nanotube separation utilizing silver(I) acetylide chemistry

5.1 Carbon nanotubes - nanoscale electrical conductivity to be exploited

Carbon nanotubes (CNTs) exist as single walled and multi walled types of which the former is the most interesting for device construction due to its well-defined structural and electrical conductivity properties.

5.1.1 Single walled carbon nanotubes

The growth of single walled carbon nanotubes (SWNTs) was first reported by two independent groups, Iijima and Ichihashi[85] and Bethune *et al.*,[86] in 1993. This discovery has had great impact on the scientific community[87] and much progress has been achieved in the investigations of SWNTs since then.

CNTs are microtubules of graphitic carbon.[88] The walls have different chiralities, defined by the angle between the orientation of the hexagonal lattice and the axis of the CNT. For SWNTs, the extreme cases are the metallic[89] and semiconducting[90] forms shown in Figure 5.1. The electrical properties of SWNTs with a given diameter and chirality can be readily predicted.[91,92]

Despite the promising properties of SWNTs, their use in electronic devices has been limited due to the fact that they have strong interactions between them, leading to either aggregation[85,93] or flocculation[94] in all solvents, thus rendering the development of the ordered arrays necessary for

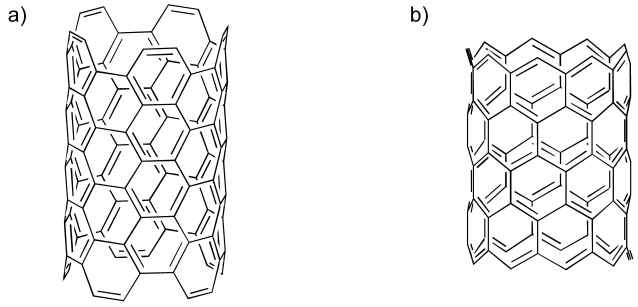


Figure 5.1: The metallic (a) and semiconducting (b) forms of SWNTs.

device construction difficult.

5.1.2 Techniques for SWNT separation

Several methods have been attempted to overcome the problem of aggregation and flocculation of SWNTs. In order to solubulize SWNTs in various solvents, covalent functionalization has been explored, both as open-end[95] and sidewall[96] modifications. However, the introduction of defects by changing the linked carbon atoms from the sp^2 to the sp^3 hybridized form may alter the electrical properties of the SWNTs.[97,98]

The use of supramolecular interactions between π-stacking and/or amphiphilic molecules and SWNTs is an attractive approach for functionalization without introducing defects. Ideally, these molecules will be able to aid in the assembling of ordered networks of SWNTs whereafter they may be readily removed.

Polymer wraps

Various polymers have been employed for non-covalent functionalization. For instance, wrapping of the substituted poly(metaphenylenevinylene) **1** (Figure 5.2) around SWNTs was reported by Stoddart and Heath.[99] The polymer was claimed to have very little consequence on the electrical properties of the SWNTs.[99]

Surfactant molecules have been widely utilized for obtaining stable suspensions of SWNTs in aqueous solutions. Recently, Dai and co-workers reported the application of new poly(ethylene glycol) (PEG) branched surfactant polymers, e.g. **2** (Figure 5.2), for functionalization of SWNTs.[100] The polymer-wrapped SWNTs showed excellent stability in aqueous solutions as well as in serum. Moreover, they exhibited long blood circulation and are

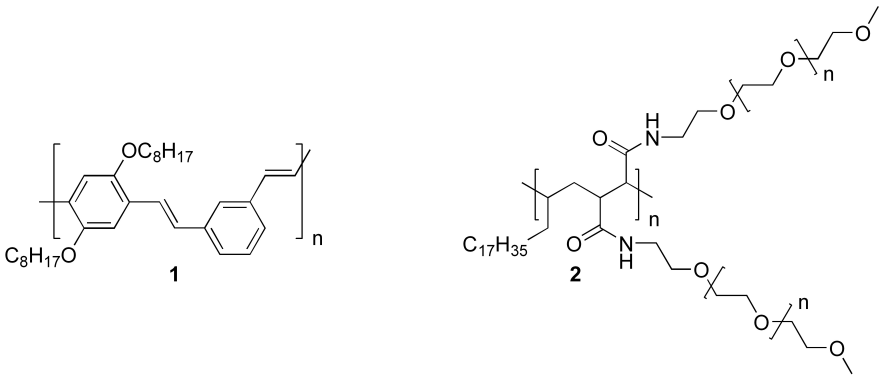


Figure 5.2: The conjugated polymer **1** and the PEG branced polymer **2**.

thus promising materials for in vivo applications.[100]

Polyaromatic modifiers

Many polyaromatic small molecules have also been used as SWNT surface modifiers. In particular, pyrene is often used, since it has been found to interact strongly with the sidewalls of SWNTs.[101] Dai and co-workers employed the succinimidyl ester derivative of 1-pyrenebutanoic acid **3** (Figure 5.3a) to append proteins to SWNTs (Figure 5.3b).[101]

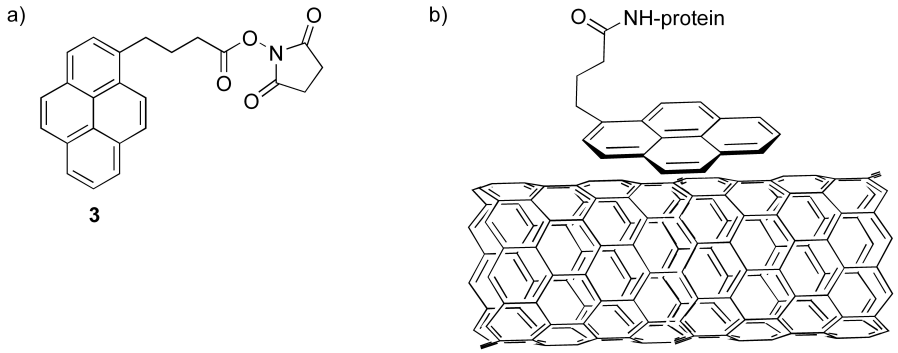


Figure 5.3: The functionalized pyrene **3** (a) and a schematic illustration of the system with the appended protein (b).

Despite the fact that bent aromatic molecules provide optimized surface contact to the cylindrical SWNTs as compared to planar molecules, they have been less utilized. However, the use of bent molecules as surface modifiers of SWNTs has been reported by a few groups.[102, 103, 104, 105] Recently, the group of Han used a triptycene moiety which is linked through two di(ethylene

glycol) spacers to two adamantane units (**4**, Figure 5.4).[102] Prior to addition of the SWNTs, the adamantane units were complexed to cyclodextrines to achieve dissolution of the resulting complex in aqueous solvent.[102]

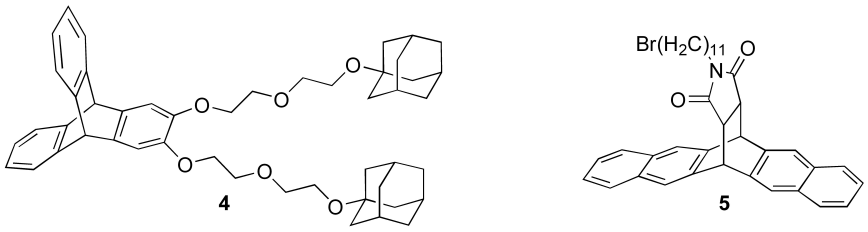


Figure 5.4: The triptycene surface modifier **4** and the pentacene-based molecular tweezer **5**.

Tromp and co-workers reported a pentacene-based molecular tweezer **5** (Figure 5.4), which, apart from circumventing the solubility problems, is diameter-selective against SWNTs with diameters smaller than ≈1.3 nm.[103]

5.2 The concept

Inspired by the previous investigations on aromatic SWNT surface modifiers, a molecular spacer consisting of two modifiers connected through a linker (see Figure 5.5) is proposed. The aim is to be able to space SWNTs apart on a surface such that the electrical conductivity properties of the modified surface might be readily controlled.

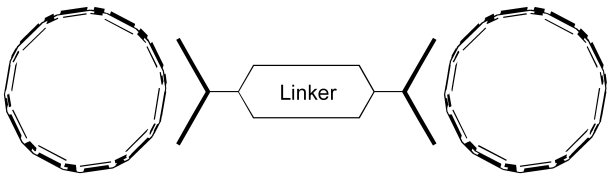


Figure 5.5: Schematic topview of the molecular spacer separating two nanotubes.

5.2.1 Design of a molecular spacer

The design of the proposed molecular spacer **6** is shown in Figure 5.6. Triptycene is chosen as the SWNT surface-binding molecule, because it is bent and has the appropriate size for binding to the SWNTs and still being susceptible to removal after the SWNTs are connected to a surface. The chosen

linkers comprise adamantane and acetylene units, as these units form a rigid system that can hold the two triptycenes at defined positions in space, along with being electrical insulators. Moreover, the adamantane units are functionalized with PEG units to alter the solubility properties of the spacer molecule. By using two linkers, the relative geometry of the triptycenes is under control. However, a molecule with only one linker, in which freedom of rotation around the adamantyl-acetylene bond would be allowed, might be more readily accessible as will be described below.

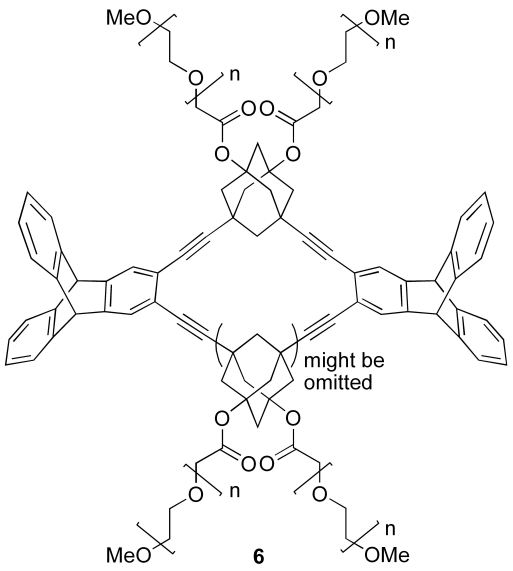


Figure 5.6: The proposed molecular spacer **6**.

5.2.2 Synthesis outline

An outline of the proposed synthesis of the molecular spacer is shown in Figure 5.7. The key step is a coupling between the disilver(I) acetylide **8** (which is formed from the known diethynyl triptycene **7**[106]) and the previously described difluoro diiodoadamantane **9**[107,108] to obtain **10**. For this purpose, the silver(I) acetylide chemistry developed by the group of Williams[109,110] (see section below) will be applied. Subsequently, PEG units may be introduced by substitution of the fluorines with bromines followed by reaction with the appropriate silver carboxylate[111] giving the functionalized spacer **6**.

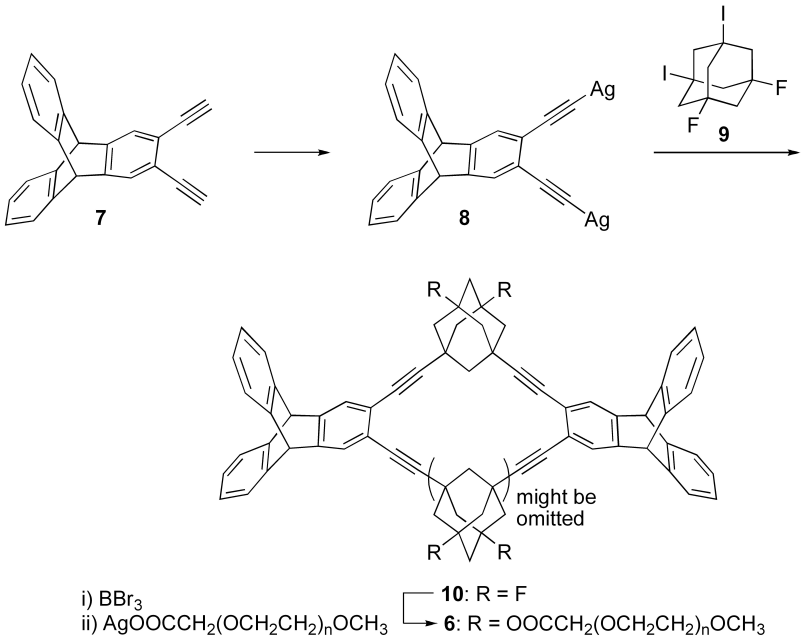


Figure 5.7: Outline of the proposed synthesis of molecular spacer **6**.

5.2.3 Alkynylation of adamantyl iodide by use of silver(I) acetylides

The coupling between **8** and **9** relies on a recently developed method for alkynylation at the bridgehead of bicyclic cages.[109,110] This involves the reaction between a silver(I) acetylide (e.g. the phenylacetylide **11**, Figure 5.8) and an iodinated bicyclic cage (e.g. 1-iodoadamantane **12**) under reflux in *N*-methylmorpholine (NMM), affording an alkynylated product (e.g. **13**).[109,110]

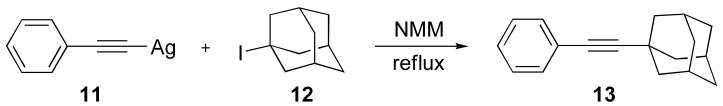


Figure 5.8: The reaction between silver(I) acetylide **11** and 1-iodoadamantane **12**, affording the alkynylated product **13**.

Surprisingly, however, the reaction of the disilver(I) acetylide **14**[112] with **12** only leads to the monoalkynylated product **15** as seen in Figure 5.9. A deargentation process, giving the monosilver(I) acetylide **16** (Figure 5.10) is thought to take place before the alkynylation.[109] In that case, since the disilver(I) acetylide **8** is also an arylacetylide, there is a likelihood that it too

will undergo a deargentation process before the alkynylation, thus yielding a spacer with only one linker.

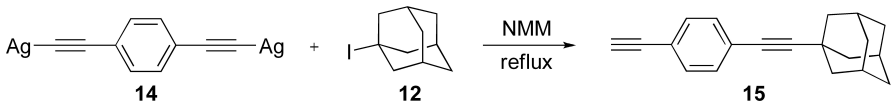


Figure 5.9: The reaction between disilver(I) acetylide **14** and 1-iodoadamantane **12**, affording the monoalkynylated product **15**.

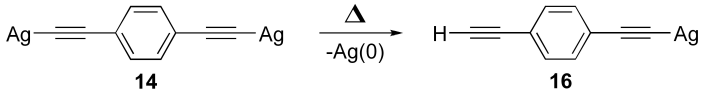


Figure 5.10: Deargentation process yielding the monosilver(I) acetylide **16**.

5.3 Results and discussion

The syntheses of the adamantane and triptycene units are described below, followed by silver(I) acetylide formation and a subsequent coupling reaction.

5.3.1 Synthesis of the adamantane unit

1,3,5,7-tetrabromoadamantane **17**[113] was formed in an acceptable yield by reacting 1-bromoadamantane with bromine and aluminum chloride according to a literature procedure (however not starting from adamantane).[114]

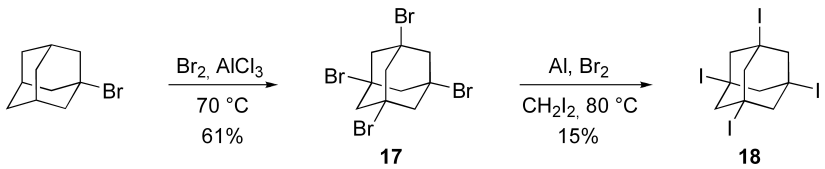


Figure 5.11: Synthesis of 1,3,5,7-tetraiodoadamantane **18** in two steps from 1-bromoadamantane.

Halogen exchange of **17** to obtain 1,3,5,7-tetraiodoadamantane **18**[115] was performed by heating of **17** with aluminum and bromine in a diiodomethane solution as described earlier.[115] However, the reaction did not proceed as

smoothly as previously described, mainly due to purification problems concerning removal of aluminum salts. When using 1.7 equivalents of aluminum foil, the reaction did not go to completion; accordingly, fragments of 1-bromo-3,5,7-triiodoadamantane and 1,3-dibromo-5,7-diiodoadamantane were identified by GCMS analysis of the crude mixture. Subjection of the crude mixture to the reported conditions[115] gave the pure product, albeit in a modest yield of 15%. Attempts at using longer reaction times did not improve the yield, and an attempt at using additional equivalents of aluminum and bromine led to full conversion but a lower isolated yield due to increased purification problems.

It was then attempted to obtain 1,3-difluoro-5,7-diiodoadamantane **9**[108] (Figure 5.12) by exchanging two of the iodines of **18** with fluorines as previously reported.[107] However, reaction of **18** with mercuric fluoride in refluxing chloroform for 3 days did not give **9**[108] as the only product. ^{19}F NMR* and GCMS† analyses indicated that a mixture of fluorinated products was obtained, including 1,3,5-trifluoro-7-iodoadamantane **19** and 1,3,5,7-tetrafluoroadamantane **20** and other fluorine containing compounds. As the reaction was found to be uncontrollable and the obtained mixture was inseparable by flash column chromatography, the fluorination was attempted by alternative reaction conditions.

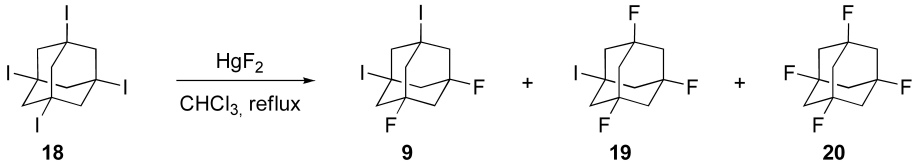


Figure 5.12: Attempt at the synthesis of 1,3-difluoro-5,7-diiodoadamantane **9** with HgF_2.

A literature method for converting bridgehead bromoadamantanes into the corresponding fluoroadamantanes by reaction with silver(I) fluoride in refluxing cyclohexane[117] was attempted. However, treatment of **18** using these conditions (Figure 5.13) gave only little conversion, resulting in a mixture of **18** and fluorinated compounds. ^{1}H NMR and ^{19}F NMR analyses revealed the mixture to consist of mainly starting material **18** and some 1-fluoro-

*The signals in ^{19}F NMR were analyzed according to literature values for 1-fluoroadamantane (–129.02 to –129.07 (m)[116]), 1,3-difluoroadamantane (–134.51 (s)[116]), 1,3,5-trifluoroadamantane (–141.43 (s)[116]), and 1,3,5,7-tetrafluoroadamantane **20** (–150.87 (s)[116]). ^{19}F NMR values for fluoro-iodoadamantanes **21**, **9**, and **19** have not been reported previously.

†Fragments of 1,3-difluoro-5,7-diiodoadamantane and 1,3,5-trifluoro-7-iodoadamantane were found in GCMS.

3,5,7-triiodoadamantane **21**. Only traces of the desired product **9** along with traces of some other fluorine containing compounds were indicated by ^{19}F NMR.

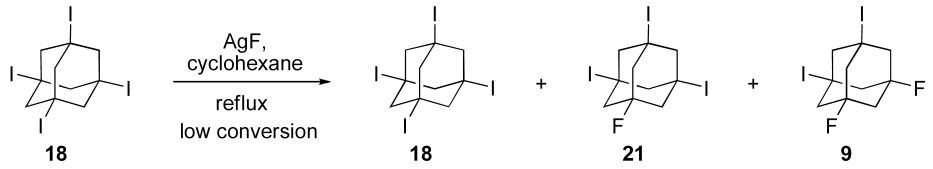


Figure 5.13: Attempt at the synthesis of 1,3-difluoro-5,7-diiodoadamantane **9** with AgF.

5.3.2 Synthesis of the triptycene unit

2,3-Dibromotriptycene **22**[118] (Figure 5.14) was obtained according to a literature procedure;[119] that is by slow addition of *n*-BuLi to a dilute solution of 1,2,4,5-tetrabromobenzene and anthracene, resulting in a Diels-Alder reaction[120] between the thus formed 4,5-dibromobenzyne and anthracene.

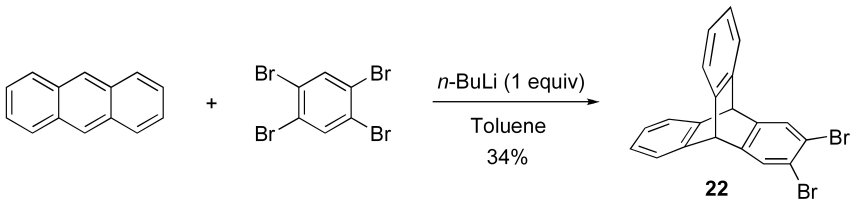


Figure 5.14: Synthesis of 2,3-dibromotriptycene **22** from anthracene and 1,2,4,5-tetrabromobenzene.

Sonogashira coupling[121] of **22** with trimethylsilylacetylene gave the disilylated 2,3-diethynyltriptycene **23**[106] (Figure 5.15). Optimization of the reported reaction conditions (18 hours of reflux[106]) led to full conversion by reaction of **22** for 3 hours under microwave heating; however 20 mol% of the palladium catalyst was needed (as compared to 2 mol%[106]). Subsequent desilylation with TBAF gave 2,3-diethynyltriptycene **7** (Figure 5.16) in a good yield.

5.3.3 Silver(I) acetylide chemistry

Pale and co-workers have demonstrated that 1-hexyne can be transformed into the silver(I) acetylide **24** (Figure 5.17) by reaction with silver triflate

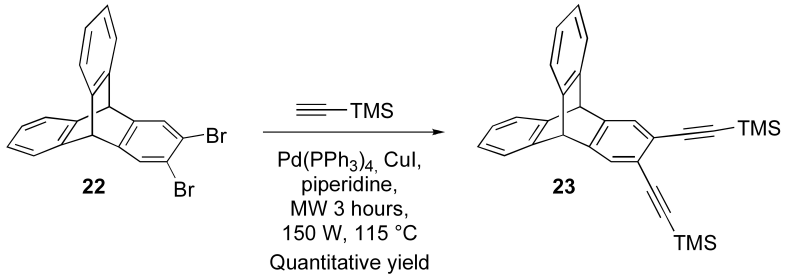


Figure 5.15: Sonogashira coupling between **22** and trimethylsilylacetylene yielding **23**.

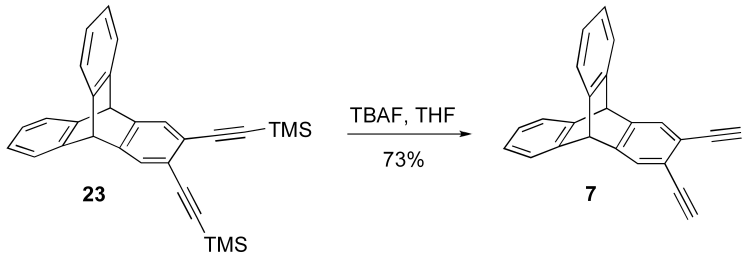


Figure 5.16: Desilylation of **23** furnishing **7**.

and base in various solvents.[122] Mechanistic studies utilizing ^{1}H, ^{13}C, and ^{109}Ag NMR led to the identification of a π-alkyne-silver complex intermediate, which is rapidly deprotonated upon addition of diisopropylethylamine (DIPEA).[122]

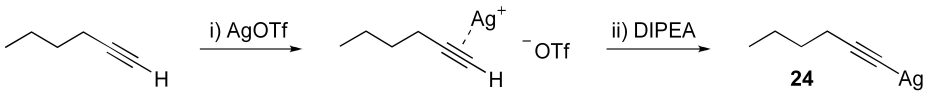


Figure 5.17: Silver(I) acetylide synthesis through the formation of a π-alkyne-silver complex.

Ideally, going toward the spacer **6** with two linkers, the disilver(I) acetylide **8** would be synthesized under the above conditions. However, reaction of **7** with silver triflate (Figure 5.18) in chloroform proceeded with full conversion to the monosilver(I) acetylide **25**. Surprisingly, base addition was not necessary to promote deprotonation. An attempt to use the reverse order of addition of the reagents was not successful (brown precipitate).

The product, which is insoluble in usual NMR solvents, was verified by HRMS, which also confirmed that **25** is the only product rather than a mixture of mono and disilver(I) acetylides. This is probably due to **25** precipi-

tating upon formation, thus preventing further reaction with silver triflate.

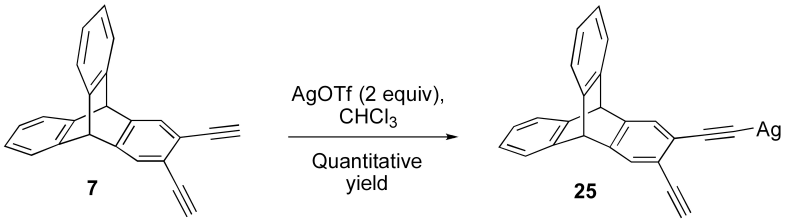


Figure 5.18: Formation of silver(I) acetylide **25** from **7**.

More recently, the formation of silver(I) acetylides from trimethylsilyl acetylenes by use of silver nitrate or triflate in protic solvents has also been reported by Pale and co-workers.[123] Mechanistic studies suggested the reaction to likewise proceed through formation of a π-alkyne-silver complex (Figure 5.19).[124]

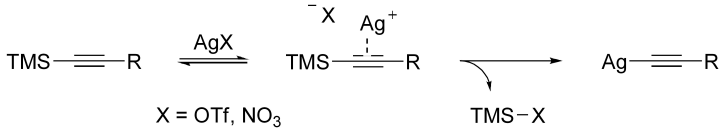


Figure 5.19: Silver(I) acetylide synthesis from trimethylsilyl acetylene through the formation of a π-alkyne-silver complex.

The disilylated compound **23** was subjected to the above reaction conditions (Figure 5.20). Interestingly, this also resulted in high-yielding formation of the monosilver(I) acetylide **25**. Hence, silver(I) acetylide formation takes place at one of the acetylenes whereas the other is deprotected. The silylated compound **26** (Figure 5.21) is thus not formed. Since precipitation usually occurs upon silver(I) acetylide formation, it is surprising that this deprotection has taken place. Accordingly, there is only little precipitation when the reaction is performed with only one equivalent of silver triflate, giving 20% of **25**, and confirming that the deprotection has to be done in connection with the silver(I) acetylide formation. With the two acetylenes of **23** being in proximity, it is likely that the mechanism goes through an intermediate **27** (Figure 5.21) with a silver ion complexed to both acetylenes simultaneously.

The silver(I) acetylide **25** was coupled with 1-iodoadamantane **12** under the previously described conditions[109,110] (Figure 5.22). The reaction went in a modest NMR yield of 21% of the product **28**, despite the use of excess of **12**, giving 2,3-diethynyltriptycene **7** as a byproduct formed through deargentation. Due to the R_f values of the triptycene derivatives **7** and **28** being

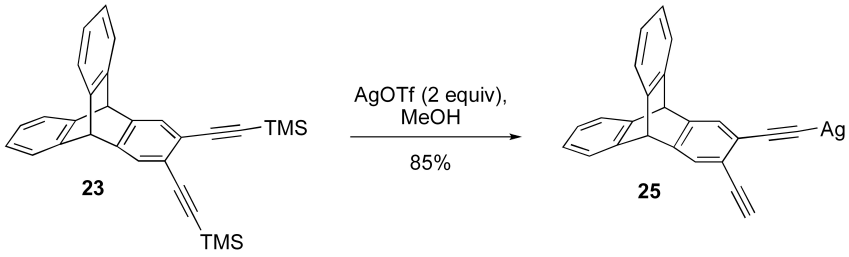


Figure 5.20: Direct formation of silver(I) acetylide **25** from **23**.

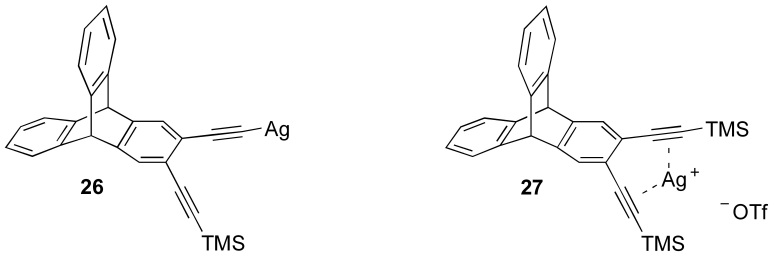


Figure 5.21: Compound **26** which is not formed and a likely intermediate **27**.

close, their separation was difficult. Attempts at separation by flash column chromatography were not successful, but purification by chromatotron led to 11% of isolated product **28**.

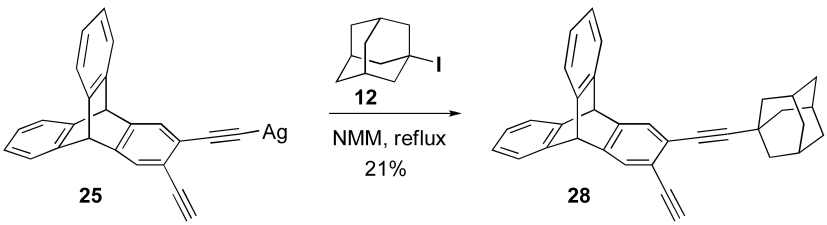


Figure 5.22: Coupling of silver(I) acetylide **25** with iodoadamantane **12** giving product **28**.

5.4 Summary and outlook

Up until this point, a product **28** (Figure 5.23a) which is interesting for investigation of its interaction with SWNTs on a surface has been synthesized by use of silver(I) acetylide chemistry. An appropriate linker can be readily attached to the terminal alkyne of **28**, e.g. by a Sonogashira coupling,

whereafter the compound can be attached along with SWNTs to a surface as illustrated in Figure 5.23b.

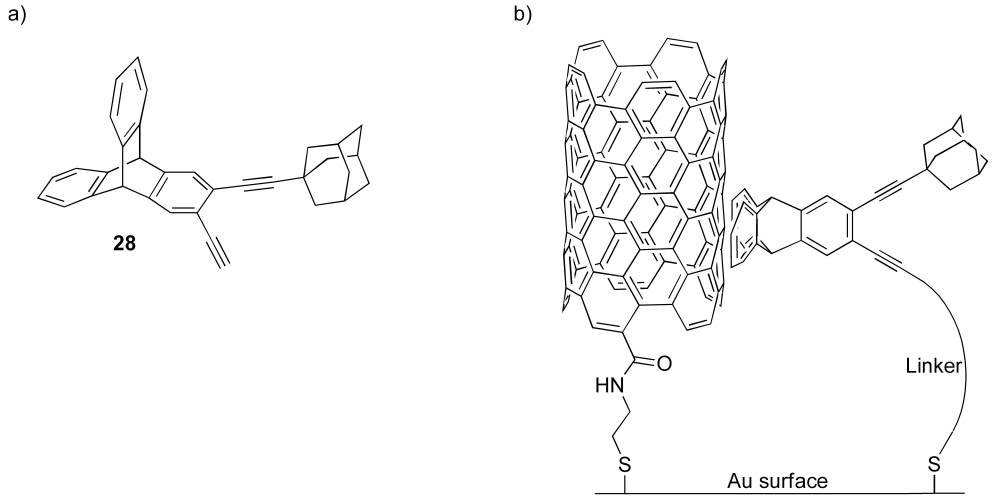


Figure 5.23: The obtained product **28** (a) and a possible application (b).

However, the route to the initially proposed spacer for SWNT separation still needs development. To sum up the results of the project (see Figure 5.24):

• The synthesis of the difluoro-diiodoadamantane unit **9** from 1,3,5,7-tetraiodoadamantane **18** failed by use of two different reagents, mercuric fluoride and silver(I) fluoride, due to an uncontrollable fluorine-iodine exchange leading to a mixture of fluorinated adamantanes.

• It was shown that the silver(I) acetylide **25** could be obtained in high yield from two different precursors **7** and **23**, one bearing terminal alkynes and one bearing terminal trimethylsilylacetylenes. Thus, in the latter case a double-deprotection was found to be necessary in connection with the silver(I) acetylide formation. Not surprisingly, with previous results in mind, the triptycene unit **8** was not formed.

• Coupling of silver(I) acetylide **25** and 1-iodoadamantane was possible, yielding **28**, albeit in a modest yield and with semi-isolation due to close separation between **28** and the byproduct **7**.

There is another route by which the synthesis of the adamantane unit **9** can be envisioned (see Figure 5.25). Starting from the commercially available 1,3-dibromoadamantane, difluoroadamantane **29** can be synthesized as previously described,[117] followed by diiodination by a radical iodination reaction under phase-transfer conditions[125] which has been reported to be applicable to 1-bromo-3-chloro-5-fluoroadamantane.[126]

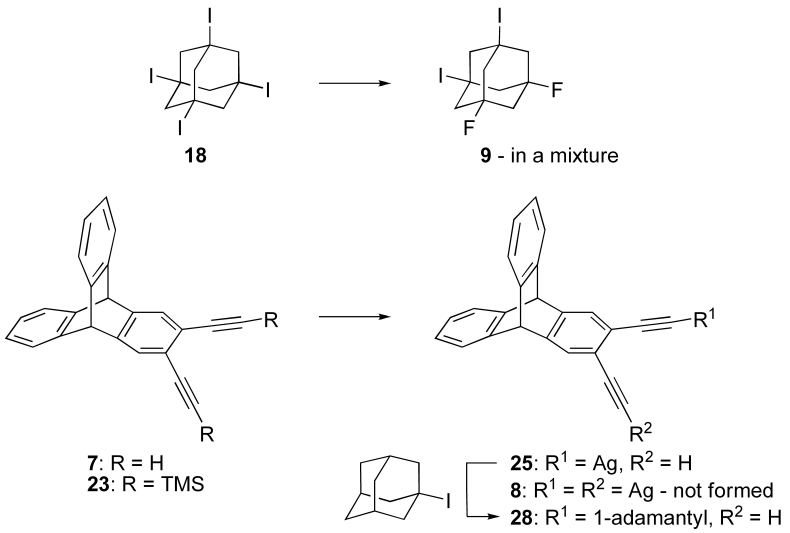


Figure 5.24: An overview of the results of the project.

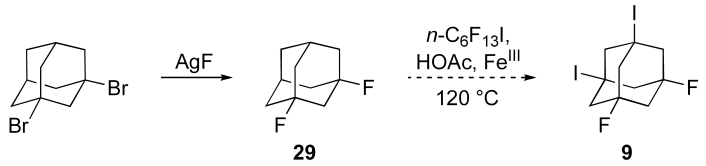


Figure 5.25: Proposed route for the synthesis of the adamantane unit **9**.

With compounds **25** and **9** in hand, it will most likely be possible to synthesize the functionalized molecular spacer **6** (Figure 5.26) with one linker, which will be a good starting point for investigating spacer interaction with SWNTs. From compound **10** with one linker, two successive sequences of silver(I) acetylide formation and coupling will probably be needed for the introduction of another linker, followed by functionalization furnishing **6**. The yields of the couplings will probably be low as was the case for the synthesis of **28**.

An alternative approach is to build the spacer by a reverse sequence, thus starting with the construction of the diethynyladamantane **30** from **9** through reaction with silver(I) triisopropylsilylacetylide followed by deprotection. A subsequent Sonogashira coupling with 2,3-dibromotriptycene is then proposed to yield compound **10**, which might then be functionalized to yield the spacer **6** with two linkers. Coupling of 1-iodoadamantane with silver(I) triisopropylsilylacetylide has been reported previously, albeit in a low yield.[110]

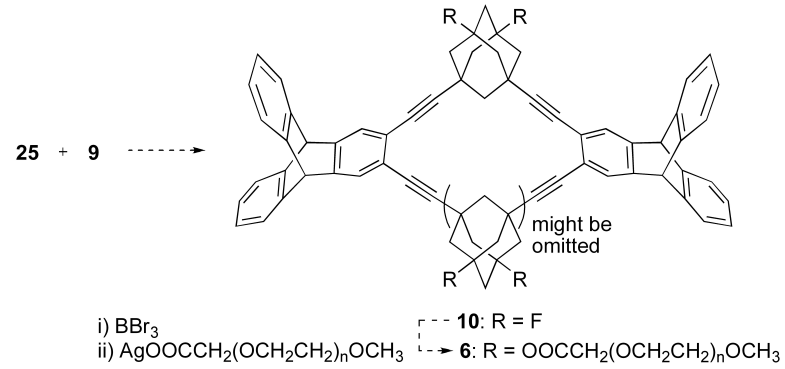


Figure 5.26: Synthesis of **6** from **25** and **9**.

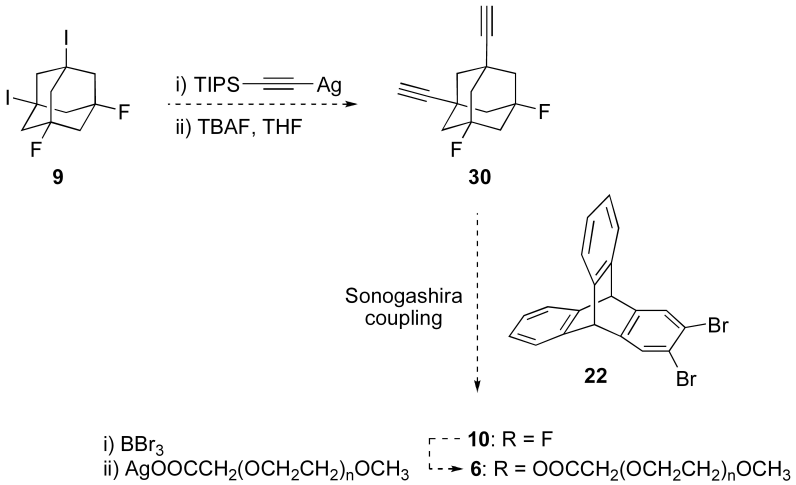


Figure 5.27: Synthesis of **6** by a reverse sequence.

5.5 Concluding remarks

It is demonstrated that a monosilver(I) acetylide of 2,3-diethynyltriptycene can be formed from both 2,3-diethynyltriptycene and 2,3-di(trimethylsilylethynyl)triptycene by use of the same reagent. The silver(I) acetylide is further coupled with 1-iodoadamantane. These results open up opportunity for constructing new molecules that can interact with SWNTs, potentially leading to the alignment needed for SWNT-based device construction.

5.6 Experimental section

Starting materials and reagents were purchased from Sigma-Aldrich Chemical Co. and used without further purification. Reactions involving air or moisture sensitive reagents were carried out under Ar. Chloroform was washed with water, dried over Na_2SO_4 and distilled from P_2O_5. Cyclohexane was distilled and stored over 4 Å molecular sieves. Toluene and pentane were dried over 4 Å molecular sieves. THF was predistilled from CaH_2 and distilled from Na under Ar. Piperidine and *N*-methylmorpholine were distilled from CaH_2 under Ar. Flash column chromatography was undertaken on silica gel (Flash Silica gel 230–400 mesh), with distilled solvents. NMR spectra were recorded using a Bruker AV300 MHz spectrometer or a Bruker AV400 MHz spectrometer. Chemical shifts were measured in ppm and coupling constants in Hz, and the field is indicated in each case. The solvent peaks from $CDCl_3$ (7.24 ppm in ^{1}H NMR and 77.16 ppm in ^{13}C NMR) and TFA (external reference, ^{19}F NMR) were used as standards. IR analysis was carried out on a Perkin-Elmer (Spectrum 2000) FTIR spectrometer. Melting points were determined with a Stuart SMP11 Melting Point apparatus and are uncorrected. High- and low-resolution ESI mass spectroscopic data for the silver(I) acetylide were recorded on a Thermo Scientific (model LTQ FT) FTICR mass spectrometer at The University of Melbourne. High- and low-resolution EI mass spectroscopic data were obtained with a KRATOS MS 25 RFA.

1,3,5,7-Tetrabromoadamantane 17
1-Bromoadamantane (1.048 g, 4.87 mmol) was added portionwise over 30 minutes to a stirred mixture of bromine (8.17 g, 51.13 mmol) and aluminum chloride (620 mg, 4.65 mmol) at 5-10 °C. The mixture was heated to 70 °C over 1 hour. After stirring at that temperature for 24 hours, the mixture was triturated with sat. aq. sodium sulfite (to remove excess bromine) with hydrochloric acid added (to dissolve aluminum salts). After cooling on an ice bath, the red-yellow solids were removed by filtration, washed with water and air dried. Recrystallization from glacial acetic acid (30 mL) gave the product **17** (1.34 g, 61%) as a tan powder; m.p. 241-242 °C (lit.[114] 245-247 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.68 (s, 12H).

1,3,5,7-Tetraiodoadamantane 18
Bromine (98 mg, 0.61 mmol) was added to small pieces of aluminum foil (49 mg, 1.82 mmol) in CH_2I_2 (5.85 mL). The mixture was heated to 80 °C and stirred at that temperature for 35 minutes. Then 1,3,5,7-tetrabromoadaman-

tane **17** (488 mg, 1.08 mmol) was added in one portion. The mixture was stirred for 15 minutes at 80 °C whereafter it was poured into cold water (10 mL) with stirring. Sodium sulfite was added (to remove excess bromine). 6M HCl (4 mL) was added, and the mixture was stirred for 1 hour (to dissolve aluminum salts). The diiodomethane phase was isolated and washed with water (10 mL). Diiodomethane was removed by distillation *in vacuo*, and the residue was washed with chloroform and then acetone. This gave an off-white product containing some 1-bromo-3,5,7-triiodoadamantane and 1,3-dibromo-5,7-diiodoadamantane. Treatment of the crude material using the above reaction conditions gave the product **18** (105 mg, 15%) as a tan powder; m.p. dec (lit.[115] 370 °C dec) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.18 (s, 12H).

Attempt at the synthesis of 1,3-difluoro-5,7-diiodoadamantane 9 with HgF_2

A solution of 1,3,5,7-tetraiodoadamantane **18** (31 mg, 0.05 mmol) in anhydrous chloroform (3.5 mL) was added to mercuric fluoride (32 mg, 0.13 mmol), and the mixture was heated to reflux under Ar. The mixture was stirred for 3 days at reflux. In this period, sonication was carried out for 1 out of every 12 hours. The reaction mixture was filtered through Celite and the solvent was removed *in vacuo*. The residue was redissolved in CH_2Cl_2 and filtered through a short silica gel column. The filtrate was concentrated *in vacuo* giving a mixture of fluorinated compounds. ^{19}F NMR ($CDCl_3$, 376 MHz) δ -138.11 (s), -139.52 (s), -145.88 (s), -147.14 (s), -150.49 (s).

Attempt at the synthesis of 1,3-difluoro-5,7-diiodoadamantane 9 with AgF

1,3,5,7-Tetraiodoadamantane **18** (24 mg, 0.04 mmol) was suspended in anhydrous cyclohexane (1 mL). Silver fluoride (10 mg, 0.08 mmol) was added. The suspension was stirred at reflux under Ar for 4 hours. The solvent was removed *in vacuo*. The mixture was redissolved in CH_2Cl_2 and filtered through Celite. The filtrate was concentrated *in vacuo*, giving a mixture of 1,3,5,7-tetraiodoadamantane **18** and fluorinated compounds. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.18 (s, 1,3,5,7-tetraiodoadamantane **18**), 3.03-2.99 (m, CF-CH_2-CI, 1-fluoro-3,5,7-triiodoadamantane **21**), 2.65 (d, J 4.8 Hz, CF-CH_2-CF, 1-fluoro-3,5,7-triiodoadamantane **21**); ^{19}F NMR ($CDCl_3$, 376 MHz) δ -128.51 (m), -136.86 (s), -140.31 (s), -147.49 (s), -151.09 (s).

2,3-Dibromotriptycene 22[119]

1,2,4,5-Tetrabromobenzene (1.005 g, 2.55 mmol) and anthracene (1.005 g, 5.61 mmol) were dissolved in anhydrous toluene (75 mL) and stirred under Ar. A solution of *n*-BuLi in anhydrous hexane (1.15 M, 2.22 mL, 2.55 mmol)

was diluted with anhydrous pentane (47.78 mL). The resulting *n*-BuLi solution (0.05 M, 50 mL, 2.55 mmol) was added over 3 hours at 20 °C. After stirring for 18 hours, the mixture was quenched with water (50 mL) and extracted with Et_2O (2×75 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography [petroleum spirit (40-60 °C)] to give the product **22** (362 mg, 34%) as a yellow solid; m.p. 184-187 °C (lit.[119] 191-192 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60 (s, 2H), 7.37-7.34 (m, 4H), 7.01-6.99 (m, 4H), 5.34 (s, 2H).

2,3-Di(trimethylsilylethynyl)triptycene 23
2,3-Dibromotriptycene **22** (369 mg, 0.89 mmol) was dissolved in anhydrous piperidine (6.44 mL), and trimethylsilylacetylene (1.24 mL, 8.94 mmol) was added. The mixture was deoxygenated by bubbling Ar through a submerged needle for 1 hour. $Pd(PPh_3)_4$ (207 mg, 0.18 mmol) and CuI (34 mg, 0.18 mmol) were added, and the mixture was flushed with Ar. The mixture was heated under microwave conditions (115 °C, 150 W, 250 PSI, 3 hours). The resulting mixture was suspended in EtOAc (35 mL) and washed with aqueous 10% NH_4OH (3×15 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography [2% EtOAc in petroleum spirit (40-60 °C)] of the residue gave the product **23** (399 mg, quantitative yield) as an orange solid; m.p. 118-120 °C; IR (neat) ν 3069(w), 2959(m), 2900(w), 2154(m), 1912(w), 1591(w), 1459(m), 1405(w), 1315(w), 1247(s), 1188(w), 1155(m), 1119(w), 1059(w), 1025(w), 834(s), 757(s), 742(s), 694(s), 654(m), 638(m), 629(m), 616(m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (2H, s), 7.33-7.31 (4H, m), 6.98-6.96 (4H, m), 5.33 (2H, s), 0.20 (18H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.3 (2C), 144.3 (4C), 127.3 (2C), 125.4 (4C), 123.7 (4C), 122.7 (2C), 103.5 (2C), 97.5 (2C), 53.6 (2C), 0.0 (6C).

2,3-Diethynyltriptycene 7
2,3-Di(trimethylsilylethynyl)triptycene **23** (397 mg, 0.89 mmol) was dissolved in anhydrous THF (13.3 mL) and stirred under Ar. TBAF (1 M in THF, 2.67 mL) was added dropwise. After stirring at 20 °C for 2 hours, the reaction mixture was concentrated *in vacuo*, and the crude was combined with EtOAc (30 mL) and sat. aq. NH_4Cl (8 mL). The organic layer was washed with sat. aq. NH_4Cl (2×8 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography [4% EtOAc in petroleum spirit (40-60 °C)] yielding the product **7** (198 mg, 73%) as a light orange solid; m.p. 186-188 °C dec (lit.[106] 188-191 °C); IR (neat) ν 3286(m), 3021(w), 2962(w), 2104(w), 1458(s), 1402(w), 1250(m), 1192(m),

1152(m), 1021(m), 938(w), 897(m), 804(w), 746(s), 627(s), 596(s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50 (s, 2H), 7.38-7.35 (m, 4H), 7.01-6.99 (m, 4H), 5.38 (s, 2H), 3.21 (s, 2H).

2-Ethynyltriptycene-3-silver(I) acetylide 25
Method A: 2,3-diethynyltriptycene **7** (40 mg, 0.13 mmol) was dissolved in anhydrous chloroform (3 mL) and silver triflate (68 mg, 0.26 mmol) was added. A yellow precipitate formed shortly after the addition. After stirring for 10 minutes at 20 °C in the dark, the precipitate was filtered off, washed with cold water and dried, giving the silver(I) acetylide **25** (54 mg, quantitative yield) as a yellow solid. **Method B**: 2,3-di(trimethylsilylethynyl)triptycene **23** (35 mg, 0.08 mmol) was dissolved in MeOH (2 mL) and silver triflate (40 mg, 0.16 mmol) was added. After stirring for 10 minutes at 20 °C in the dark, a yellow precipitate was filtered off, washed with cold MeOH and dried, yielding the product **25** (27 mg, 85%) as a yellow solid; m.p. 182-184 °C dec; IR (neat) ν 3431(m), 3066(m), 2961(m), 2361(m), 1995(m), 1691(m), 1600(m), 1458(s), 1223(s), 1169(s), 1021(s), 940(m), 898(m), 804(m), 758(s), 692(w), 632(s), 606(s), 574(m) cm^{-1}; LRMS (ESI) 450.08 $[(M+H)+CH_3CN]^+$; HRMS (ESI) $[(M+H)+CH_3CN]^+$ $C_{26}H_{17}AgN$ calcd. 450.0406; found 450.0410.

2-(1-Adamantyl)ethynyl-3-ethynyltriptycene 28
2-Ethynyltriptycene-3-silver(I) acetylide **25** (100 mg, 0.25 mmol) was suspended in anhydrous *N*-methylmorpholine (8.5 mL). 1-Iodoadamantane (257 mg, 0.98 mmol) was added, and the suspension was stirred at reflux under Ar in the dark. After 3 days, the solvent was evaporated *in vacuo*. The residue was diluted with CH_2Cl_2 (20 mL) and filtered through Celite. The filtrate was washed with aqueous NaN_3 (0.1 M, 20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was passed through a short silica gel column (EtOAc) and then purified by chromatotron [petroleum spirit (40-60 °C)] giving the product **28** (12 mg, 11%) as a white solid. Another fraction containing a mixture of the product **28** and 2,3-diethynyltriptycene **7** (24 mg) was obtained. Total NMR yield of product: 23 mg, 21%; m.p. 213-216 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.44 (s, 1H), 7.40 (s, 1H), 7.35-7.31 (m, 4H), 6.99-6.96 (m, 4H), 5.34 (s, 1H), 5.33 (s, 1H), 3.13 (s, 1H), 1.95-1.91 (m, 9H), 1.68 (t, *J* 2.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.6, 144.4 (2C), 144.3 (2C), 144.2, 127.2, 126.7, 125.4 (2C), 125.4 (2C), 124.3, 123.7 (2C), 123.7 (2C), 121.3, 102.1, 82.7, 79.5, 78.1, 53.6, 53.5, 42.8 (3C), 36.4 (3C), 30.3, 28.0 (3C); LRMS (EI) 436.6 $[M]^+$; HRMS (EI) $[M]^+$ $C_{34}H_{28}$ calcd. 436.2186; found 436.2195.

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Appendix A

Abbreviations

Ac	Acetyl
Alloc	Allyloxycarbonyl
anal.	Analysis
Arg	Arginine
aq.	Aqueous
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
br	Broad (IR, NMR)
Bu	Butyl
Bz	Benzoyl
18-C-6	18-Crown-6
calcd.	Calculated
CAN	Ceric ammonium nitrate
CNT	Carbon nanotube
4CR	Four-component reaction
d	Doublet (NMR)
DAD	Diode array detector
Dap	2,3-Diaminopropionic acid
dba	Dibenzylideneacetone
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
de	Diastereomeric excess
dec	Decomposition
δ	Chemical shift
DIBAL-H	Diisobutylaluminium hydride
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMB	3,4-dimethoxybenzyl
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide

DNA	Deoxyribonucleic acid
DOS	Diversity-oriented synthesis
dr	Diastereomeric ratio
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
EI	Electron ionization
equiv	Equivalent(s)
ESI	Electrospray ionization
Et	Ethyl
FG	Functional group
Fmoc	9-Fluorenylmethoxycarbonyl
FT	Fourier transform
GC	Gas chromatography
Hol	Homoleucine
HR	High resolution
IBX	2-Iodoxybenzoic acid
ICR	Ion cyclotron resonance
IR	Infrared
J	Coupling constant
L	Ligand
LC	Liquid Chromatography
lit.	Literature
LR	Low resolution
m	Multiplet (NMR); Medium (IR)
M^+	Molecular ion
maj	Major
MCR	Multicomponent reaction
Me	Methyl
MiB	Multiple multicomponent macrocyclization including bifunctional building blocks
min	Minor
MMP	Matrix metalloproteinase
m.p.	Melting point
MS	Mass spectrometry
MW	Microwave
m/z	Mass-to-charge ratio
n	*normal*
NMM	*N*-methylmorpholine
NMR	Nuclear magnetic resonance
Ns	2-Nitrobenzenesulfonyl
Nva	Norvaline

p	*para*
Pbf	2,2,4,6,7-Pentamethyldihydrobenzofuran-5-sulfonyl
PEG	Poly(ethylene glycol)
Ph	Phenyl
PMB	*p*-Methoxybenzyl
PMBTCA	*p*-Methoxybenzyl trichloroacetimidate
PMP	*p*-Methoxyphenyl
PNP	*p*-Nitrophenyl
PNPCC	*p*-Nitrophenyl chlorocarbonate
ppm	parts per million
PPTS	Pyridinium *p*-toluenesulfonate
RCM	Ring-closing metathesis
R_f	Retention value
s	Singlet (NMR); Strong (IR)
SAR	Structure-activity relationship
sat.	Saturated
SWNT	Single walled carbon nanotube
t	Triplet (NMR)
t	*tert*
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TOS	Target-oriented synthesis
TPS	Triphenylsilyl
Ts	*p*-Toluenesulfonyl
Tyr	Tyrosine
ν	Frequency
w	Weak (IR)

Appendix B

Articles

Synthesis of new diverse macrocycles from diol precursors; Charlotte M. Madsen; Martin Hansen; Marie V. Thrane; Mads H. Clausen, *submitted.*

Rapid synthesis of macrocycles from diol precursors; Magnus J. Wingstrand; Charlotte M. Madsen; Mads H. Clausen *Tetrahedron Lett.* **2009**, *50*, 693-695.

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Synthesis of new diverse macrocycles from diol precursors

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ABSTRACT

The formation of a library of diverse macrocycles with different ring sizes from two easily accessible building blocks is presented. Reacting diol precursors with electrophilic reagents lead to 17-membered sulfites and 19-membered malonates in 34-79% yield. Double-reductive amination of dialdehyde analogs of the diol precursors leads to 15-membered amines in yields ranging from 9 to 60%, reflecting large differences in reactivity based on steric environment.

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1. Introduction

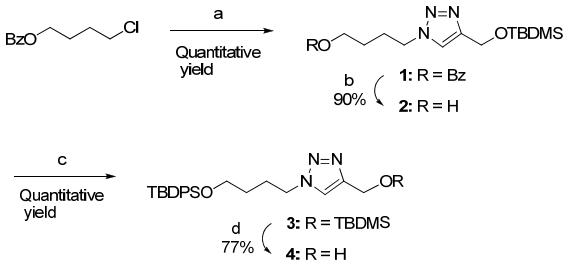
Macrocyclic compounds are attractive targets within drug discovery due to the fact that naturally occurring macrocycles often display diverse and interesting biological activities. This arises from several structural advantages characteristic for this compound class. Macrocycles are conformationally preorganized, enabling them to bind selectively to targets with minimal entropic loss. However, they have a certain flexibility, which, in combination with their functionally independent subregions, enables them to bind non-covalently to each other or to mediate the assembly of other macromolecules by non-covalent interactions. Furthermore, they have the ability of burying away polar functionalities, leading to improved membrane permeability as compared to their linear analogs. Proteolytic and metabolic stability is also improved as a consequence of the reduced accessible conformational space.[1]

The substructures of naturally occurring macrocycles provide valuable inspiration for the design of new synthetic macrocycles, because of the above mentioned biological activity of this compound class. Substructures frequently present in naturally occurring macrocycles are, for example, polyketides, heterocycles, peptide, biphenyl and (bi)aryl ether domains.[2] A drawback of traditional natural product chemistry is the often complex structures and the synthetic effort thus required. Hence, an approach combining natural product drug discovery and combinatorial chemistry has been suggested.[3,4] This strategy, designing synthetic compounds from easily accessible building blocks containing naturally occurring substructural motifs, and hence providing rapid access to synthetic libraries, is providing an increased chance of finding a potent drug. Despite the challenge in forming large ring systems, macrocyclic compounds are interesting targets for this strategy and the generation of libraries of macrocycles has received significant attention recently.[5]

Encouraged by our recently reported method on formation of macrocyclic rings from diol precursors,[6] we were interested in generating a library of diverse macrocycles based on this strategy. According to the above, we aimed at producing macrocycles in a few diversity-generating steps starting from two simple building blocks, one containing a heterocycle (triazole) and one containing a hydroxy alkene (a fragment inspired by polyketides). Four structurally isomeric diol precursors are formed through combinations of the two building blocks by esterifications. These are then cyclized, either in one step by reaction with bis-electrophilic reagents, or in two steps by forming the dialdehyde derivatives and then reacting them with a nucleophilic reagent.

2. Results and discussion

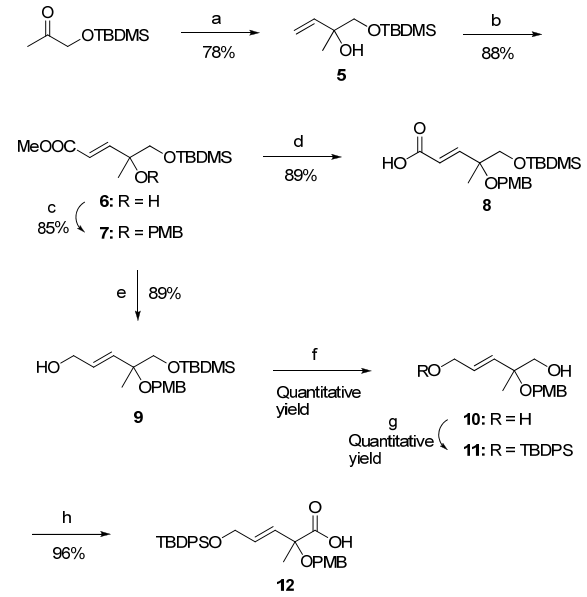
The building blocks for the synthesis of diol precursors were readily obtained in good yields from simple, commercially available starting materials (Scheme 1 and 2). Substitution of 4-chlorobutyl benzoate with sodium azide, followed by a copper (I) catalyzed alkyne-azide cycloaddition reaction[7] of the resulting azide with TBDMS protected propargyl alcohol afforded the protected triazole building block **1** (Scheme 1). Reductive cleavage of the benzoyl group gave one of the desired alcohol derivatives **2** (ready for esterification). The other desired alcohol derivative **4** was obtained by TBDPS protection of **2** and subsequent selective monodeprotection by acidic solvolysis. Preliminary attempts to use a triphenylsilyl (TPS) ether as protection group instead of TBDPS did not give the desired selectivity, as the TPS group was found to be more prone to hydrolysis than the TBDMS group.



Scheme 1. Reagents and conditions: (a) [i] NaN_3, Bu_4NI, DMF, 60 ºC, [ii] *tert*-butyldimethyl(prop-2-ynyloxy)silane, DIPEA, CuI, THF; (b) DIBAL-H, CH_2Cl_2, -78 ºC; (c) TBDPSCl, imidazole, DMF; (d) PPTS, MeOH, 55 ºC.

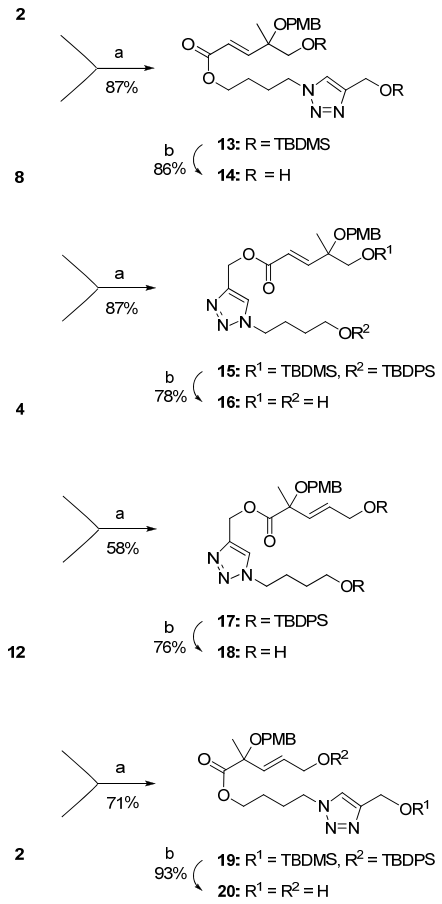
Grignard reaction of TBDMS protected hydroxy acetone with vinyl magnesium chloride followed by a cross-metathesis reaction[8] with methyl acrylate gave the (*E*)-enol building block **6** (Scheme 2). The Hoveyda-Grubbs second generation catalyst[9] was more efficient in this transformation than the Grubbs second generation catalyst.[10] Interestingly, despite the reaction being somewhat slower with 0.5% catalyst loading as compared to 5%, we found the overall conversion to be higher with the lower loading.

PMB protection of **6** with *p*-methoxybenzyl trichloroacetimidate (PMBTCA)[11] under mild conditions[12] gave **7**, which could be hydrolyzed under basic conditions to yield one of the desired carboxylic acid derivatives **8**. The alcohol **9** was obtained from **7** by reductive cleavage of the methyl ester. Deprotection with TBAF went smoothly, giving the diol **10** in an excellent yield. Most satisfyingly, the allylic hydroxy group could be selectively TBDPS protected at -78 ºC in dichloromethane. Swern[13] and sodium chlorite[14] oxidations yielded the other desired carboxylic acid **12**. Preliminary attempts to selectively cleave the TBDMS group from the TPS protected analog of **9** proved unsuccessful for the same reason as specified above for the triazole building block.



Scheme 2. Reagents and conditions: (a) vinyl magnesium chloride, THF, 0 ºC; (b) Hoveyda-Grubbs' 2nd gen. cat., methyl acrylate, CH_2Cl_2, 40 ºC; (c) PMBTCA, $La(OTf)_3$, toluene; (d) LiOH, THF/H_2O 3:1; (e) DIBAL-H, CH_2Cl_2, -78 ºC; (f) TBAF, THF; (g) TBDPSCl, imidazole, CH_2Cl_2, -78 ºC; (h) [i] DMSO, $(COCl)_2$, -78 ºC, Et_3N, [ii] $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, THF.

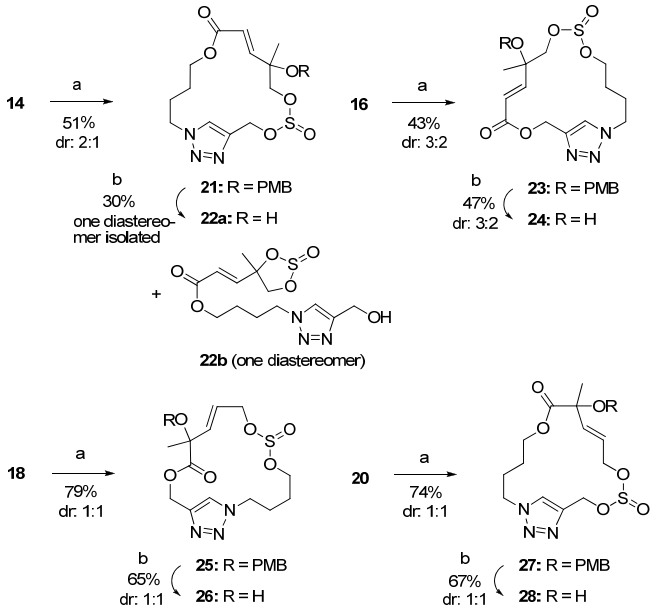
The alcohols **2** and **4** were combined with the carboxylic acids **8** and **12** by carbodiimide promoted esterifications[15] (Scheme 3) yielding the four esters **13**, **15**, **17**, and **19**, which were deprotected smoothly with TBAF to give the desired diol precursors.



Scheme 3. Reagents and conditions: (a) EDC·HCl, DMAP, CH_2Cl_2; (b) TBAF, THF.

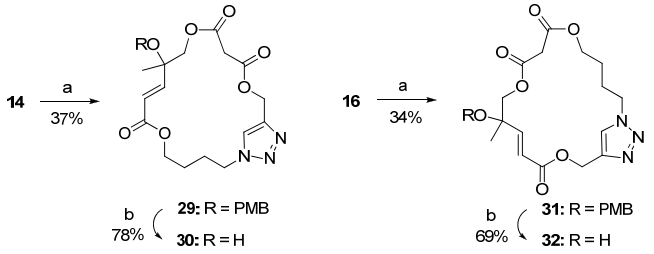
The diols **14**, **16**, **18** and **20** were treated with thionyl chloride, triethylamine and DMAP under our standard conditions[6] to obtain the 17-membered macrocyclic sulfites **21**, **23**, **25** and **27**, respectively (Scheme 4). The sulfites were obtained in yields ranging from 43% to 79% reflecting a difference in the steric environment of the cyclization precursors. This is further emphasized by the fact that the diastereomeric ratio of **21**, formed from the most sterically hindered diol precursor, differs from the diastereomeric ratios of the other sulfites in being 2:1 as compared to 1:1 (or 3:2). Not surprisingly, cyclizations of the two least sterically hindered diol precursors **18** and **20** result in higher yields than cyclizations of the more hindered substrates **14** and **16**.

Subsequent deprotection of the PMB ethers with DDQ to obtain the sulfites **22a**, **24**, **26** and **28** resulted in yields ranging from 30% to 67%. The low yield for the deprotection of **21** is caused by lability of the product to column chromatography. This was proven by the isolation of a 5-membered cyclic sulfite by-product **22b** formed upon nucleophilic attack by the tertiary hydroxy group on the macrocyclic sulfite. The identification of the product **22a** and the by-product **22b** as single diastereomers confirms that only one of the diastereomers of the deprotected sulfite is susceptible to the intramolecular transesterification of the sulfite.



Scheme 4. Reagents and conditions: (a) $SOCl_2$, Et_3N, DMAP, CH_2Cl_2; (b) DDQ, CH_2Cl_2/H_2O 18:1.

Next, we were interested in extending the above cyclization method to the formation of malonates. Diol precursors **14** and **16** were treated with malonyl chloride under the above conditions, giving the 19-membered malonates **29** and **31** (Scheme 5) in 37 and 34% yield, respectively. Thus, the yields for formation of malonates are slightly lower than for the formation of sulfites, possibly related to the difference in ring sizes formed and/or the relative reactivity of the reagents.

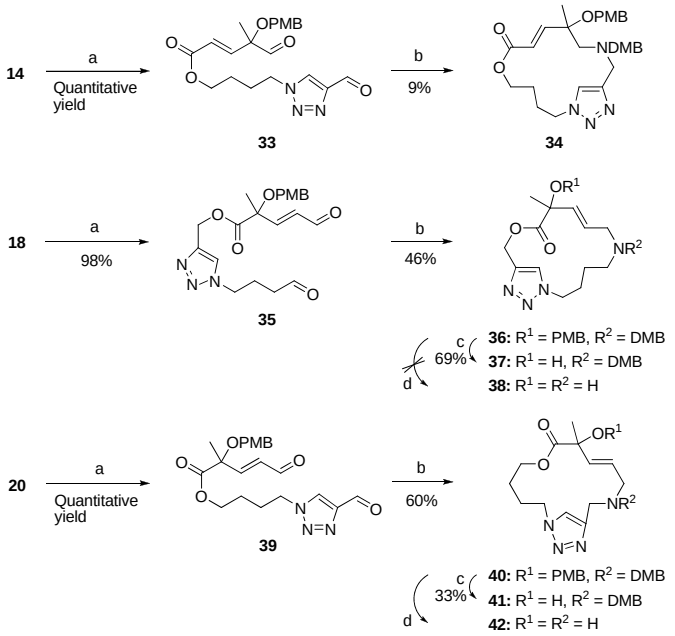


Scheme 5. Reagents and conditions: (a) malonyl chloride, Et_3N, DMAP, CH_2Cl_2; (b) DDQ, CH_2Cl_2/H_2O 18:1.

The malonates were deprotected analogously to the sulfites, giving **30** and **32**. The products were obtained in higher yields than their sulfite analogs, presumably because the malonates are more stable than the sulfites.

Our next target was the 15-membered macrocyclic amine **34** (Scheme 6). The dialdehyde cyclization precursor **33** was prepared by oxidation of **14** in excellent yield. For this reaction, IBX[16] was found to be superior to the Dess-Martin periodinane[17] as oxidizing agent. Our choice of amine was 3,4-dimethoxybenzylamine ($DMBNH_2$) since it has been reported that removal of the DMB group from a dialkylated amine can be accomplished under mild conditions by the use of DDQ.[18] Unfortunately, double-reductive amination of **33** by use of our previously reported method[6] resulted in only 9% yield of the

product **34**. The reason for this low yield was likely to be found in the steric environment of the aldehyde groups of **33**, especially in one of them being an α, α, α-trisubstituted carbonyl group. As several attempts to optimize the yield by altering the reaction conditions (change of reductive agents and amines, addition of acid and longer imine formation times) failed, we decided to investigate the cyclizations of the two less sterically hindered dialdehydes **35** and **39**, obtained in excellent yields from **18** and **20**. We were pleased to find that the products **36** and **40** of these cyclizations were obtained in highly improved yields, 46% and 60%, respectively. Thus, these results confirm that **33** is too sterically hindered to undergo double-reductive amination in a satisfactory yield.



Scheme 6. Reagents and conditions: (a) IBX, CH_3CN, 55 ºC; (b) $DMBNH_2$, $Na(OAc)_3BH$, CH_2Cl_2; (c) DDQ, CH_2Cl_2/H_2O 5:1; (d) DDQ, CH_2Cl_2/MeOH 9:1.

The deprotection of the amines turned out to be a very slow reaction, especially for the removal of the DMB group. Hence, the PMB group of the amines **36** and **40** could be selectively cleaved by use of 3 equivalents of DDQ, yielding the amines **37** and **41**. Several attempts at the full deprotection of **40** to **42** were carried out with DDQ and CAN; use of the former was found to give little conversion whereas use of the latter was unsuccessful. It has been reported that deprotection of DMB protected amines can be inefficient for some substrates.[19] Substituting the usual biphasic CH_2Cl_2/H_2O solvent to a miscible solvent (CH_2Cl_2/MeOH 9:1) led to the highest conversion, although the use of as much as 20 equivalents of DDQ over 7 days gave a modest NMR yield of 15%. Attempts at the isolation of **42** (verified by LCMS) from a mixture of the amines **41** and **42** by flash column chromatography were not successful, presumably due to the two compounds having the same R_f value. Unfortunately, the full deprotection of **36** to **38** was not successful by use of the above conditions.

3. Conclusion

We have demonstrated that a library of diverse macrocycles with different ring sizes and functionalities can be formed in a few steps from simple building blocks containing primary alcohols. The structural and biological properties of the macrocycles are currently under investigation.

4. Experimental section

Starting materials, reagents, and solvents were purchased from Sigma-Aldrich Chemical Co. and used without further purification. Reactions involving air or moisture sensitive reagents were carried out under N_2. CH_2Cl_2, DMF, and DMSO were dried over 4 Å molecular sieves. THF and toluene were distilled from Na under N_2. Et_3N was distilled from CaH_2 under N_2. TLC was performed on Merck aluminum sheets precoated with silica gel 60 F_{254}. Compounds were visualized by charring after dipping in a solution of *p*-anisaldehyde (10 mL of H_2SO_4 and 10 mL of *p*-anisaldehyde in 200 mL of 95% EtOH), or cerium sulfate (6.25 g of $(NH_4)_6Mo_7O_{24}$ and 1.5 g of $Ce(SO_4)_2$ in 250 mL of 10% aqueous H_2SO_4). Flash column chromatography was performed using Merck silica gel 60 (particle size 0.040–0.063 mm). NMR spectra were recorded using a Varian Mercury 300 MHz spectrometer or a Varian Unity Inova 500 MHz spectrometer. Chemical shifts were measured in ppm and coupling constants in Hz, and the field is indicated in each case. The solvent peaks from $CDCl_3$ (7.26 ppm in ^{1}H NMR and 77.16 ppm in ^{13}C NMR) or CD_3OD (3.31 ppm in ^{1}H NMR) were used as standards. In case of diastereomeric mixtures, the following abbreviations are used; maj: major diastereomer, min: minor diastereomer, both: both diastereomers, one: one diastereomer. Elemental analyses were obtained from H. Kolbe, Mikroanalytisches Laboratorium, Mülheim/Ruhr, Germany. IR analysis was carried out on a Perkin-Elmer 1600 series FTIR spectrometer or on a Bruker Alpha FTIR spectrometer. Melting points were measured with a Buch & Holm melting point apparatus and are uncorrected. High-resolution LC-DAD-MS was performed on an Agilent 1100 system equipped with a photodiode array detector (DAD) and coupled to an LCT orthogonal time-of-flight mass spectrometer (Waters-Micromass) with a *Z*-spray electrospray ionization (ESI) source and a LockSpray probe (M + H 556.2771) and controlled by MassLynx 4.0 software.

*4.1. 4-(4-((tert-Butyldimethylsilyloxy)methyl)-1H-1,2,3-triazol-1-yl)butyl benzoate (**1**)*

4-Chlorobutyl benzoate (10.02 g, 47.09 mmol) and Bu_4NI (1.74 g, 4.71 mmol) were dissolved in anhydrous DMF (94 mL). NaN_3 (3.83 g, 58.86 mmol) was added cautiously. The solution was slowly heated to 60 ºC and stirred for 23 hours. The mixture was transferred to a separation funnel and diluted with Et_2O (600 mL). After washing with water (3×320 mL), the resulting organic phase was concentrated *in vacuo* to afford a yellow oil, which was used without further purification. The crude was dissolved in THF (422 mL) and DIPEA (12.09 mL, 70.64 mmol) was added followed by CuI (8.97 g, 47.09 mmol) and *tert*-butyldimethylsilyl propargyl ether (9.55 mL, 47.09 mmol). After stirring at 20 ºC for 18 hours, the yellow mixture was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo* giving a green oil. The residue was dissolved in EtOAc (500 mL) and washed with water (2×330 mL) and brine (330 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford an oil which was purified by flash column chromatography (MeOH/CH_2Cl_2 3:97) to give the triazole **1** (18.34 g, quantitative yield) as a yellow oil. R_f 0.60 (EtOAc/heptane 1:1); IR (neat, AgCl) *v* 3428 (w), 3138 (m), 3069 (m), 2956 (s), 1719 (s), 1602 (m), 1585 (m), 1451 (s), 1389 (m), 1361 (m), 1271 (s), 1219 (m), 1176 (m), 1096 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04-8.01 (2H, m), 7.60-7.52 (2H, m), 7.47-7.42 (2H, m), 4.88 (2H, s), 4.46 (2H, t, *J* 7.1 Hz), 4.36 (2H, t, *J* 6.3 Hz), 2.15-2.05 (2H, m), 1.87-1.77 (2H, m), 0.91 (9H, s), 0.10 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 149.0, 133.2, 130.1, 129.6 (2C), 128.5 (2C), 121.5, 64.0, 58.1, 49.9, 27.3, 26.0 (3C), 25.9, 18.4, -5.2 (2C).

*4.2. 4-(4-((tert-Butyldimethylsilyloxy)methyl)-1H-1,2,3-triazol-1-yl)-butan-1-ol (**2**)*

A solution of the triazole **1** (1.98 g, 5.08 mmol) in anhydrous CH_2Cl_2 (49 mL) was cooled to -78 ºC. DIBAL-H (1.0 M in hexane, 11.2 mL, 11.2 mmol) was added, and the mixture was stirred at -78 ºC for 3 hours. The reaction was quenched with MeOH (2.0 mL) and allowed to reach 20 ºC. A sat. aq. solution of Rochelle's salt (60 mL), water (40 mL) and Et_2O (250 mL) were added, and the viscous mixture was stirred vigorously for 15 minutes. The mixture was transferred to a separatory funnel and the organic layer was isolated. The aqueous layer was extracted with EtOAc (3×80 mL) and the pooled organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. The product was purified by flash column chromatography (EtOAc/heptane 1:1 → EtOAc) to afford the alcohol **2** (1.31 g, 90%) as a colorless oil. R_f 0.10 (EtOAc/heptane 1:1); IR (neat, AgCl) *v* 3372 (m), 2929 (s), 1734 (w), 1636 (w), 1559 (w), 1473 (m), 1257 (m), 1006 (s), 840 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (1H, s), 4.85 (2H, s), 4.41 (2H, t, *J* 7.1 Hz), 3.69 (2H, t, *J* 6.2 Hz), 2.07-1.98 (2H, m), 1.81 (1H, bs, OH), 1.63-1.54 (2H, m), 0.91 (9H, s), 0.10 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 121.6, 61.9, 58.0, 50.2, 29.4, 27.1, 26.0 (3C), 18.5, -5.2 (2C); Anal. calcd. for $C_{13}H_{27}N_3O_2Si$: C, 54.70; H, 9.53; N, 14.72. Found: C, 54.63; H, 9.50; N, 14.81.

*4.3. 4-((tert-Butyldimethylsilyloxy)methyl)-1-(4-(tert-butyldiphenylsilyloxy)butyl)-1H-1,2,3-triazole (**3**)*

The alcohol **2** (5.95 g, 20.85 mmol) was dissolved in anhydrous DMF (41.7 mL). Imidazole (2.84 g, 41.70 mmol) and TBDPSCl (8.13 mL, 31.28 mmol) were added. After stirring for 1 hour at 20 ºC, the mixture was diluted with EtOAc (140 mL) and then washed with water (70 mL) and brine (70 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/heptane 1:1) to give **3** (10.92 g, quantitative yield) as a colorless oil. R_f 0.85 (EtOAc/heptane 3:1); IR (neat) 3135 (w), 3071 (w), 3050 (w), 2998 (w), 2953 (m), 2930 (s), 2886 (m), 2857 (s), 1589 (w), 1471 (m), 1463 (m), 1428 (m), 1389 (m), 1361 (w), 1334 (w), 1308 (w), 1255 (m), 1218 (w), 1188 (w), 1134 (m), 1105 (s), 1088 (s), 1045 (m), 1022 (m), 1007 (m), 972 (w), 938 (w), 910 (w), 836 (m), 777 (m), 736 (m), 687 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66-7.63 (4H, m), 7.43-7.35 (7H, m), 4.85 (2H, s), 4.34 (2H, t, *J* 7.2 Hz), 3.68 (2H, t, *J* 6.0 Hz), 2.06-1.96 (2H, m), 1.61-1.52 (2H, m), 1.04 (9H, s), 0.91 (9H, s), 0.10 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 135.7 (4C), 133.8 (2C), 129.8 (2C), 127.8 (4C), 121.4, 63.1, 58.1, 50.2, 29.4, 27.2, 27.0 (3C), 26.0 (3C), 19.3, 18.5, -5.1 (2C).

*4.4. (1-(4-(tert-Butyldiphenylsilyloxy)butyl)-1H-1,2,3-triazol-4-yl)methanol (**4**)*

The disilylprotected compound **3** (10.92 g, 20.85 mmol) was dissolved in MeOH (350 mL). PPTS (262 mg, 1.04 mmol) was added, and the solution was heated to 55 ºC. After stirring for 23 hours, the solvent was removed *in vacuo*. The residue was redissolved in EtOAc (420 mL) and washed with brine (420 mL) and water (420 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/heptane 3:7 → EtOAc) to give the alcohol **4** (6.54 g, 77%) as white crystals. R_f 0.39 (EtOAc/heptane 3:1); m.p. 111-112 ºC; IR (neat) *v* 3232 (s), 3126 (m), 2927 (s), 2854 (m), 1472 (w), 1427 (m), 1359 (w), 1225 (w), 1145 (w), 1109 (s), 1081 (s), 1020 (m), 980 (m), 817 (w), 708 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65-7.62 (4H, m), 7.47 (1H, s), 7.43-7.35 (6H, m), 4.79 (2H, d, *J* 6.1 Hz), 4.35 (2H, t, *J* 7.2 Hz), 3.68 (2H, t, *J* 6.0 Hz), 2.23 (1H, t, *J* 6.1 Hz, OH), 2.07-1.97 (2H, m), 1.63-1.52 (2H, m), 1.04 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 135.6 (4C), 133.7 (2C), 129.8 (2C), 127.8 (4C), 121.7, 63.0, 56.3, 50.3, 29.4, 27.0, 27.0 (3C), 19.3; anal. calcd. for $C_{23}H_{31}N_3O_2Si$: C, 67.44; H, 7.63; N, 10.26. Found: C, 67.52; H, 7.59; N, 10.22.

*4.5. (±)-1-(tert-Butyldimethylsilyloxy)-2-methylbut-3-en-2-ol (**5**)*

1-(*tert*-Butyldimethylsilyloxy)propan-2-one (12 mL, 62.18 mmol) was dissolved in anhydrous THF (114 mL). The mixture was stirred at 0 ºC, and vinyl magnesium chloride (1.6 M in THF, 47 mL, 74.62 mmol) was added dropwise over 20 minutes. The cooling bath was removed and after two hours, the reaction mixture was diluted with Et_2O (480 mL) and washed with sat. aq. NH_4Cl (290 mL) and water (290 mL). The combined aqueous phases were extracted with Et_2O (200 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give **5** as a colorless oil (10.43 g, 78%), which was used without further purification. R_f 0.63 (EtOAc/heptane 1:1); IR (neat, AgCl) *v* 3447 (br), 3088 (w), 2931 (s), 1718 (w), 1653 (w), 1472 (m), 1362 (m), 1257 (m), 1100 (s), 1006 (m), 922 (m), 838 (s), 778 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (1H, dd, *J* 17.4 Hz, 10.8 Hz), 5.29 (1H, dd, *J* 17.4 Hz, 1.4 Hz), 5.11 (1H, dd, *J* 10.8 Hz, 1.4 Hz), 3.47 (1H, d, *J* 9.5 Hz), 3.42 (1H, d, *J* 9.5 Hz), 1.23 (3H, s), 0.90 (9H, s), 0.06 (3H, s), 0.06 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 113.6, 73.1, 70.4, 26.0 (3C), 23.9, 18.5, -5.2, -5.3.

*4.6. (±)-(E)-Methyl 5-(tert-butyldimethylsilyloxy)-4-hydroxy-4-methylpent-2-enoate (**6**)*

Alcohol **5** (8.40 g, 38.82 mmol) was dissolved in anhydrous CH_2Cl_2 (400 mL) and methyl acrylate (69.45 mL, 776.4 mmol) was added. Hoveyda-Grubbs' 2nd generation catalyst (0.122 g, 0.195 mmol) was added, and the mixture was heated to reflux. After stirring for 48 hours, the mixture was concentrated *in vacuo* to give a green semisolid, which was recrystallized from EtOAc/heptane, and a crystalline byproduct was filtered off. The filtrate was concentrated *in vacuo* to give a green oil. The crude product was purified by flash column chromatography (EtOAc/heptane 1:7) to afford the methyl ester **6** (9.31 g, 88 %) as a pale yellow oil. R_f 0.30 (EtOAc/heptane 1:4); IR (neat, AgCl) *v* 3482 (br), 2954 (s), 2858 (s), 1728 (s), 1662 (m), 1472 (m), 1437 (m), 1363 (m), 1259 (s), 1100 (s), 981 (m), 838 (s), 778 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (1H, d, *J* 15.7 Hz), 6.10 (1H, d, *J* 15.7 Hz), 3.74 (3H, s), 3.53 (1H, d, *J* 9.6 Hz), 3.48 (1H, d, *J* 9.6 Hz), 1.26 (3H, s), 0.88 (9H, s), 0.06 (3H, s), 0.04 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 152.1, 119.9, 73.1, 69.8, 51.7, 25.9 (3C), 23.6, 18.4, -5.3, -5.4.

*4.7. (±)-(E)-Methyl 5-(tert-butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-4-methylpent-2-enoate (**7**)*

The methyl ester **6** (4.16 g, 15.16 mmol) and PMBTCA[20] (8.14 g, 30.32 mmol) were dissolved in anhydrous toluene (125 mL), and $La(OTf)_3$ (622 mg, 1.06 mmol) was added. After stirring at 20 ºC for 16 hours, the mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to give a yellowish oil which was purified by flash column chromatography (EtOAc/toluene/heptane 1:50:50) to give the PMB-protected methyl ester **7** (5.07 g, 85%) as a colorless oil. R_f 0.73 (toluene/heptane 1:4); IR (neat, AgCl) *v* 2952 (s), 2856 (s), 2061 (w), 1883 (w), 1726 (s), 1658 (m), 1613 (m), 1587 (m), 1515 (s), 1465 (m), 1382 (m), 1250 (s), 1113 (s), 939 (m), 840 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* 8.6 Hz), 6.99 (1H, d, *J* 16.0 Hz), 6.88 (2H, d, *J* 8.6 Hz), 6.06 (1H, d, *J* 16.0

Hz), 4.44 (1H, d, *J* 10.7 Hz), 4.38 (1H, d, *J* 10.7 Hz), 3.81 (3H, s), 3.77 (3H, s), 3.63 (2H, s), 1.41 (3H, s), 0.89 (9H, s), 0.05 (3H, s), 0.04 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 159.1, 151.2, 131.1, 129.1 (2C), 121.6, 113.9 (2C), 78.3, 69.0, 65.3, 55.4, 51.8, 25.9 (3C), 20.3, 18.3, -5.3 (2C).

*4.8. (±)-(E)-5-(tert-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-4-methylpent-2-enoic acid (**8**)*

The methyl ester **7** (3.47 g, 8.79 mmol) was dissolved in THF (132 mL) and cooled to 0 ºC. A solution of LiOH (631 mg, 26.37 mmol) in H_2O (44 mL) was added, and the resulting mixture was stirred at 20 ºC. After 46 hours, the reaction was quenched with sat. aq. NaH_2PO_4 (100 mL), and EtOAc (100 mL) was added. The organic phase was isolated, and the aqueous phase was extracted with EtOAc (3×100 mL). The pooled organic phases were washed with water (200 mL) and brine (200 mL). Subsequently, they were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/heptane/AcOH 9:90:1) to afford the carboxylic acid **8** (2.97 g, 89%) as a white solid. R_f 0.60 (EtOAc/heptane/AcOH 70:30:1); m.p. 68-71 ºC; IR (neat) *v* 2927 (br), 1880 (w), 1698 (s), 1652 (m), 1614 (m), 1587 (m), 1515 (s), 1463 (m), 1373 (m), 1254 (s), 939 (m), 845 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* 8.6 Hz), 7.09 (1H, d, *J* 16.0 Hz), 6.87 (2H, d, *J* 8.6 Hz), 6.06 (1H, d, *J* 16.0 Hz), 4.44 (1H, d, *J* 10.7 Hz), 4.38 (1H, d, *J* 10.7 Hz), 3.80 (3H, s), 3.63 (2H, s), 1.42 (3H, s), 0.88 (9H, s), 0.04 (3H, s), 0.03 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 159.1, 153.8, 131.0, 129.1 (2C), 121.4, 113.9 (2C), 78.3, 68.9, 65.4, 55.4, 25.9 (3C), 20.3, 18.3, -5.3 (2C); anal. calcd. for $C_{20}H_{32}O_5Si$: C, 63.12; H, 8.48. Found: C, 63.20; H, 8.36.

*4.9. (±)-(E)-5-(tert-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-4-methylpent-2-en-1-ol (**9**)*

The methyl ester **7** (703 mg, 1.78 mmol) was dissolved in anhydrous CH_2Cl_2 (16 mL) and cooled to –78 ºC. DIBAL-H (1.0 M in hexanes, 3.92 mL, 3.92 mmol) was added, and the mixture was stirred at –78 ºC for 3 hours. The reaction was quenched with MeOH (1.0 mL) and the cold bath was removed. At 20 ºC, a sat. aq. solution of Rochelle's salt (20 mL), water (10 mL) and Et_2O (100 mL) was added, and the viscous mixture was stirred vigorously for 15 minutes. The organic phase was isolated, and the aqueous phase was extracted with EtOAc (3×50 mL). The pooled organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. The oil was purified by flash column chromatography (EtOAc/heptane 1:2) to afford the alcohol **9** (0.583 g, 89%) as a colorless oil. R_f 0.87 (MeOH/EtOAc 1:99); IR (neat, AgCl) *v* 3418 (br), 2930 (s), 1740 (m), 1613 (m), 1587 (m), 1514 (s), 1464 (m), 1379 (m), 1250 (s), 1172 (m), 1110 (s) cm^{-1}: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* 8.5 Hz), 6.86 (2H, d, *J* 8.5 Hz), 5.88 (1H, dt, *J* 16.2 Hz, 5.3 Hz), 5.74 (1H, d, *J* 16.2 Hz), 4.39 (2H, s), 4.19 (2H, dd, *J* 5.3 Hz, 1.0 Hz), 3.79 (3H, s), 3.59 (1H, d, *J* 9.9 Hz), 3.55 (1H, d, *J* 9.9 Hz), 1.36 (3H, s), 0.89 (9H, s), 0.04 (3H, s), 0.03 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 134.5, 131.8, 130.7, 129.0 (2C), 113.8 (2C), 78.0, 69.6, 64.7, 63.6, 55.4, 26.0 (3C), 20.3, 18.4, -5.2, -5.2; anal. calcd for $C_{20}H_{34}O_4Si$: C, 65.53; H, 9.35. Found: C, 65.45; H, 9.31.

*4.10. (±)-(E)-4-(4-Methoxybenzyloxy)-4-methylpent-2-en-1,5-diol (**10**)*

The alcohol **9** (8.80 g, 24.01 mmol) was dissolved in anhydrous THF (59 mL) and TBAF (1.0 M in THF, 36.01 mL, 36.01 mmol) was added dropwise. After stirring for 19 hours, the mixture was diluted with EtOAc (150 mL) and washed with sat. aq. NH_4Cl (120 mL) and water (2×120 mL). The combined aqueous phases were extracted with EtOAc (2×120 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/heptane 1:1 → MeOH/EtOAc 1:99) giving the diol **10** (6.06 g, quantitative yield) as a colorless oil, which crystallizes upon storage at 5 ºC to give a white solid. R_f 0.54 (MeOH/EtOAc 1:99); m.p. 44-45 ºC; IR (neat, AgCl) *v* 3379 (br), 2935 (s), 1613 (m), 1586 (m), 1514 (s), 1465 (m), 1381 (m), 1302 (m), 1248 (s), 1173 (m), 1112 (m), 1036 (s), 981 (m), 913 (w), 891 (w), 822 (m), 733 (m) cm^{-1}: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* 8.6 Hz), 6.87 (2H, d, *J* 8.6 Hz), 5.91 (1H, dt, 16.1 Hz, 5.2 Hz), 5.78 (1H, d, *J* 16.1 Hz), 4.33 (2H, s), 4.19 (2H, d, *J* 5.2 Hz), 3.80 (3H, s), 3.50 (2H, s), 2.08 (2H, br s), 1.38 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 132.9, 131.8, 131.1, 129.2 (2C), 113.9 (2C), 77.9, 69.7, 64.6, 63.0, 55.4, 19.3.

*4.11. (±)-(E)-5-(tert-Butyldiphenylsilyloxy)-2-(4-methoxybenzyloxy)-2-methylpent-3-en-1-ol (**11**)*

The diol **10** (1.41 g, 5.60 mmol) was dissolved in anhydrous CH_2Cl_2 (65 mL) and imidazole (539 mg, 8.41 mmol) was added. The mixture was cooled to –78 ºC, and a solution of TBDPSCl (1.46 mL, 5.60 mmol) in anhydrous CH_2Cl_2 (10 mL) was added over 5 minutes. After 3 hours, the mixture was diluted with CH_2Cl_2 (60 mL) and washed with brine (40 mL) and water (40 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (EtOAc/heptane 1:2) affording the TBDPS-protected alcohol **11** (2.75 g, quantitative yield) as a colorless oil. R_f 0.30 (EtOAc/heptane 1:2); IR (neat, AgCl) *v* 3457 (br), 2932 (s), 1613 (m), 1588 (m), 1514 (s), 1473 (m), 1428 (m), 1380 (m), 1302 (m), 1249 (s), 1173 (m), 1112 (s), 978 (m), 823 (m), 741 (m), 702 (m) cm^{-1}: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.66 (4H, m), 7.45-7.33 (6H, m), 7.23 (2H, d, *J* 8.5 Hz), 6.86 (2H, d, *J* 8.5 Hz), 5.81-5.80 (2H, m), 4.29-4.28 (4H, m), 3.80 (3H, s), 3.52 (1H, d, *J* 10.9 Hz), 3.41 (1H, d, *J* 10.9 Hz), 1.98 (1H, br s), 1.36 (3H, s), 1.07 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 135.6 (4C), 133.7, 133.7, 131.9, 131.5, 131.2, 129.8 (2C), 129.3 (2C), 127.8 (4C), 113.9 (2C), 77.9, 69.8, 64.7, 64.1, 55.4, 27.0 (3C), 19.4, 19.3; anal. calcd. for $C_{30}H_{38}O_4Si$: C, 73.43; H, 7.81. Found: C, 73.27; H, 7.75.

*4.12. (±)-(E)-5-(tert-Butyldiphenylsilyloxy)-2-(4-methoxybenzyloxy)-2-methylpent-3-enoic acid (**12**)*

Anhydrous CH_2Cl_2 (220 mL) and DMSO (5.79 mL, 81.66 mmol) were mixed and cooled to –78 ºC. Oxalyl chloride (3.45 mL, 40.83 mmol) was added dropwise, followed by dropwise addition of a solution of the alcohol **11** (10.02 g, 20.42 mmol) in anhydrous CH_2Cl_2 (110 mL). After 30 minutes, anhydrous Et_3N (28.50 mL, 204.15 mmol) was added. After further 15 minutes, the mixture was allowed to reach 20 ºC and then diluted with CH_2Cl_2 (600 mL) and washed with sat. aq. NH_4Cl (400 mL) and water (400 mL) The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude aldehyde, which was used without further purification. The crude aldehyde was dissolved in THF (120 mL). *t*-BuOH (240 mL) and 2-methyl-2-butene (86 mL, 811.23 mmol) were added followed by a solution of $NaClO_2$ (23.26 g, 257.14 mmol) and NaH_2PO_4 (30.85 g, 257.14 mmol) in water (160 mL). After 1½ hours, the mixture was diluted with sat. aq. NaH_2PO_4 (500 mL) and stirred for 15 minutes. Subsequently, the mixture was extracted with EtOAc (3×500 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/heptane/AcOH 66:33:1) to afford the carboxylic acid **12** (9.89 g, 96%) as a

colorless oil. R_f 0.25 (MeOH/toluene 5:95); IR (neat) *v* 3071 (m), 3049 (m), 2997 (m), 2956 (m), 2931 (m), 2893 (m), 2857 (m), 1712 (m), 1613 (m), 1588 (w), 1513 (m), 1462 (m), 1428 (m), 1380 (m), 1302 (m), 1247 (s), 1202 (m), 1174 (m), 1107 (s), 1028 (m), 998 (m), 971 (m), 939 (m), 909 (m), 821 (m), 735 (m), 700 (s) cm^{-1}: ^1H NMR (300 MHz, $CDCl_3$) δ 7.68-7.65 (4H, m), 7.42-7.34 (6H, m), 7.25 (2H, d, *J* 8.7 Hz), 6.89 (2H, d, *J* 8.7 Hz), 6.01 (1H, dt, *J* 15.7 Hz, 3.4 Hz), 5.92 (1H, m), 4.43 (1H, d, *J* 10.5 Hz), 4.38 (1H, d, *J* 10.5 Hz), 4.29 (2H, dd, *J* 3.4 Hz, 1.1 Hz), 3.82 (3H, s), 1.65 (3H, s), 1.07 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 159.5, 135.6 (4C), 133.5, 133.2 (2C), 129.9 (2C), 129.8, 129.6 (2C), 128.1, 127.9 (4C), 114.0 (2C), 80.2, 66.5, 63.6, 55.4, 26.9 (3C), 22.1, 19.4; anal. calcd. for $C_{30}H_{36}O_5Si$: C, 71.39; H, 7.19. Found: C, 70.67; H, 7.17.

*4.13. Representative procedure for the preparation of esters (**13**, **15**, **17**, **19**)*

*(±)-(E)-4-(4-((tert-Butyldimethylsilyloxy)methyl)-1H-1,2,3-triazol-1-yl)butyl 5-(tert-butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-4-methylpent-2-enoate (**13**)*

The carboxylic acid **8** (0.624 g, 1.640 mmol) and the alcohol **2** (0.515 g, 1.804 mmol) were dissolved in anhydrous CH_2Cl_2 (25 mL) and DMAP (0.040 g, 0.328 mmol) and EDC·HCl (0.472 g, 2.460 mmol) were added. The reaction was stirred for 18 hours at 20 ºC and then concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/heptane 1:2) to afford the ester **13** (0.930 g, 87%) as a colorless oil. R_f 0.31 (MeOH/toluene 5:95); IR (neat, AgCl) *v* 2927 (s), 1734 (s), 1653 (m), 1613 (m), 1516 (m), 1472 (m), 1374 (m), 1249 (s), 1104 (s), 939 (w), 839 (m), 779 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (1H, s), 7.25 (2H, d, *J* 8.4 Hz), 6.97 (1H, d, *J* 16.0 Hz), 6.86 (2H, d, *J* 8.4 Hz), 6.02 (1H, d, *J* 16.0 Hz), 4.84 (2H, s), 4.42 (1H, d, *J* 11.1 Hz), 4.38 (2H, t, *J* 7.4 Hz), 4.37 (1H, d, *J* 11.1 Hz), 4.18 (2H, t, *J* 6.3 Hz), 3.79 (3H, s), 3.61 (2H, s), 2.05-1.95 (2H, m), 1.76-1.65 (2H, m), 1.40 (3H, s), 0.91 (9H, s), 0.87 (9H, s), 0.09 (6H, s), 0.02 (3H, s), 0.01 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 159.1, 151.5, 148.9, 131.1, 129.0 (2C), 121.6, 121.5, 113.9 (2C), 78.3, 68.9, 65.3, 63.5, 58.1, 55.4, 49.9, 27.2, 26.0 (3C), 25.9 (3C), 25.9, 20.2, 18.5, 18.3, -5.1 (2C), -5.3 (2C).

*(±)-(E)-(1-(4-(tert-Butyldiphenylsilyloxy)butyl)-1H-1,2,3-triazol-4-yl)methyl 5-(tert-butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-4-methylpent-2-enoate (**15**)*

Colorless oil, 87% yield. R_f 0.40 (MeOH/toluene 5:95); IR (neat) *v* 3139 (w), 3071 (w), 3048 (w), 2998 (w), 2954 (s), 2930 (s), 2894 (m), 2857 (s), 1720 (s), 1656 (w), 1613 (w), 1588 (w), 1514 (m), 1463 (m), 1442 (m), 1428 (m), 1387 (m), 1361 (w), 1301 (m), 1249 (s), 1169 (m), 1105 (s), 1033 (m), 1007 (m), 938 (w), 910 (w), 836 (s), 823 (m), 777 (m), 731 (m), 701 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65-7.62 (4H, m), 7.56 (1H, s), 7.45-7.36 (6H, m), 7.23 (2H, d, *J* 8.5 Hz), 7.00 (1H, d, *J* 16.1 Hz), 6.85 (2H, d, *J* 8.5 Hz), 6.05 (1H, d, *J* 16.1 Hz), 5.30 (2H, s), 4.46-4.32 (4H, m), 3.79 (3H, s), 3.68 (2H, t, *J* 6.0 Hz), 3.60 (2H, s), 2.07-1.97 (2H, m), 1.61-1.52 (2H, m), 1.38 (3H, s), 1.04 (9H, s), 0.86 (9H, s), 0.01 (3H, s), 0.00 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 164.4, 157.3, 148.2, 141.0 (4C), 139.0 (2C), 136.4, 135.2 (2C), 134.4 (2C), 133.2 (4C), 129.1, 126.7, 119.2 (2C), 83.6, 74.3, 70.6, 68.4, 63.2, 60.7, 55.7, 34.7, 32.4, 32.3 (3C), 31.3 (3C), 25.6, 24.7, 23.7, 0.0, 0.0.

*(±)-(E)-(1-(4-(tert-Butyldiphenylsilyloxy)butyl)-1H-1,2,3-triazol-4-yl)methyl 5-(tert-butyldiphenylsilyloxy)-2-(4-methoxybenzyloxy)-2-methylpent-3-enoate (**17**)*

Colorless oil, 58% yield. R_f 0.40 (MeOH/toluene 5:95); IR (neat) *v* 3136 (w), 3071 (w), 3048 (w), 3013 (w), 2998 (w), 2955 (m), 2931 (m), 2892 (m), 2857 (m), 1736 (m), 1613 (w), 1588 (w), 1514 (m), 1471 (m), 1462 (m), 1427 (m), 1387 (m), 1362 (w), 1302 (w), 1248 (m), 1174 (m), 1105 (s), 1047 (m), 1032 (m), 998 (m), 968 (m), 939 (w), 910 (w), 822 (m), 735 (m), 700 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67-7.62 (8H, m), 7.48 (1H, s), 7.44-7.32 (12H, m), 7.26 (2H, d, *J* 8.7 Hz), 6.84 (2H, d, *J* 8.7 Hz), 6.03 (1H, dt, *J* 15.7 Hz, 1.6 Hz), 5.91 (1H, dt, *J* 15.7 Hz, 4.0 Hz), 5.31 (2H, s), 4.42 (1H, d, *J* 10.6 Hz), 4.36 (1H, d, *J* 10.6 Hz), 4.28 (2H, t, *J* 7.3 Hz), 4.24 (2H, dd, *J* 4.0 Hz, 1.6 Hz), 3.78 (3H, s), 3.66 (2H, t, *J* 6.0 Hz), 2.01-1.91 (2H, m), 1.56 (3H, s), 1.55-1.48 (2H, m), 1.05 (9H, s), 1.04 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 159.2, 142.7, 135.6 (4C), 135.6 (4C), 133.7 (2C), 133.6 (2C), 131.6, 130.7, 129.8 (4C), 129.4, 129.4 (2C), 127.8 (4C), 127.8 (4C), 123.7, 113.8 (2C), 80.1, 66.9, 63.8, 63.0, 58.6, 55.4, 50.3, 29.4, 27.0, 27.0 (3C), 26.9 (3C), 24.2, 19.4, 19.3.

*(±)-(E)-4-(4-((tert-Butyldimethylsilyloxy)methyl)-1H-1,2,3-triazol-1-yl)butyl 5-(tert-butyldiphenylsilyloxy)-2-(4-methoxybenzyloxy)-2-methylpent-3-enoate (**19**)*

Colorless oil, 71% yield. R_f 0.31 (MeOH/toluene 5:95); IR (neat) *v* 3136 (w), 3071 (w), 3048 (w), 2997 (w), 2954 (m), 2931 (s), 2893 (m), 2856 (m), 1734 (m), 1613 (m), 1588 (w), 1514 (m), 1462 (m), 1428 (m), 1381 (m), 1362 (m), 1301 (m), 1247 (s), 1174 (m), 1105 (s), 1043 (m), 970 (m), 939 (w), 836 (m), 777 (m), 740 (m), 701 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68-7.64 (4H, m), 7.42-7.33 (7H, m), 7.28 (2H, d, *J* 8.6 Hz), 6.85 (2H, d, *J* 8.6 Hz), 6.04 (1H, dt, *J* 15.7 Hz, 1.5 Hz), 5.92 (1H, dt, *J* 15.7 Hz, 3.8 Hz), 4.83 (2H, s), 4.44 (1H, d, *J* 10.8 Hz), 4.38 (1H, d, *J* 10.8 Hz), 4.31 (2H, t, *J* 7.0 Hz), 4.26 (2H, dd, *J* 3.9 Hz, 1.5 Hz), 4.18 (2H, t, *J* 6.4 Hz), 3.79 (3H, s), 2.01-1.90 (2H, m), 1.73-1.60 (2H, m), 1.58 (3H, s), 1.06 (9H, s), 0.91 (9H, s), 0.09 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 159.2, 148.8, 135.6 (4C), 133.6 (2C), 131.5, 130.8, 129.9 (2C), 129.6, 129.2 (2C), 127.8 (4C), 121.5, 113.8 (2C), 80.2, 66.8, 64.3, 63.8, 58.1, 55.4, 49.7, 27.1, 26.9 (3C), 26.0 (3C), 25.7, 24.0, 19.4, 18.5, -5.1 (2C).

*4.14. Representative procedure for the preparation of diols (**14**, **16**, **18**, **20**)*

*(±)-(E)-4-(4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)butyl 5-hydroxy-4-(4-methoxybenzyloxy)-4-methylpent-2-enoate (**14**)*

The ester **13** (2.034 g, 3.14 mmol) was dissolved in anhydrous THF (27.7 mL) and TBAF (1.0 M in THF, 9.42 mL, 9.42 mmol) was added dropwise. The mixture was stirred for 4½ hours and then diluted with EtOAc (140 mL), washed with sat. aq. NH_4Cl (80 mL) and water (2×80 mL). The combined aqueous phases were extracted with EtOAc (2×80 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (MeOH/EtOAc 1:99 → 5:95) to afford the diol **14** (1.133 g, 86%) as a colorless oil. R_f 0.10 (MeOH/EtOAc 1:99); IR (neat) *v* 3374 (br), 3142 (m), 2938 (m), 2873 (m), 2839 (m), 1712 (s), 1654 (m), 1612 (m), 1513 (m), 1462 (m), 1443 (m), 1383 (m), 1301 (m), 1247 (s), 1171 (m), 1110 (m), 1031 (s), 895 (w), 821 (m), 778 (w), 754 (w), 726 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (1H, s), 7.25 (2H, d, *J* 8.8 Hz), 6.97 (1H, d, *J* 16.1 Hz), 6.88 (2H, d, *J* 8.8 Hz), 6.04 (1H, d, *J* 16.1 Hz), 4.77 (2H, s), 4.40 (2H, t, *J* 7.1 Hz), 4.39 (1H, d, *J* 10.6 Hz), 4.32 (1H, d, *J* 10.6 Hz), 4.17 (2H, t, *J* 6.3 Hz), 3.80 (3H, s), 3.60 (1H, d, *J* 11.5 Hz), 3.55 (1H, d, *J* 11.5 Hz), 2.07-1.97 (2H, m), 1.75-1.66 (2H, m), 1.42 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 159.3, 150.0, 147.9, 130.4, 129.3 (2C), 122.5, 121.8, 114.0 (2C), 78.1, 68.9, 65.3, 63.7, 56.7, 55.4, 49.9, 27.1, 25.7, 19.3; anal. calcd. for $C_{21}H_{29}N_3O_6$: C, 60.13; H, 6.97; N, 10.02. Found: C, 60.02; H, 7.06; N, 9.88.

*(±)-(E)-(1-(4-Hydroxybutyl)-1H-1,2,3-triazol-4-yl)methyl 5-hydroxy-4-(4-methoxybenzyloxy)-4-methylpent-2-enoate (**16**)*

White solid, 78% yield. R_f 0.15 (MeOH/EtOAc 1:99); m.p. 70-71 ºC; IR (neat) *v* 3332 (br), 3120 (m), 3072 (w), 3034 (w), 2935 (m), 2870 (m), 2838 (m), 1716 (s), 1655 (m), 1612 (m), 1586 (w), 1513 (m), 1462 (m), 1442 (m), 1381 (m), 1316 (m), 1301 (m), 1249 (m), 1218 (m), 1171 (s), 1108 (m), 1046 (s), 1007 (m), 973 (m), 942 (w), 900 (w), 871 (m), 827 (m), 815 (m), 781 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (1H, s), 7.24 (2H, d, *J* 8.7 Hz), 7.00 (1H, d, *J* 16.1 Hz), 6.87 (2H, d, *J* 8.7 Hz), 6.07 (1H, d, *J* 16.1 Hz), 5.30 (2H, s), 4.41 (2H, t, *J* 7.1 Hz), 4.37 (1H, d, *J* 10.4 Hz), 4.31 (1H, d, *J* 10.4 Hz), 3.80 (3H, s), 3.67 (2H, t, *J* 6.2 Hz), 3.57 (1H, d, *J* 11.5 Hz), 3.52 (1H, d, *J* 11.5 Hz), 2.07-1.97 (2H, m), 1.62-1.53 (2H, m), 1.41 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 159.3, 150.4, 142.7, 130.4, 129.2 (2C), 124.1, 122.2, 114.0 (2C), 78.1, 68.8, 65.2, 61.9, 57.8, 55.4, 50.3, 29.3, 27.0, 19.3; anal. calcd. for $C_{21}H_{29}N_3O_6$: C, 60.13; H, 6.97; N, 10.02. Found: C, 60.04; H, 7.08; N, 9.94.

*(±)-(E)-(1-(4-Hydroxybutyl)-1H-1,2,3-triazol-4-yl)methyl 5-hydroxy-2-(4-methoxybenzyloxy)-2-methylpent-3-enoate (**18**)*

Colorless oil, 76% yield. R_f 0.15 (MeOH/EtOAc 1:99); IR (neat) *v* 3362 (br), 3143 (m), 3042 (w), 2937 (m), 2870 (m), 2839 (m), 1732 (s), 1612 (m), 1586 (w), 1513 (s), 1456 (m), 1443 (m), 1381 (m), 1302 (m), 1245 (s), 1175 (m), 1107 (s), 1084 (m), 1051 (m), 1027 (s), 968 (m), 821 (m), 784 (w), 755 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (1H, s), 7.27 (2H, d, *J* 8.8 Hz), 6.85 (2H, d, *J* 8.8 Hz), 5.96 (1H, dt, *J* 15.8 Hz, 4.4 Hz), 5.87 (1H, d, *J* 15.8 Hz), 5.35 (1H, d, *J* 12.7 Hz), 5.29 (1H, d, *J* 12.7 Hz), 4.44 (1H, d, *J* 10.4 Hz), 4.39 (2H, t, *J* 7.0 Hz), 4.37 (1H, d, *J* 10.4 Hz), 4.15 (2H, dd, *J* 4.4 Hz, 0.9 Hz), 3.79 (3H, s), 3.63 (2H, t, *J* 6.2 Hz), 2.08-1.93 (2H, m), 1.60 (3H, s), 1.57-1.48 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 159.2, 142.5, 131.9, 130.6, 130.5, 129.4 (2C), 123.9, 113.8 (2C), 80.0, 66.8, 62.5, 61.7, 58.4, 55.4, 50.3, 29.3, 26.9, 23.1; anal. calcd. for $C_{21}H_{29}N_3O_6$: C, 60.13; H, 6.97; N, 10.02. Found: C, 60.45; H, 7.06; N, 10.08.

*(±)-(E)-4-(4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)butyl 5-hydroxy-2-(4-methoxybenzyloxy)-2-methylpent-3-enoate (**20**)*

Colorless oil, 93% yield. R_f 0.10 (MeOH/EtOAc 1:99); IR(neat) *v* 3360 (br), 3144 (m), 2961 (m), 2936 (m), 2872 (m), 2839 (m), 1730 (s), 1668 (w), 1613 (m), 1586 (w), 1553 (w), 1513 (s), 1457 (m), 1382 (m), 1301 (m), 1246 (s), 1175 (m), 1112 (m), 1084 (m), 1031 (s), 979 (m), 880 (w), 821 (m), 778 (m), 756 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, s), 7.28 (2H, d, *J* 8.7 Hz), 6.85 (2H, d, *J* 8.7 Hz), 6.00 (1H, dt, *J* 15.8 Hz, 4.5 Hz), 5.90 (1H, d, *J* 15.8 Hz), 4.73 (2H, s), 4.45 (1H, d, *J* 10.6 Hz), 4.38 (1H, d, *J* 10.6 Hz), 4.34 (2H, t, *J* 7.0 Hz), 4.20-4.16 (4H, m), 3.78 (3H, s), 3.30 (2H, br s), 1.98 (2H, tt, *J* 7.3 Hz, 7.3 Hz), 1.71-1.62 (2H, m), 1.59 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 159.1, 147.9, 131.9, 130.5, 130.5, 129.2 (2C), 122.2, 113.8 (2C), 80.0, 66.6, 64.3, 62.3, 56.1, 55.4, 49.8, 27.0, 25.5, 22.9; anal. calcd. for $C_{21}H_{29}N_3O_6$: C, 60.13; H, 6.97; N, 10.02. Found: C, 59.71; H, 7.19; N, 9.94.

*4.15. Representative procedure for the preparation of macrocyclic sulfites (**21**, **23**, **25**, **27**)*

*Sulfite (**21**)*

The diol **14** (107 mg, 0.26 mmol) was dissolved in anhydrous CH_2Cl_2 (21 mL). Anhydrous Et_3N (0.11 mL, 0.77 mmol) and DMAP (6 mg, 0.05 mmol) were added. A solution of $SOCl_2$ in anhydrous CH_2Cl_2 (0.36 M, 1 mL, 0.36 mmol) was added over 10 min at 20 ºC, under vigorous stirring. After stirring for 1 hour, the reaction mixture was concentrated *in vacuo*. The residue was redissolved in EtOAc, filtered through Celite and concentrated *in vacuo*. Purification by flash column chromatography (MeOH/CH_2Cl_2 1:99) gave the sulfite **21** (60 mg, 51%) as white crystals. R_f 0.60 (MeOH/EtOAc 1:99); m.p. 91-93 ºC; dr: 2:1, de: 33% (NMR); IR (neat) *v* 3133 (w), 2963 (m), 2933 (m), 2879 (m), 2841 (m), 1716 (s), 1657 (m), 1613 (m), 1587 (w), 1515 (m), 1457 (m), 1390 (m), 1361 (w), 1317 (m), 1304 (m), 1286 (m), 1247 (m), 1194 (m), 1168 (s), 1111 (m), 1028 (s), 1001 (m), 939 (m), 899 (m), 828 (m), 777 (m), 729 (m), 706 (m), 690 (m), 669 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (maj, s), 7.56 (min, s), 7.24 (min, d, *J* 8.6 Hz), 7.21 (maj, d, *J* 8.6 Hz), 6.87 (min, d, *J* 8.7 Hz), 6.86 (maj, d, *J* 8.7 Hz), 6.82 (both, d, *J* 16.1 Hz), 6.05 (min, d, *J* 16.1 Hz), 6.03 (maj, d, *J* 16.1 Hz), 5.55 (maj, d, *J* 13.3 Hz), 5.49 (min, d, *J* 13.0 Hz), 4.96 (min, d, *J* 13.0 Hz), 4.95 (maj, d, *J* 13.3 Hz), 4.48-4.33 (m), 4.30-4.24 (m), 4.19-4.11 (m), 4.14 (min, d, *J* 10.1 Hz), 4.13 (maj, *J* 11.0 Hz), 3.92 (maj, d, *J* 11.0 Hz), 3.87 (min, d, *J* 10.1 Hz), 3.79 (both, s), 2.09-2.02 (m), 1.76-1.66 (m), 1.45 (min, s), 1.43 (maj, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6 (min), 165.5 (maj), 159.3 (min), 159.2 (maj), 149.2 (min), 148.6 (maj), 143.8 (maj), 143.4 (min), 130.2 (maj), 130.2 (min), 129.1 (2C, min), 128.9 (2C, maj), 123.0 (min), 122.9 (maj), 122.8 (maj), 122.5 (min), 114.0 (2C, min), 113.9 (2C, maj), 76.3 (maj), 76.2 (min), 69.3 (maj), 67.7 (min), 65.3 (maj), 65.2 (min), 63.5 (both), 56.6 (min), 56.0 (maj), 55.4 (both), 49.5 (both), 26.8 (both), 25.0 (min), 24.9 (maj), 20.2 (min), 19.6 (maj); HRMS (ESI): *m/z* calcd. for $C_{21}H_{27}N_3O_6S$ $[M+H]^+$ 466.1643, found 466.1637.

*Sulfite (**23**)*

White crystals, 43% yield; R_f 0.60 (MeOH/EtOAc 1:99); m.p. 130-131 ºC; dr: 3:2 (NMR); IR(neat) *v* 3133 (w), 3075 (w), 3034 (w), 2963 (m), 2875 (m), 2841 (w), 1714 (s), 1643 (w), 1612 (m), 1585 (w), 1514 (m), 1462 (m), 1446 (m), 1384 (m), 1304 (m), 1250 (s), 1225 (m), 1203 (m), 1174 (m), 1141 (m), 1115 (m), 1056 (m), 1031 (m), 1001 (m), 977 (m), 897 (m), 884 (m), 854 (m), 824, 806, 773, 733, 711 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (both, s), 7.22 (both, d, *J* 8.6 Hz), 6.87 (both, d, *J* 8.6 Hz), 6.85 (both, d, *J* 16.1 Hz), 6.04 (min, d, *J* 16.1 Hz), 6.03 (maj, d, *J* 16.1 Hz), 5.39-5.38 (m), 4.53-4.37 (m), 4.40 (both, d, *J* 10.6 Hz), 4.34 (both, d, *J* 10.6 Hz), 3.94 (min, d, *J* 10.3 Hz), 3.91 (maj, d, *J* 9.6 Hz), 3.79 (both, s), 3.78 (min, d, *J* 10.3 Hz), 3.74 (maj, d, *J* 9.6 Hz), 3.65-3.48 (m), 1.97-1.86 (m), 1.54-1.46 (m), 1.44 (both, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0 (maj), 165.9 (min), 159.3 (maj), 159.3 (min), 150.3 (maj), 150.0 (min), 144.2 (both), 130.2 (min), 130.2 (maj), 129.1 (2C, maj), 129.0 (2C, min), 123.9 (maj), 123.8 (min), 122.8 (maj), 122.7 (min), 114.0 (2C, maj), 114.0 (2C, min), 76.4 (min), 76.3 (maj), 68.3 (min), 67.4 (maj), 65.3 (maj), 65.2 (min), 62.7 (maj), 62.1 (min), 57.7 (both), 55.4 (both), 50.1 (both), 27.1 (min), 27.0 (maj), 26.3 (min), 26.3 (maj), 19.6 (maj), 19.4 (min).

*Sulfite (**25**)*

White crystals, 79% yield; R_f 0.60 (MeOH/EtOAc 1:99); m.p. 130-131 ºC; dr: 1:1 (NMR); IR (neat) *v* 3127 (w), 3071 (w), 3044 (w), 3001 (w), 2954 (m), 2930 (m), 2877 (w), 2858 (w), 2836 (w), 1730 (s), 1680 (w), 1613 (m), 1586 (w), 1512 (m), 1454 (m), 1390 (m), 1331 (w), 1303 (m), 1274 (w), 1246 (m), 1233 (m), 1199 (m), 1172 (m), 1133 (m), 1106 (m), 1053 (m), 1036 (m), 1011 (m), 994 (m), 971 (m), 951 (m), 919 (m), 898 (m), 820 (m), 780 (m), 754 (m), 732 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (both, s), 7.33 (both, d, *J* 8.7 Hz), 6.88 (both, d, *J* 8.7 Hz), 5.76-5.73 (m), 5.49 (one, d, *J* 12.5 Hz), 5.46 (one, d, *J* 12.5 Hz), 5.32 (one, d, *J* 12.5 Hz), 5.30 (one, d, *J* 12.5 Hz), 4.54-4.31 (m), 4.28-4.26 (m), 4.12-4.02 (m), 3.80 (both, s), 3.77-3.67 (m), 2.04-1.92 (m), 1.63 (one, s), 1.63 (one, s), 1.59-1.47 (m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4 (both), 159.3 (both), 143.0 (both), 134.9 (one), 134.4 (one), 130.3 (one), 130.3 (one), 129.4 (2C, both), 125.8 (one), 125.6 (one), 124.3 (one), 124.2 (one), 113.9 (2C, both), 80.0 (one), 79.9 (one), 67.0 (both), 62.3 (one), 62.1 (one), 62.0 (one), 61.7 (one), 58.2 (both), 55.4 (both), 50.0

(both), 27.0 (one), 27.0 (one), 26.4 (one), 26.4 (one), 22.2 (one), 22.1 (one); anal. calcd. for $C_{21}H_{27}N_3O_7S$: C, 54.18; H, 5.85; N, 9.03. Found: C, 54.28; H, 5.77; N, 8.95.

*Sulfite (**27**)*

White crystals, 74% yield; R_f 0.60 (MeOH/EtOAc 1:99); m.p. 92 ºC; dr: 1:1 (NMR); IR(neat) *v* 3145 (w), 3046 (w), 2994 (m), 2960 (m), 2941 (m), 2922 (m), 2877 (m), 2837 (m), 1735 (s), 1614 (m), 1587 (w), 1512 (m), 1458 (m), 1440 (m), 1387 (m), 1303 (m), 1243 (m), 1201 (m), 1189 (m), 1172 (m), 1145 (m), 1107 (s), 1038 (m), 1006 (m), 981 (m), 941 (m), 924 (m), 904 (s), 839 (m), 813 (m), 804 (m), 786 (m), 757 (m), 739 (m), 717 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (one, s), 7.64 (one, s), 7.28 (one, d, *J* 8.6 Hz), 7.27 (one, d, *J* 8.6 Hz), 6.86 (both, d, *J* 8.6 Hz), 5.86-5.84 (m), 5.60 (one, d, *J* 13.4 Hz), 5.55 (one, d, *J* 13.4 Hz), 4.96 (one, d, *J* 13.4 Hz), 4.93 (one, d, *J* 13.4 Hz), 4.51-4.22 (m), 3.79 (both, s), 1.99-1.84 (m), 1.76-1.64 (m), 1.59 (one, s), 1.58 (one, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3 (both), 159.3 (both), 143.4 (one), 143.3 (one), 134.7 (one), 134.7 (one), 130.2 (one), 130.2 (one), 129.3 (2C, both), 125.4 (one), 125.3 (one), 124.1 (one), 124.1 (one), 113.9 (2C, both), 79.9 (one), 79.9 (one), 66.8 (both), 64.1 (one), 64.1 (one), 62.7 (one), 62.6 (one), 55.4 (both), 55.3 (one), 55.1 (one), 49.5 (both), 27.5 (one), 27.5 (one), 25.5 (both), 22.3 (both).

*4.16. Representative procedure for the preparation of deprotected sulfites (**22a**, **22b**, **24**, **26**, **28**)*

*Sulfite (**22a**)*

The sulfite **21** (259 mg, 0.56 mmol) was dissolved in CH_2Cl_2 (52.8 mL) and water (2.9 mL). DDQ (152 mg, 0.67 mmol) was added, and the mixture was stirred at 20 ºC for 6 hours. Then the mixture was diluted with EtOAc (260 mL) and washed with 40% aqueous $NaHSO_3$ (260 mL) and water (2×260 mL). The aqueous phase was extracted with EtOAc (260 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified twice by flash column chromatography (EtOAc/toluene 1:1) to give the deprotected sulfite **22a** (58 mg, 30%, one diastereomer) as white crystals and the sulfite **22b** (one diastereomer). **22a**: R_f 0.42 (MeOH/EtOAc 1:99); m.p. 121-123 ºC; IR(neat) *v* 3362 (m), 3134 (m), 2961 (m), 2929 (m), 2876 (m), 1716 (s), 1658 (m), 1467 (m), 1455 (m), 1408 (w), 1392 (w), 1378 (w), 1362 (w), 1304 (m), 1284 (m), 1248 (m), 1194 (m), 1177 (m), 1133 (m), 1105 (m), 1059 (m), 1049 (m), 1033 (m), 1004 (m), 989 (m), 947 (m), 886 (m), 815 (m), 766 (m), 731 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (1H, s), 6.78 (1H, d, *J* 15.8 Hz), 6.05 (1H, d, *J* 15.8 Hz), 5.66 (1H, d, *J* 13.2 Hz), 4.87 (1H, d, *J* 13.2 Hz), 4.50 (1H, ddd, *J* 13.9 Hz, 7.0 Hz, 5.1 Hz), 4.38 (1H, ddd, *J* 13.9 Hz, 7.0 Hz, 5.1 Hz), 4.22 (2H, t, *J* 5.5 Hz), 4.03 (1H, d, *J* 10.3 Hz), 3.86 (1H, d, *J* 10.3 Hz), 2.99 (1H, br s), 2.17-2.01 (2H, m), 1.77-1.65 (2H, m), 1.33 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 150.8, 143.1, 123.8, 120.9, 71.9, 71.3, 63.3, 55.3, 49.7, 26.6, 25.2, 23.7; HRMS (ESI): *m/z* calcd. for $C_{13}H_{19}N_3O_6S$ $[M+H]^+$ 346.1067, found 346.1048; anal. calcd. for $C_{13}H_{19}N_3O_6S$: C, 45.21; H, 5.55; N, 12.17. Found: C, 45.30; H, 5.51; N, 12.08. **22b**: R_f 0.12 (MeOH/EtOAc 1:99); ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (1H, s), 6.81 (1H, d, *J* 15.5 Hz), 6.04 (1H, d, *J* 15.5 Hz), 4.81 (2H, s), 4.56 (1H, d, *J* 8.9 Hz), 4.42 (1H, d, *J* 8.9 Hz), 4.43-4.39 (2H, m), 4.18 (2H, t, *J* 6.3 Hz), 2.05-1.97 (2H, m), 1.78 (3H, s), 1.74-1.67 (2H, m); HRMS (ESI): *m/z* calcd. for $C_{13}H_{19}N_3O_6S$ $[M+H]^+$ 346.1067, found 346.1094.

*Sulfite (**24**)*

White crystals, 47% yield; R_f 0.42 (MeOH/EtOAc 1:99); m.p. 115-118 ºC; dr: 3:2 (NMR); IR(neat) *v* 3152 (w), 3065 (w), 2965 (m), 2944 (m), 2917 (w), 2872 (w), 2842 (w), 1747 (m), 1725 (m), 1711 (s), 1657 (m), 1611 (w), 1514 (m), 1466 (w), 1449 (m), 1413 (w), 1382 (m), 1324 (m), 1300 (m), 1283 (m), 1264 (m), 1249 (m), 1220 (m), 1179 (m), 1149 (m), 1134 (m), 1027 (m), 1003 (m), 975 (m), 928 (m), 892 (m), 846 (w), 821 (m), 802 (w), 787 (m), 757 (m), 741 (m), 700 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (maj, s), 7.63 (min, s), 6.84 (maj, d, *J* 15.6 Hz), 6.82 (min, d, *J* 15.6 Hz), 6.07 (both, d, *J* 15.6 Hz), 5.46 (maj, d, *J* 12.2 Hz), 5.41 (min, d, *J* 12.3 Hz), 5.32 (min, d, *J* 12.3 Hz), 5.27 (maj, d, *J* 12.2 Hz), 4.52-4.37 (m), 3.91 (min, d, *J* 10.1 Hz), 3.87 (maj, d, *J* 10.0 Hz), 3.77 (maj, d, *J* 10.0 Hz), 3.72 (min, d, *J* 10.1 Hz), 3.68 (min, dt, *J* 7.2 Hz, 7.2 Hz), 3.64 (maj, dt, *J* 7.1 Hz, 7.1 Hz), 3.51 (maj, dt, *J* 7.6 Hz, 7.6 Hz), 3.47 (min, dt, *J* 7.6 Hz, 7.6 Hz), 2.69 (both, br s), 2.02-1.78 (m), 1.52-1.41 (m), 1.33 (min, s), 1.32 (maj, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2 (maj), 166.2 (min), 151.8 (maj), 151.8 (min), 144.3 (maj), 144.2 (min), 123.9 (min), 123.8 (maj), 120.8 (both), 72.2 (min), 72.1 (maj), 70.7 (maj), 69.0 (min), 62.6 (min), 62.0 (maj), 57.5 (min), 57.5 (maj), 50.1 (maj), 50.1 (minor), 27.1 (both), 26.2 (both), 23.6 (both); HRMS (ESI): *m/z* calcd. for $C_{13}H_{19}N_3O_6S$ $[M+H]^+$ 346.1067, found 346,1068; anal. calcd. for $C_{13}H_{19}N_3O_6S$: C, 45.21; H, 5.55; N, 12.17. Found: C, 45.06; H, 5.48; N, 12.07.

*Sulfite (**26**)*

White crystals, 65% yield; R_f 0.36 (MeOH/EtOAc 1:99); m.p. 129-130 ºC; dr: 1:1 (NMR); IR (neat) *v* 3503 (br), 3142 (w), 2970 (m), 2941 (m), 2889 (w), 2871 (w), 1713 (s), 1470 (w), 1447 (m), 1364 (m), 1342 (w), 1264 (m), 1228 (m), 1197 (s) 1150 (m), 1135 (m), 1069 (m), 1053 (m), 983 (m), 970 (m), 946 (m), 920 (m), 871 (m), 839 (w), 821 (w), 805 (w), 777 (m), 731 (m), 678 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (both, s), 5.88-5.82 (one, m), 5.81 (one, d, *J* 15.4 Hz), 5.75 (one, d, *J* 15.4 Hz), 5.70 (both, d, *J* 12.5 Hz), 5.16 (one, d, *J* 12.5 Hz), 5.15 (one, d, *J* 12.5 Hz), 4.58-4.42 (m), 4.39-4.23 (m), 4.07-4.01 (m), 3.74-3.65 (m), 3.28 (both, br s), 2.07-1.97 (m), 1.96-1.85 (m), 1.66-1.54 (m), 1.53 (both, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9 (one), 174.8 (one), 142.7 (one), 142.7 (one), 136.3 (one), 135.2 (one), 124.1 (both), 124.1 (one), 123.9 (one), 74.3 (both), 62.2 (one), 62.0 (one), 61.9 (one), 61.8 (one), 58.9 (one), 58.8 (one), 50.0 (one), 50.0 (one), 26.9 (one), 26.9 (one), 26.4 (one), 26.3 (one), 25.2 (both); HRMS (ESI): *m/z* calcd. for $C_{13}H_{19}N_3O_6S$ $[M+H]^+$ 346.1067, found 346.1073; anal. calcd. for $C_{13}H_{19}N_3O_6S$: C, 45.21; H, 5.55; N, 12.17. Found: C, 44.59; H, 5.78; N, 12.07.

*Sulfite (**28**)*

White crystals, 67% yield; R_f 0.36 (MeOH/EtOAc 1:99); m.p. 93-95 ºC; dr: 1:1 (NMR); IR (neat) *v* 3500 (m), 3151 (w), 2966 (m), 2872 (w), 1719 (s), 1676 (w), 1454 (m), 1443 (m), 1373 (m) 1278 (m), 1198 (m), 1171 (s), 1134 (m), 1075 (w), 1049 (m), 1027 (m), 978 (m), 940 (m), 925 (m), 889 (m), 854 (m), 835 (m), 788 (m), 767 (m), 736 (m), 710 (m), 670 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (one, s), 7.61 (one, s), 5.94-5.74 (m), 5.63 (one, dd, *J* 13.6 Hz, 0.4 Hz), 5.54 (one, dd, *J* 13.6 Hz, 0.4 Hz), 4.97 (one, dd, *J* 13.6 Hz, 0.4 Hz), 4.91 (one, dd, *J* 13.6 Hz, 0.4 Hz), 4.61-4.18 (m), 4.05-3.98 (m), 3.36 (both, br s), 1.99-1.62 (m), 1.46 (one, s), 1.45 (one, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1 (one), 175.0 (one), 143.7 (one), 143.7 (one), 135.4 (one), 135.3 (one), 124.1 (one), 124.0 (one), 123.8 (one), 123.6 (one), 74.1 (one), 74.1 (one), 64.6 (one), 64.6 (one), 63.0 (one), 62.2 (one), 55.7 (one), 54.6 (one), 49.5 (one), 49.5 (one), 27.4 (one), 27.3 (one), 26.0 (one), 25.9 (one), 25.8 (one), 25.8 (one); HRMS (ESI): *m/z* calcd. for $C_{13}H_{19}N_3O_6S$ $[M+H]^+$ 346.1067, found 346,1063; anal. calcd. for $C_{13}H_{19}N_3O_6S$: C, 45.21; H, 5.55; N, 12.17. Found: C, 45.56; H, 5.76; N, 11.85.

*4.17. Representative procedure for the preparation of macrocyclic malonates (**29, 31**)*

*Malonate (**29**)*

The diol **14** (55 mg, 0.13 mmol) was dissolved in anhydrous CH_2Cl_2 (9.74 mL) and anhydrous Et_3N (0.05 mL, 0.36 mmol) and DMAP (3 mg, 0.03 mmol) were added. A solution of malonyl chloride in anhydrous CH_2Cl_2 (0.18 M, 1 mL, 0.18 mmol) was added over 10 min at 20 ºC, under vigorous stirring. After stirring for 1½ hours, the reaction mixture was concentrated *in vacuo*. The residue was redissolved in EtOAc, filtered through Celite and concentrated *in vacuo*. Purification by flash column chromatography (MeOH/CH_2Cl_2 1:99) gave the malonate **29** (23 mg, 37%) as a colorless oil. R_f 0.54 (MeOH/EtOAc 1:99); IR (neat) *v* 3146 (w), 2956 (m), 2872 (w), 2838 (w), 1751 (s), 1733 (s), 1715 (s), 1656 (w), 1613 (m), 1586 (w), 1514 (m), 1463 (m), 1443 (m), 1409 (w), 1385 (m), 1364 (m), 1300 (m), 1247 (s), 1172 (m), 1146 (m), 1130 (m), 1030 (m), 993 (m), 911 (m), 822 (m), 727 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (1H, s), 7.24 (2H, d, *J* 8.7 Hz), 6.91 (1H, d, *J* 16.0 Hz), 6.87 (2H, d, *J* 8.7 Hz), 6.04 (1H, d, *J* 16.0 Hz), 5.36 (1H, d, *J* 12.7 Hz), 5.21 (1H, d, *J* 12.7 Hz), 4.46 (2H, t, *J* 6.4 Hz), 4.42 (1H, d, *J* 10.5 Hz), 4.36 (1H, d, *J* 10.5 Hz), 4.29 (1H, d, *J* 11.1 Hz), 4.22 (1H, d, *J* 11.1 Hz), 4.28-4.13 (2H, m), 3.80 (3H, s), 3.48 (1H, d, *J* 16.3 Hz), 3.42 (1H, d, *J* 16.3 Hz), 2.05-1.89 (2H, m), 1.67-1.59 (2H, m), 1.45 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 165.9, 165.9, 159.3, 149.3, 143.0, 130.3, 129.0 (2C), 124.0, 122.4, 114.0 (2C), 76.1, 69.5, 65.2, 63.0, 59.1, 55.4, 49.5, 41.2, 27.0, 25.5, 20.6.

*Malonate (**31**)*

White crystals, 34% yield; m.p. 113-115 ºC; R_f 0.54 (MeOH/EtOAc 1:99); IR(neat) *v* 3153 (w), 3064 (w), 3039 (w), 2998 (w), 2944 (m), 2916 (w), 2872 (m), 2842 (w), 1747 (s), 1726 (s), 1712 (s), 1657 (m), 1611 (m), 1587 (w), 1514 (m), 1465 (w), 1449 (m), 1413 (w), 1383 (m), 1324 (m), 1300 (m), 1283 (m), 1265 (m), 1249 (m), 1220 (m), 1179 (s), 1149 (m), 1135 (m), 1122 (m), 1059 (m), 1027 (s) 976 (m), 928 (m), 847 (m), 821 (m), 803 (m), 788 (m), 757 (m), 742 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (1H, s), 7.24 (2H, d, *J* 8.5 Hz), 6.94 (1H, d, *J* 16.0 Hz), 6.87 (2H, d, *J* 8.5 Hz), 6.08 (1H, d, *J* 16.0 Hz), 5.38 (1H, d, *J* 12.8 Hz), 5.35 (1H, d, *J* 12.8 Hz), 4.48-4.43 (2H, m), 4.42 (1H, d, *J* 10.7 Hz), 4.37 (1H, d, *J* 10.7 Hz), 4.27 (1H, d, *J* 11.2 Hz), 4.15 (1H, d, *J* 11.2 Hz), 4.00-3.90 (2H, m), 3.80 (3H, s), 3.34 (1H, d, *J* 15.9 Hz), 3.30 (1H, d, *J* 15.9 Hz), 1.96-1.91 (2H, m), 1.54-1.47 (2H, m), 1.44 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 166.1, 165.7, 159.3, 149.4, 148.6, 130.3, 129.0 (2C), 124.2, 122.5, 113.9 (2C), 76.3, 69.5, 65.2, 64.2, 58.1, 55.4, 49.6, 41.3, 26.1, 25.3, 20.2.

*4.18. Representative procedure for the preparation of deprotected macrocyclic malonates (**30, 32**)*

*Malonate (**30**)*

The malonate **29** (100 mg, 0.21 mmol) was dissolved in CH_2Cl_2 (19.5 mL) and water (1.1 mL). DDQ (56 mg, 0.25 mmol) was added, and the mixture was stirred at 20 ºC for 5½ hours. Then the mixture was diluted with EtOAc (100 mL) and washed with 40% aqueous $NaHSO_3$ (120 mL) and water (2×80 mL). The aqueous phase was extracted with EtOAc (120 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified twice by flash column chromatography (EtOAc/toluene 1:1) to give the deprotected malonate **30** (59 mg, 78%) as a colorless oil. R_f 0.38 (MeOH/EtOAc 1:99); IR (neat) *v* 3468 (br), 3148 (w), 2958 (m), 1713 (s), 1658 (m), 1444 (m), 1373 (m), 1328 (m), 1264 (s), 1182 (m), 1136 (s), 1046 (m), 1024 (m), 979 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (1H, s), 6.92 (1H, d, *J* 15.7 Hz), 6.04 (1H, d, *J* 15.7 Hz), 5.44 (1H, d, *J* 12.6 Hz), 5.17 (1H, d, *J* 12.6 Hz), 4.48 (1H, d, *J* 10.9 Hz), 4.46 (2H, t, *J* 6.4 Hz), 4.42 (1H, m), 4.03 (1H, d, *J* 10.9 Hz), 4.02 (1H, m), 3.48 (1H, d, *J* 17.5 Hz), 3.45 (1H, d, *J* 17.5 Hz), 2.13 (1H, m), 2.04 (1H, m), 1.73 (1H, m), 1.57 (1H, m), 1.36 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 166.1, 165.7, 151.5, 142.5, 124.6, 120.2, 72.2, 71.1, 63.2, 59.1, 49.5, 41.1, 26.9, 25.1, 23.6; HRMS (ESI): *m/z* calcd. for $C_{16}H_{21}N_3O_7$ $[M+H]^+$ 368.1452, found 368.1449; anal. calcd. for $C_{16}H_{21}N_3O_7$: C, 52.31; H, 5.76; N, 11.44. Found: C, 52.23; H, 5.71; N, 11.40.

*Malonate (**32**)*

White crystals, 69% yield; m.p. 105-106 ºC; R_f 0.38 (MeOH/EtOAc 1:99); IR (neat) *v* 3308 (br), 3156 (w), 2986 (w), 2968 (m), 2941 (w), 2873 (w), 1727 (s), 1711 (s), 1650 (w), 1462 (w), 1447 (w), 1422 (w), 1376 (w), 1351 (m), 1324 (m), 1295 (m), 1259 (m), 1239 (m), 1224 (m), 1169 (m), 1075 (m), 1065 (m), 1030 (m), 1007 (m), 981 (m), 841 (m), 782 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (1H, s), 6.96 (1H, d, *J* 15.7 Hz), 6.10 (1H, d, *J* 15.7 Hz), 5.39 (1H, d, *J* 12.6 Hz), 5.33 (1H, d, *J* 12.6 Hz), 4.49-4.40 (2H, m), 4.24 (1H, d, *J* 11.2 Hz), 4.17 (1H, d, *J* 11.2 Hz), 3.92 (2H, t, *J* 7.3 Hz), 3.35 (1H, d, *J* 16.4 Hz), 3.32 (1H, d, *J* 16.4 Hz), 1.96-1.90 (2H, m), 1.52-1.45 (2H, m), 1.35 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 166.1, 165.9, 151.4, 143.8, 124.2, 120.4, 72.3, 71.4, 64.3, 57.8, 49.7, 41.2, 25.9, 25.4, 24.1; HRMS (ESI): *m/z* calcd. for $C_{16}H_{21}N_3O_7$ $[M+H]^+$ 368.1452, found 368,1450; anal. calcd. for $C_{16}H_{21}N_3O_7$: C, 52.31; H, 5.76; N, 11.44. Found: C, 52.18; H, 5.74; N, 11.29.

*4.19. Representative procedure for the preparation of dialdehydes (**33, 35, 39**)*

*(±)-(E)-4-(4-Formyl-1H-1,2,3-triazol-1-yl)butyl 2-(4-methoxybenzyloxy)-2-methyl-5-oxopent-3-enoate (**39**)*

The diol **20** (51 mg, 0.12 mmol) was dissolved in CH_3CN (2.1 mL). IBX[21] (202 mg, 0.72 mmol) was added, and the suspension was heated to 55 ºC. After stirring at 55 ºC for 3½ hours, the suspension was concentrated *in vacuo*. The residue was redissolved in ether, filtered and concentrated *in vacuo* giving the dialdehyde **39** (50 mg, quantitative yield) as a colorless oil. R_f 0.46 (MeOH/CH_2Cl_2 5:95); IR (neat) *v* 3133 (w), 2960 (m), 2937 (m), 2872 (m), 2837 (m), 1733 (s), 1688 (s), 1612 (m), 1531 (m), 1513 (s), 1463 (m), 1443 (m), 1384 (m), 1301 (m), 1245 (s), 1174 (m), 1110 (s), 1092 (s), 1028 (s), 979 (m), 822 (m), 782 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.13 (1H, s), 9.62 (1H, d, *J* 7.7 Hz), 8.02 (1H, s), 7.27 (2H, d, *J* 8.5 Hz), 6.99 (1H, d, *J* 15.9 Hz), 6.87 (2H, d, *J* 8.5 Hz), 6.43 (1H, dd, *J* 15.9 Hz, 7.7 Hz), 4.44 (2H, s), 4.43 (2H, t, *J* 7.1 Hz), 4.23 (2H, t, *J* 6.3 Hz), 3.80 (3H, s), 2.07-1.97 (2H, m), 1.77-1.70 (2H, m), 1.67 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.2, 185.1, 171.3, 159.4, 155.1, 147.9, 132.3, 129.6, 129.1 (2C), 125.3, 113.9 (2C), 80.3, 67.4, 64.9, 55.4, 50.2, 26.9, 25.5, 23.6.

*(±)-(E)-(1-(4-Oxobutyl)-1H-1,2,3-triazol-4-yl)methyl 2-(4-methoxybenzyloxy)-2-methyl-5-oxopent-3-enoate (**35**)*

Colorless oil, 98% yield; R_f 0.35 (MeOH/CH_2Cl_2 5:95); IR (neat) *v* 3143 (w), 2957 (m), 2938 (m), 2837 (m), 2733 (w), 1723 (s), 1688 (s), 1613 (m), 1514 (s), 1461 (m), 1443 (m), 1386 (m), 1302 (m), 1247 (s), 1175 (m), 1106 (s), 1048 (m), 1028 (m), 979 (m), 913 (m), 821 (m), 729 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (1H, s), 9.58 (1H, d, *J* 7.8 Hz), 7.58 (1H, s), 7.25 (2H, d, *J* 8.6 Hz), 6.99 (1H, d, *J* 15.9 Hz), 6.86 (2H, d, *J* 8.6 Hz), 6.38 (1H, dd, *J* 15.9 Hz, 7.8 Hz), 5.37 (1H, d, *J* 13.2 Hz), 5.32 (1H, d, *J* 13.2 Hz), 4.44-4.37 (4H, m), 3.80 (3H, s), 2.52 (2H, t, *J* 6.8 Hz), 2.24-2.15 (2H, m), 1.66 (3H, s); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 200.3, 193.2, 171.3, 159.4, 155.1, 142.3, 132.2, 129.6, 129.4 (2C), 124.1, 113.9 (2C), 80.2, 67.5, 58.9, 55.4, 49.4, 40.2, 23.8, 22.7.

*(±)-(E)-4-(4-Formyl-1H-1,2,3-triazol-1-yl)butyl 4-(4-methoxybenzyloxy)-4-methyl-5-oxopent-2-enoate (**33**)*

Colorless oil, quantitative yield; R_f 0.55 (MeOH/EtOAc 1:99); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.15 (1H, s), 9.51 (1H, s), 8.11 (1H, s), 7.29 (2H, d, *J* 8.8 Hz), 6.90 (2H, d, *J* 8.8 Hz), 6.87 (1H, d, *J* 15.9 Hz), 6.20 (1H, d, *J* 15.9 Hz), 4.51-4.45 (4H, m), 4.20 (2H, t, *J* 6.3 Hz), 3.81 (3H, s), 2.11-2.01 (2H, m), 1.77-1.68 (2H, m), 1.52 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 185.3, 165.6, 159.6, 148.0, 145.0, 129.6, 129.4 (2C), 125.2, 123.7, 114.1 (2C), 83.3, 66.8, 63.6, 55.4, 50.4, 27.0, 25.7, 19.6.

*4.20. Representative procedure for the preparation of macrocyclic amines (**34**, **36**, **40**)*

*Amine (**40**)*

The dialdehyde **39** (43 mg, 0.10 mmol) was dissolved in anhydrous CH_2Cl_2 (6.9 mL). The mixture was cooled to 0 ºC, and a solution of veratrylamine in anhydrous CH_2Cl_2 (0.11 M, 1 mL, 0.11 mmol) was added. After stirring at 0 ºC for 25 min, $Na(OAc)_3BH$ (65 mg, 0.31 mmol) was added. After stirring at 0 ºC for further 15 minutes, powdered 3 Å molecular sieves (40 mg) were added. The suspension was then stirred at 0 ºC for 3 h, whereafter it was quenched with ether (10 mL) and then water (20 mL). After filtration, the mixture was transferred to a separatory funnel with ether (40 mL) and CH_2Cl_2 (20 mL). The organic phase was isolated and washed with a mixture of sat. aq. $NaHCO_3$ (40 mL) and water (20 mL). The aqueous phase was extracted with CH_2Cl_2 (2×30 mL) and ether (30 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc/heptane 3:1) gave the azalide **40** (34 mg, 60%) as an amorphous solid. R_f 0.30 (MeOH/CH_2Cl_2 5:95); IR (neat) *ν* 3134 (w), 3034 (m), 2996 (m), 2934 (m), 2872 (m), 2834 (m), 1730 (s), 1612 (m), 1589 (m), 1512 (s), 1453 (m), 1418 (m), 1367 (m), 1329 (m), 1301 (m), 1244 (s), 1175 (m), 1108 (s), 1025 (s), 980 (m), 943 (m), 893 (m), 853 (m), 810 (m), 764 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, s), 7.27 (2H, d, *J* 8.8 Hz), 6.96 (1H, s), 6.89 (1H, d, *J* 8.2 Hz), 6.85 (2H, d, *J* 8.8 Hz), 6.79 (1H, d, *J* 8.2 Hz), 5.77 (1H, d, *J* 15.7 Hz), 5.64 (1H, dt, *J* 15.7 Hz, 4.9 Hz), 4.43 (1H, d, *J* 10.6 Hz), 4.41-4.36 (2H, m), 4.31 (1H, d, *J* 10.6 Hz), 4.26-4.11 (2H, m), 3.86 (3H, s), 3.84 (3H, s), 3.81 (2H, s), 3.79 (3H, s), 3.74 (1H, d, *J* 13.3 Hz), 3.68 (1H, d, *J* 13.3 Hz), 3.21 (2H, d, *J* 4.9 Hz), 2.10-2.01 (2H, m), 1.68-1.62 (2H, m), 1.53 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 159.2, 149.0, 148.2, 147.4, 131.7, 131.6, 131.0, 130.7, 129.3 (2C), 122.0, 121.1, 113.8 (2C), 112.1, 110.9, 80.3, 66.7, 63.4, 60.6, 56.1, 56.0, 56.0, 55.4, 50.1, 49.4, 26.6, 26.5, 22.4; HRMS (ESI): *m/z* calcd. for $C_{30}H_{38}N_4O_6$ $[M+H]^+$ 551.2864, found 551.2859.

*Amine (**36**)*

White solid, 46% yield; R_f 0.17 (MeOH/CH_2Cl_2 5:95); m.p. 141-143 ºC; IR(neat) *ν* 3129 (w), 2994 (w), 2966 (w), 2937 (m), 2915 (w), 2875 (w), 2837 (w), 2797 (m), 1718 (s), 1614 (m), 1589 (w), 1516 (s), 1452 (m), 1420 (w), 1389 (w), 1375 (w), 1328 (w), 1252 (s), 1237 (m), 1184 (m), 1160 (m), 1122 (s), 1058 (w), 1024 (m), 966 (w), 929 (w), 879 (w), 856 (w), 826 (m), 805 (m), 761 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (1H, s), 7.32 (2H, d, *J* 8.7 Hz), 6.87 (2H, d, *J* 8.7 Hz), 6.83 (1H, s), 6.76 (2H, s), 5.66 (1H, dt, *J* 15.7 Hz, 6.0 Hz), 5.49 (1H, d, *J* 12.1 Hz), 5.44 (1H, d, *J* 15.7 Hz), 5.31 (1H, d, *J* 12.1 Hz), 4.49 (1H, d, *J* 10.6 Hz), 4.41 (1H, d, *J* 10.6 Hz), 4.39-4.28 (2H, m), 3.85 (3H, s), 3.84 (3H, s), 3.80 (3H, s), 3.47 (1H, d, *J* 13.9 Hz), 3.42 (1H, d, *J* 13.9 Hz), 2.89 (2H, d, *J* 6.0 Hz), 2.15-2.09 (2H, m), 1.90-1.79 (2H, m), 1.58 (3H, s), 1.27-1.15 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 159.2, 149.0, 148.1, 142.9, 132.3, 132.3, 131.9, 130.6, 129.3 (2C), 124.7, 120.9, 113.8 (2C), 111.8, 110.8, 80.4, 66.7, 59.3, 58.0, 56.0, 56.0, 55.4, 54.8, 52.7, 50.1, 27.7, 22.7, 20.9; HRMS (ESI): *m/z* calcd. for $C_{30}H_{38}N_4O_6$ $[M+H]^+$ 551.2864, found 551.2862.

*Amine (**34**)*

9% yield; R_f 0.30 (MeOH/EtOAc 1:99); ^{1}H NMR (500 MHz, CD_3OD) δ 7.57 (1H, s), 7.18 (2H, d, *J* 8.6 Hz), 7.05 (1H, m), 6.90-6.83 (2H, m), 6.78 (2H, d, *J* 8.6 Hz), 6.65 (1H, d, *J* 16.1 Hz), 5.85 (1H, d, *J* 16.1 Hz), 4.41 (1H, d, *J* 11.0 Hz), 4.35 (1H, m), 4.28 (1H, d, *J* 11.0 Hz), 4.27 (1H, m), 4.23 (1H, m), 4.16 (1H, d, *J* 13.6 Hz), 4.08 (1H, m), 3.82 (3H, s), 3.74 (6H, s), 3.65 (1H, d, *J* 14.3 Hz), 3.57 (1H, d, *J* 13.6 Hz), 3.43 (1H, d, *J* 14.3 Hz), 3.05 (1H, d, *J* 14.2 Hz), 2.85 (1H, d, *J* 14.2 Hz), 2.10-1.97 (2H, m), 1.84-1.74 (2H, m), 1.35 (3H, s); HRMS (ESI): *m/z* calcd. for $C_{30}H_{38}N_4O_6$ $[M+H]^+$ 551.2864, found 551.2845.

*4.21. Representative procedure for the preparation of monodeprotected macrocyclic amines (**37**, **41**)*

*Amine (**37**)*

The amine **36** (15 mg, 0.027 mmol) was dissolved in CH_2Cl_2 (0.70 mL) and water (0.14 mL). DDQ (18 mg, 0.08 mmol) was added, and the reaction mixture was stirred at 20 ºC for 21 hours. Subsequently, the mixture was concentrated *in vacuo*, and the residue was purified by flash column chromatography (EtOAc/toluene 4:1 + 0.5% Et_3N) to give the monodeprotected amine **37** (8 mg, 69%) as a colorless film. R_f 0.07 (MeOH/CH_2Cl_2 5:95); ^{1}H NMR (300 MHz, CD_3OD) δ 7.94 (1H, s), 6.95 (1H, d, *J* 1.6 Hz), 6.89 (1H, d, *J* 8.2 Hz), 6.83 (1H, dd, *J* 8.2 Hz, 1.6 Hz), 5.71 (1H, ddd, *J* 15.4 Hz, 8.5 Hz, 4.4 Hz), 5.60 (1H, d, *J* 12.3 Hz), 5.44 (1H, d, *J* 15.4 Hz), 5.11 (1H, d, *J* 12.3 Hz), 4.46-4.41 (2H, m), 3.83 (3H, s), 3.81 (3H, s), 3.58 (1H, d, *J* 13.0 Hz), 3.51 (1H, d, *J* 13.0 Hz), 3.07 (1H, ddd, *J* 14.7 Hz, 4.4 Hz, 1.6 Hz), 2.85 (1H, dd, *J* 14.7 Hz, 8.5 Hz), 2.15 (2H, t, *J* 8.1 Hz), 1.90 (1H, m), 1.75 (1H, m), 1.43 (3H, s), 1.33 (1H, m), 1.07 (1H, m); HRMS (ESI): *m/z* calcd. for $C_{22}H_{30}N_4O_5$ $[M+H]^+$ 431.2289, found 431.2289.

*Amine (**41**)*

33% yield; R_f 0.10 (MeOH/CH_2Cl_2 5:95); ^{1}H NMR (500 MHz, CD_3OD) δ 7.87 (1H, s), 7.07 (1H, s), 6.94 (1H, d, *J* 8.2 Hz), 6.91 (1H, d, *J* 8.2 Hz), 5.65 (1H, d, *J* 15.6 Hz), 5.57 (1H, ddd, *J* 15.6 Hz, 6.2 Hz, 4.8 Hz), 4.47 (1H, m), 4.39 (1H, m), 4.27 (1H, m), 4.03 (1H, m), 3.85 (3H, s), 3.82 (3H, s), 3.78 (2H, d, *J* 6.9 Hz), 3.74 (2H, s), 3.25 (1H, m), 3.18 (1H, dd, *J* 15.5 Hz, 6.2 Hz), 2.04 (2H, m), 1.66 (1H, m), 1.57 (1H, m), 1.36 (3H, s); HRMS (ESI): *m/z* calcd. for $C_{22}H_{30}N_4O_5$ $[M+H]^+$ 431.2289, found 431.2281.

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Supplementary Material

Copies of NMR spectra for compounds **1-37**, **39-41**.

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Rapid synthesis of macrocycles from diol precursors

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ABSTRACT

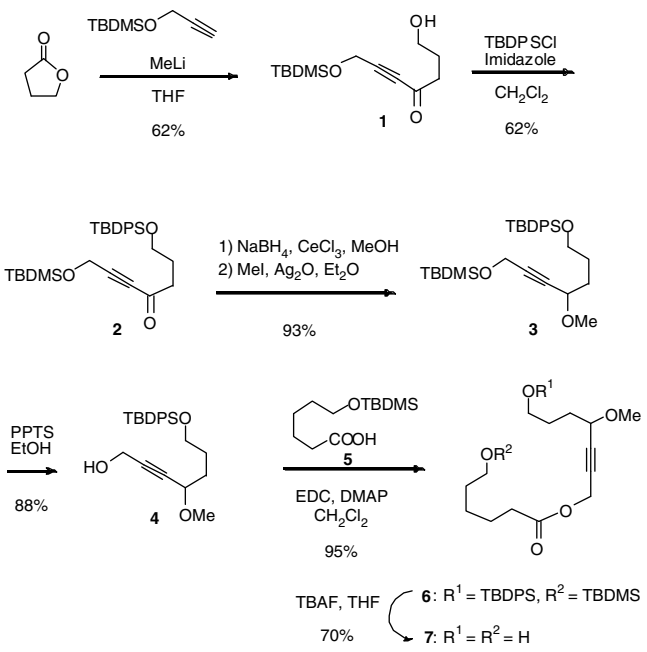
A method for the formation of synthetic macrocycles with different ring sizes from diols is presented. Reacting a simple diol precursor with electrophilic reagents leads to a cyclic carbonate, sulfite, or phosphate in a single step in 25–60% yield. Converting the cyclization precursor to a bis-electrophilic iodide or aldehyde enables preparation of a cyclic sulfide and amine, respectively, the latter using a double-reductive amination to induce ring closure.

In connection with an ongoing program to produce libraries of macrocyclic compounds from simple building blocks, we were interested in the possibility of forming large rings from bifunctional precursors.

An important challenge in forming large ring molecules is the fact that it is often necessary to tailor reaction conditions to individual substrates,[1] which can render the generation of libraries impractical. With this in mind, we decided to investigate the cyclization in one to two synthetic steps with the added potential for diversity in the ring-forming step. Our initial efforts, reported here, have been focused on using a diol and its electrophilic derivatives as cyclization precursors, and reacting them with bifunctional reagents in a single cyclization step.

In order to test different cyclization methods, we synthesized the simple precursor **7** (Scheme 1). Addition of lithium 3-(*tert*-butyldimethylsilyloxy)propynide to γ-butyrolactone followed by TBDPS protection of the resulting alcohol afforded the acetylenic ketone **2**. Reduction of the alkynone[2] followed by neutral methylation[3] gave **3**, which could be selectively monodeprotected by acidic solvolysis. Esterification with the known[4] acid **5** and deprotection with TBAF yielded the desired diol **7**.

Our first macrocyclic target was the carbonate **8** (Scheme 2 and Table 1). Treatment of the precursor **7** with carbonyl diimidazole (entry 1) or phosgene,[5] either as a solution (entry 2) or prepared in situ from triphosgene (entries 3 and 4), all resulted in no or low conversion. Using *p*-nitrophenyl chlorocarbonate (PNPCC) with DMAP as the base led to a 19% yield of **8** by NMR (entry 6), and enabled isolation of the desired product. Optimized conditions called for slow addition of separate solutions of DMAP and the car-



Scheme 1. Synthesis of the cyclization precursor.

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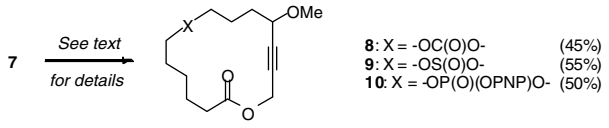


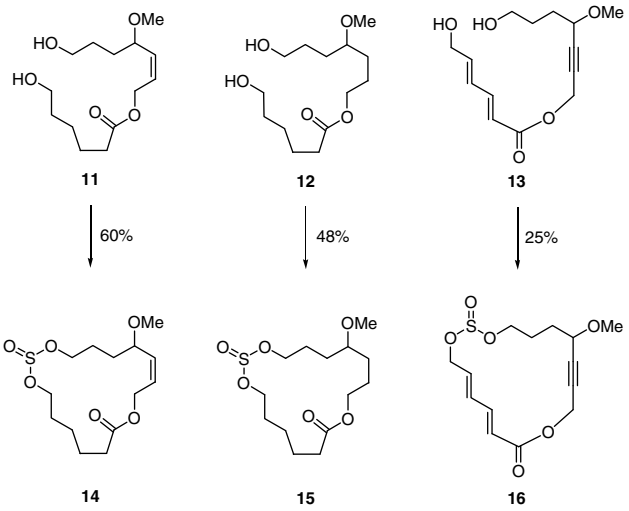
Scheme 2. Formation of macrocycles from diol precursors.

bonate to a methylene chloride solution of the diol over 24 h with a final concentration of 25 mM (entry 7). This protocol gave the desired product in 45% yield. By-products were of an oligomeric nature; we did not isolate any larger cyclic structures in any of the experiments.

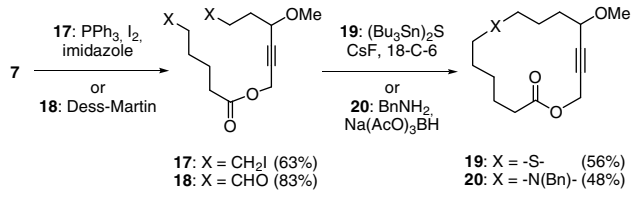
Encouraged by the results of the one-pot approach to the carbonate, we next prepared a cyclic sulfite.[6] Dropwise addition of thionyl chloride to a 10 mM solution of **7**, triethylamine and DMAP in methylene chloride led to the isolation of cyclic sulfite **9** in 55% yield as a 1:1 mixture of inseparable diastereoisomers. Similarly, we were able to prepare the macrocyclic phosphate **10** by reaction with *p*-nitrophenyl phosphorodichloridate ($PNPOPOCl_2$) in 50% yield.

Due to the large influence of the conformations of the precursors on macrocyclizations,[7] it was important to test other substrates under the standard conditions for cyclization. To elucidate whether the approach was general, we studied the formation of cyclic sulfites from other diols (Scheme 3).[8] Gratifyingly, partial (substrate **11**) or full (precursor **12**) reduction of the triple bond did not negatively affect the yield of the cyclization under our standard conditions in a significant manner. On the other hand, combining **4** with a sorbic acid derivative to form precursor **13** did result in a decreased yield for the cyclization—perhaps not surprising, considering that the resulting 17-membered macrocycle **16** contains 5 sp^2 and 2 sp-hybridized carbon atoms. Substrates that cyclize reluctantly under these conditions generally led to oligomers or eventually conversion of the alcohols into chlorides, which was also the case for the reaction of **13**. Overall, we were pleased that identical conditions led to a reasonable isolated yield for all the cyclizations without the need for optimization of the individual reactions.

To investigate the potential of macrocyclizations involving reactions with nucleophiles, we prepared two bis-electrophilic derivatives of **7**, the diiodide **17** and the dialdehyde **18** (Scheme 4). Reaction of **17** with sodium or lithium sulfide in a range of solvents did not afford the desired product. However, using the organic sulfide equivalent bis(tributyltin)sulfide in the presence of CsF and 18-crown-6[9] led to the isolation of the 15-membered



Scheme 3. 17-Membered cyclic sulfites.



Scheme 4. Electrophilic precursors and their reactions with nucleophiles.

cyclic sulfide **19** in 56% yield. To the best of our knowledge, the use of double-reductive amination of dialdehydes with a monoamine to prepare macrocyclic compounds has never been reported.[10] It was therefore with great pleasure we noted that benzylamine reacted with **18** in the presence of sodium triacetoxyborohydride to give the product **20**, proving that cyclization is also feasible when nucleophilic reagents are reacted with bis-electrophiles.

In conclusion, we have demonstrated that a simple diol and its electrophilic derivatives can serve as precursors for cyclic molecules formed in a single step under standard conditions. We believe that this method will help gain easy access to large ring

Table 1
Conditions for the formation of cyclic carbonate **8** from diol **7**

Entry	CDI[a] (equiv)	$COCl_2$ (equiv)	Triphosgene (equiv)	PNPCC[b] (equiv)	Pyridine (equiv)	Et_3N (equiv)	DMAP (equiv)	Concn of **7** (mM)	Yield of **8**[c] (%)
1	1	—	—	—	—	—	0.1	10	No conv.
2[d]	—	1.2	—	—	—	1.4	0.2	10	<5
3[d]	—	—	0.5[e]	—	3	3	0.05	20	<5
4[d]	—	—	0.6[f]	—	5	—	0.05	10	<5
5	—	—	—	1.2	—	—	2.4	25	<10
6	—	—	—	1.35	—	—	2.4	12.5	19
7[g]	—	—	—	1	—	—	1.3	25	45

[a] Carbonyl diimidazole.
[b] *p*-Nitrophenyl chlorocarbonate.
[c] Determined by ^1H NMR of the crude after aqueous work-up.
[d] Reagents added at −78 °C.
[e] 0.05 equiv of LiCl added.
[f] 0.02 equiv of Aliquot 336 added.
[g] Separate CH_2Cl_2 solutions of DMAP and PNPCC added over 24 h.

molecules, and we are currently pursuing libraries of macrocycles based on this strategy.

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Supplementary data

Supplementary data (experimental procedures, characterization data and copies of NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.100.

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