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Catalytic Enantioselective Synthesis of Tetrahydocarbazoles and *Exocyclic* Pictet-Spengler-Type Reactions

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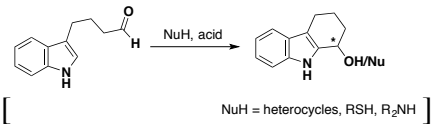
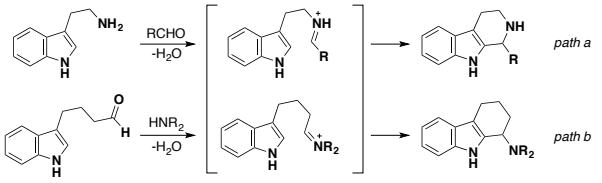
Supporting Information Placeholder



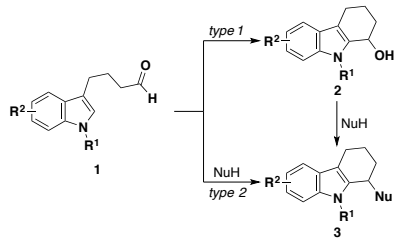
ABSTRACT: A synthetic strategy for the synthesis of chiral tetrahydrocarbazoles (THCAs) has been developed. The strategy relies on two types of 6-*exo-trig* cyclization of 3-substituted indole substrates. Enantioselective domino Friedel-Crafts-type reactions leading to THCAs can be catalyzed by chiral phosphoric acid derivatives (with up to >99% *ee*), and the first examples of exocyclic Pictet-Spengler reactions to form THCAs are reported.

The classical Pictet-Spengler reaction, in which an amine is condensed with an aldehyde to form a six-membered *N*-heterocycle via an iminium intermediate (**Figure 1**, *path a*, 6-*endo-trig*) is a robust and well-established process.[1,2,3] However, to our knowledge, an exocyclic version of this reaction has not yet been reported to give the pharmaceutically interesting indole-containing tetrahydrocarbazole (THCA) skeleton (**Figure 1**, *path b*, 6-*exo-trig*),[4] probably due to the instability of the starting aldehyde.[5]

Figure 1. The classical Pictet-Spengler reaction (*path a*) and the exocyclic Pictet-Spenger reaction (*path b*).

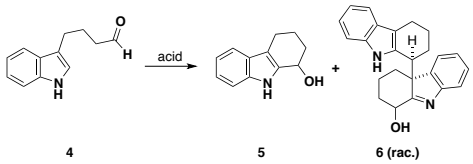


This paper describes the development of exocyclic Pictet-Spengler reactions and related cyclizations, including a highly enantioselective route to 1-substituted THCAs. Our overall plan was to trigger two types of 6-*exo* cyclization using the same starting aldehyde (**1**) (Scheme 1): direct cyclization providing hydroxyl-containing THCAs (**2**) (*type 1*), and cyclization in the presence of external nucleophiles (*type 2*), including the exocyclic Pictet-Spengler reaction. Furthermore, we reasoned that it should be possible to convert **2** to **3** by reaction with external nucleophiles, and we envisioned enantioselective versions of all these processes.



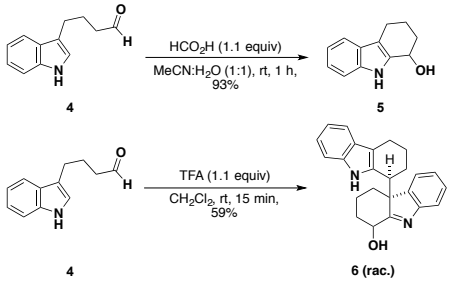
Scheme 1. Strategy for the synthesis of THCAs.

Initial investigations focused on the "*type 1*" conversion of **4** to THCA **5** but, surprisingly, formation of compound **6** (Scheme 2, see also the ESI for a full account of reaction optimization) was observed in most cases. Generally, strong Brønsted and Lewis acids provided **6**; however the use of formic acid in acetonitrile:water (1:1) provided a clean conversion to the desired THCA **5** in excellent yield (93%, Scheme 3).



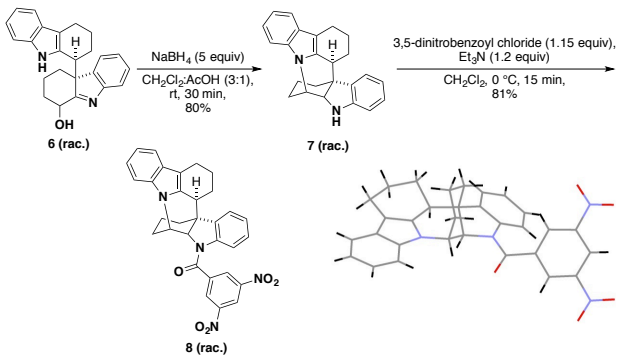
Scheme 2. Cyclization of aldehyde 4.

Compound **6** could be obtained in reasonably good yield when **4** was treated with TFA (59%, Scheme 3). The formation of **6** is accompanied by the formation of 3 stereocenters, of which two are formed in a highly diastereoselective fashion (as evidenced by the crystal structure of **8**, Scheme 4). As an indication of the reactivity of **4**, the formation of **5** and **6** was observed simply upon storage of the aldehyde at ambient temperature.



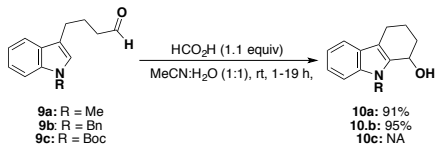
Scheme 3. Selective cyclizations of aldehyde 4.

To confirm the structure of **6**, the imine was reduced to the corresponding amine (Scheme 4). However, NMR analysis indicated occurrence of an additional reaction, involving the indole nitrogen, giving compound **7** in 80% yield. The structure of **7** was confirmed after acylation with 3,5-dinitrobenzoyl chloride to give **8** as a single diasteromer. The crystal structure of **8** is shown in Scheme 4.



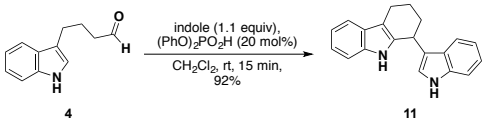
Scheme 4. Validation of the structure of 6 and crystal structure of 8.

Not unexpectedly, the ease of the "*type 1*" cyclization was very dependent on the electronic properties of the indole (Scheme 5). The electron-rich indoles **9a** and **9b** gave the desired products (**10a** and **10b**) in superb yields (91 – 95%), while for the less nucleophilic **9c** no conversion was observed, even at elevated temperatures. Notably, when the aldehyde functionality was changed to a ketone, no conversion was observed for any of the substrates.



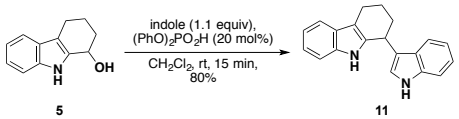
Scheme 5. "*Type 1*" cyclization to THCAs.

The formation of compound **6** indicated that a "*type 2*" reaction (cf. **Figure 1**) should also be possible. Aldehyde **4** was therefore reacted with indole as external nucleophile in the present of catalytic amounts of diphenyl phosphate and the desired THCA **11** was isolated in excellent yield (92%).



Scheme 6. "*Type 2*" cyclization to THCAs.

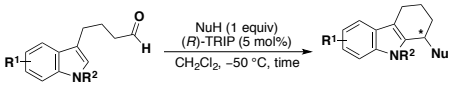
Careful monitoring of these reactions via both TLC and LC/MS indicated that the cyclization did indeed occur first, followed by external nucleophilic attack, in a domino Friedel-Crafts type of process.[6,7] Furthermore, alcohol **5** could be converted to **11** upon reaction with indole and diphenyl phosphate in CH_2Cl_2 in 80% yield (Scheme 7), thus validating the overall strategy outlined in Scheme 1.



Scheme 7. Conversion of a "*type 1*" product into a "*type 2*" product.

We then addressed the question of enantioselectivity by using chiral phosphoric acids[8,9] to catalyze the "*type 2*" cyclization. After preliminary screening experiments, reaction conditions were optimized for the use of (*R*)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate ((*R*)-TRIP) in CH_2Cl_2 at −50 °C.[10] When aldehyde **4** was exposed to a range of external nucleophiles, the desired products were obtained only with electron-rich heterocycles and thiols (Table 1). Attempted reactions with poorer carbon nucleophiles such as furan and trimethoxybenzene, as well as with alcohols, gave no conversion to the desired products. As shown in Table 1 (entries 1 – 10) the substitution pattern and the steric bulk of the external indole nucleophile had considerable impact on both the yields (35 – 74%) and the enantioselectivity (11 – 94% *ee*). For example, the highest enantioselectivity (94 % *ee*) was obtained using 2-*tert*-butyl-indole, which can be compared with the 2-methyl analog (25% *ee*), the isolated yields being comparable (Table 1, entries 2 and 3). The substituent pattern of the aldehyde (**9b**, **12a-d**) also proved highly important, as the products **13k-o** were isolated in moderate to excellent yields (35 – 94%, generally >78%) and with low to moderately high *ee* (6 – 78%, Table 1, entries, 11 – 15).

Table 1. Enantioselective synthesis of THCAs via domino *"type 2"* cyclization/Friedel-Crafts-type reactions.



4, 12a-e 13a-t

Entry	Substrate	R^1	R^2	NuH	Time [h]	Product, yield (%)[a]	ee (%)[b]
1	**4**	H	H	indole	4	**13a**, 74	54
2	**4**	H	H	2-methylindole	5	**13b**, 64	25
3	**4**	H	H	2-tert-butyl-indole	22	**13c**, 54	94
4	**4**	H	H	3-methylindole	6	**13d**, 51	26
5	**4**	H	H	4-methylindole	4	**13e**, 73	63
6	**4**	H	H	4-methoxyindole	5	**13f**, 60	43
7	**4**	H	H	5-methylindole	5	**13g**, 73	28
8	**4**	H	H	6-methylindole	10	**13h**, 71	11
9	**4**	H	H	7-methylindole	6	**13i**, 71	53
10	**4**	H	H	7-(benzyloxy)indole	9	**13j**, 35	56
11	**9b**	H	Bn	indole	8	**13k**, 53	11
12	**12a**	4-OMe	H	indole	3	**13l**, 80	28
13	**12b**	5-Br	H	indole	16	**13m**, 78	6
14	**12c**	5-F	H	indole	5	**13n**, 90	21
15	**12d**	7-Me	H	indole	4	**13o**, 94	78
16	**4**	H	H	1,2,4-triazole	48	**13p**, 44	0[c]
17	**4**	H	H	pyrazole	5	**13q**, 74	10[d]
18	**4**	H	H	indazole	4	**13r**, 94	11[c]
19	**4**	H	H	thiophenol	6	**13s**, 92	42
20	**4**	H	H	benzyl mercaptan	6	**13t**, 95	46

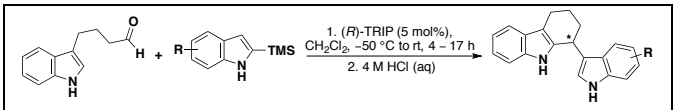
[a] Isolated yield after flash column chromatography. [b] Determined by chiral NP-HPLC. [c] Reaction carried out at -20 °C. [d] Reaction carried out at rt.

Returning to reactions of aldehyde **4**, reactions of some other heterocyclic carbon nucleophiles (Table 1, entries 16 – 18) and sulfur nucleophiles (entries 19 and 20) gave good to excellent yields (up to 95%) but generally low enantioselectivity (46% *ee* at best).

Encouraged by the excellent enantioselectivity provided by 2-*tert*-butyl-indole (Table 1, entry 3), we explored the possibility of using the removable TMS group in the 2-position of the indole nucleophile (Table 2). When aldehyde **4** was exposed to a range of readily available 2-TMS-indoles (**14a-f**), followed by removal of the TMS group, the desired products (**15a-f**) were generally isolated in excellent enantiopurity (95 to > 99% *ee*) and moderate to good yields (33 – 70%,

Table 2, entries 1 – 4). The lower *ee* for **15e** was due to racemization during the deprotection, as cyclized material of 96% *ee* was obtained prior to TMS removal. The poor yield and enantioselectivity observed for the reaction of **14f** (entry 6) can be explained by the instability of this nucleophile under the reaction conditions (e.g. desilylation was observed to occur).

Table 2. Enantioselective synthesis of THCAs using 2-TMS-indoles.



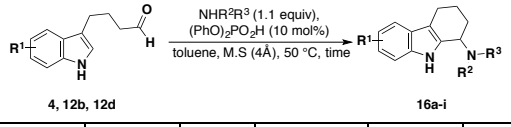
4 14a-f 15a-f

Entry	Indole	R	Product, yield (%)[a]	ee (%)[b]
1	**14a**	H	**15a**, 52	>99
2	**14b**	5-OBn	**15b**, 70	97
3	**14c**	5-Cl	**15c**, 33	97
4	**14d**	5-CF_3	**15d**, 43	95
5	**14e**	5-OCF_3	**15e**, 47	77
6	**14f**	6-CO_2Me	**15f**, 12	22

[a] Isolated yield after flash column chromatography. [b] Determined by chiral NP-HPLC. [c] Reaction temp −20 ° C

Finally, we turned our attention to the long-sought exocyclic Pictet-Spengler reaction, for which a new optimization study proved to be necessary.[10] As shown in Table 3, a variety of functional groups is tolerated, and yields are generally acceptable. Unfortunately, reactions catalyzed by (*R*)-TRIP gave only low enantioselectivity (< 10% *ee*) and a synthetically useful asymmetric version of the exocyclic Pictet-Spengler reaction remains elusive.

Table 3. Exocyclic Pictet-Spengler Reactions.



4, 12b, 12d — 16a-i

Entry	Substrate	R^1	R^2	R^3	Time [h]	Product, Yield (%)[a]
1	**4**	H	Bn	Bn	20	**16a**, 61
2	**4**	H	Bn	Allyl	20	**16b**, 62
3	**4**	H	Bn	CH_2CH_2OTBS	20	**16c**, 53
4	**4**	H	Bn	CH_2CO_2Et	2	**16d**, 77
5	**4**	H	Ph	Et	2	**16e**, 15
6	**4**	H	Ph	H	20	**16f**, 76
7	**12b**	4-Br	Bn	Bn	20	**16g**, 24
8	**12d**	7-Me	Bn	Me	74	**16h**, 43
9	**12d**	7-Me	Bn	Bn	48	**16i**, 61

[a] Isolated yield after flash column chromatography.

In conclusion, we have developed a synthetic strategy for the synthesis of chiral tetrahydrocarbazoles (THCAs) which relies on 6-e*xo*-*trig* cyclizations. Enantioselective domino Friedel-Crafts-type reactions leading to THCAs can be catalyzed by chiral phosphoric acid derivatives (with up to >99% *ee*) and the first examples of exocyclic Pictet-Spengler reactions are also described.

ASSOCIATED CONTENT

Supporting Information

Experimental details, procedures and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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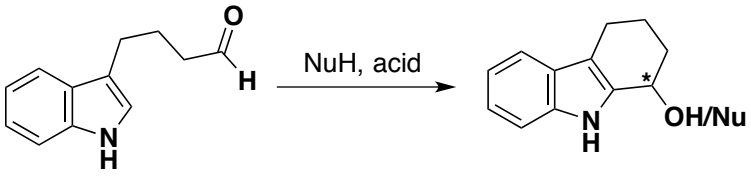

NuH = heterocycles, RSH, R_2NH