Organic LETTERS

Letter

pubs.acs.org/OrgLett

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

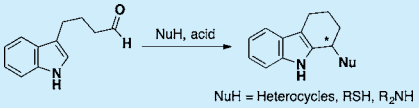
Casper L. Hansen,[†] Ragnhild G. Ohm,[†] Lasse B. Olsen,[†] Erhad Ascic,[†] David Tanner,[†] and Thomas E. Nielsen*[,†,‡]

[†]Department of Chemistry, Technical University of Denmark, DK-2800 Kgs Lyngby, Denmark

[‡]Singapore Centre on Environmental Life Sciences Engineering, Nanyang Technological University, Singapore 637551, Singapore

Supporting Information

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.[1−3] 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]

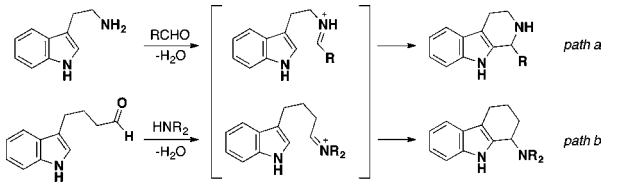
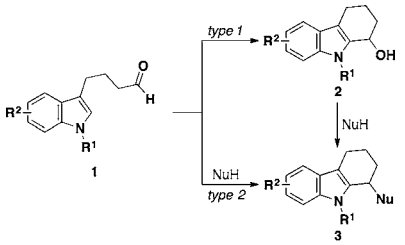


Figure 1. Classical Pictet–Spengler reaction (path a) and the exocyclic Pictet–Spenger reaction (path b).

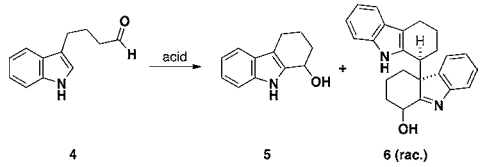
This paper describes the development of exocyclic Pictet–Spengler reactions and related cyclizations, including a highly enantioselective route to 1-substituted THCAs. Our overall plan was to trigger two types of 6-*exo* cyclization using the same starting aldehyde (**1**) (Scheme 1): direct cyclization 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.[6]

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 Supporting Information 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



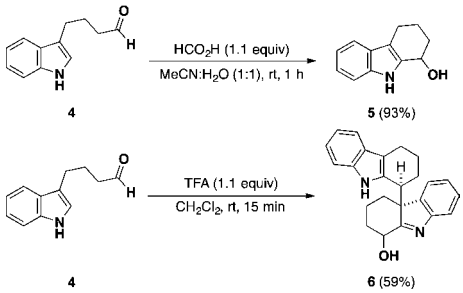
Compound **6** could be obtained in reasonably good yield when **4** was treated with trifluoroacetic acid (TFA) (59%, Scheme 3). The formation of **6** is accompanied by the formation of three stereocenters, of which two are formed in a highly diastereoselective fashion (as evidenced by the crystal 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.

To confirm the structure of **6**, the imine was reduced to the corresponding amine (Scheme 4). However, nuclear magnetic resonance (NMR) analysis indicated occurrence of an addi-

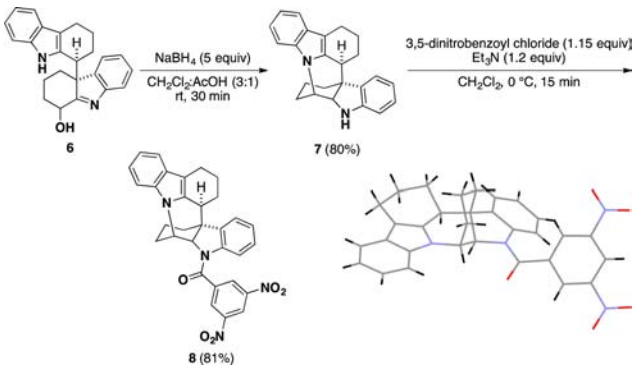
Received: September 9, 2016
Published: November 16, 2016

DOI: 10.1021/acs.orglett.6b02718
Org. Lett. 2016, 18, 5990–5993

Scheme 3. Selective Cyclizations of Aldehyde 4



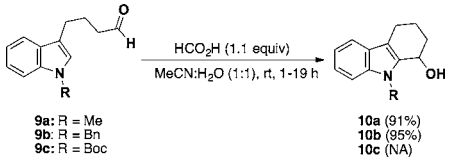
Scheme 4. Validation of the Structure of 6 and Crystal Structure of 8



tional 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 diastereomer. The crystal structure of **8** is shown in Scheme 4.

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

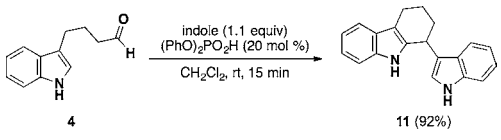
Scheme 5. Type 1 Cyclization to THCAs



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.

The formation of compound **6** indicated that a type 2 reaction (cf. Figure 1) should also be possible (Scheme 6). Aldehyde **4** was therefore reacted with indole as external nucleophile in the present of catalytic amounts of diphenyl

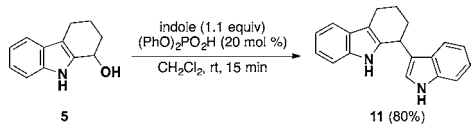
Scheme 6. Type 2 Cyclization to THCAs



phosphate, and the desired THCA **11** was isolated in excellent yield (92%).

Careful monitoring of these reactions via both thin-layer chromatography (TLC) and liquid chromatography−mass spectrometry (LC−MS) indicated that the cyclization did indeed occur first, followed by external nucleophilic attack, in a domino Friedel−Crafts type of process.[7,8] 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[9,10] 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 hydrogen phosphate ((*R*)-TRIP) in CH_2Cl_2 at −50 °C.[11] When aldehyde **4** was exposed to a range of external nucleophiles, the desired products were obtained only with electron-rich heterocycles and thiols (Scheme 8). 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 Scheme 8 (**13a−j**), 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*-butylindole, which can be compared with the 2-methyl analogue (25% ee), the isolated yields being comparable (Scheme 8, **13b−c**). 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%, Scheme 8).

Returning to reactions of aldehyde **4**, reactions of some other nucleophilic heterocycles and thiols 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*-butylindole, we explored the possibility of using the removable trimethylsilyl (TMS) group in the 2-position of the indole nucleophile (Table 1). 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 1, entries 1−4).

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 2, a variety of functional groups are 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.

DOI: 10.1021/acs.orglett.6b02718
Org. Lett. 2016, 18, 5990−5993

Scheme 8. Enantioselective Synthesis of THCAs via Domino Type 2 Cyclization/Friedel–Crafts-Type Reactions

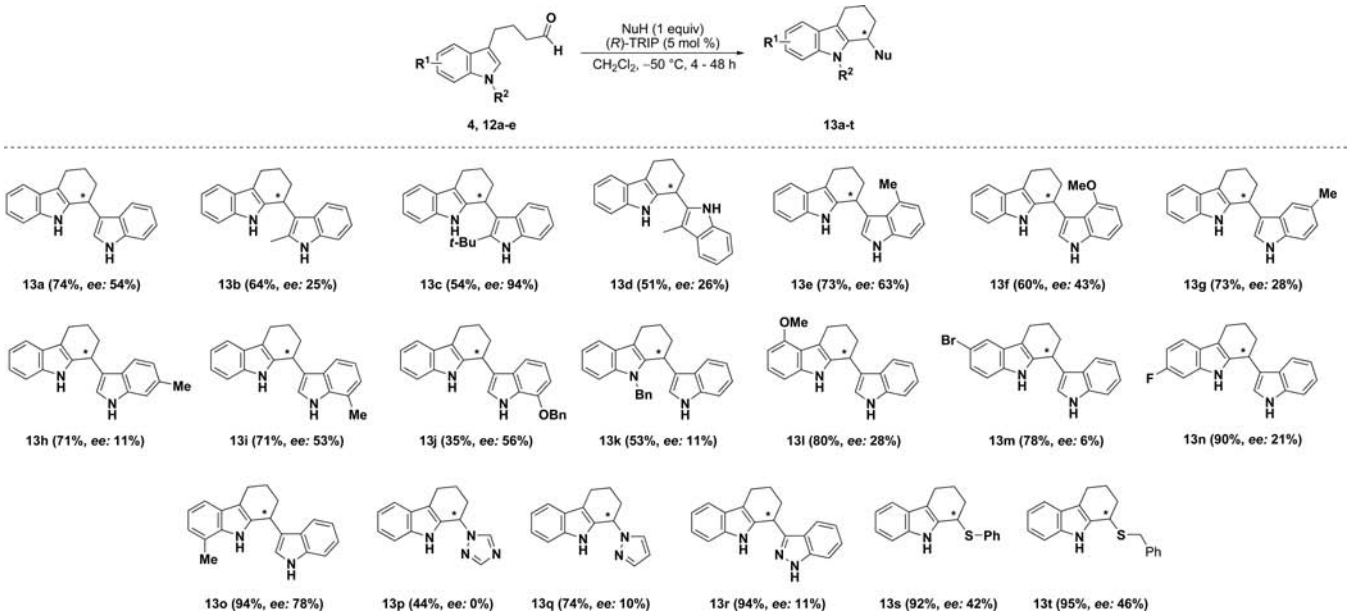
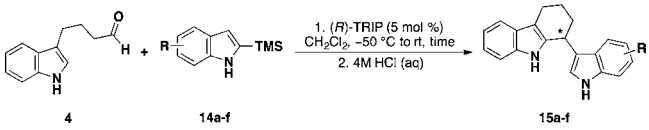


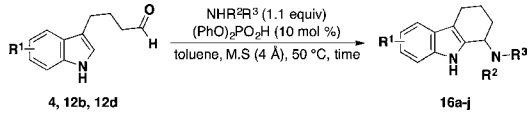
Table 1. Enantioselective Synthesis of THCAs Using 2-TMS-indoles



entry	indole	R	product, yield[a] (%)	ee[b] (%)
1[c]	**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 temperature −20 °C.

Table 2. Exocyclic Pictet–Spengler Reactions



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-*exo-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

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02718.

Experimental details, procedures, and characterization of all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ten@sund.ku.dk.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The Technical University of Denmark, the Lundbeck Foundation, and the DSF Center for Antimicrobial Research (CAR) are gratefully acknowledged for financial support.

■ REFERENCES

(1) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030–2036.

(2) For selected reviews on the Pictet–Spengler reaction, see: (a) Stöckigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 8538–8564. (b) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797–1842. (c) Nielsen, T. E.; Diness, F.; Meldal, M. *Curr. Opin. Drug. Discovery Devel.* **2003**, *6*, 801–814. (d) Laine, A. E.; Lood, C.; Koskinen, A. M. P. *Molecules* **2014**, *19*, 1544–1567.

(3) For reviews on iminium ion cyclization, see: Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628. (b) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311–2352. (c) Speckamp, W. N.; Moolenaar, M. J.

DOI: 10.1021/acs.orglett.6b02718
Org. Lett. 2016, 18, 5990–5993

Tetrahedron **2000**, *56*, 3817−3856. (d) Le Quement, S. T.; Petersen, R.; Meldal, M.; Nielsen, T. E. *Biopolymers* **2010**, *94*, 242−256.
(4) For selected reviews on THCAs, see: (a) Bergman, J.; Pelcman, B. *Pure Appl. Chem.* **1990**, *62*, 1967−1976. (b) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303−4427. (c) Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev.* **2012**, *112*, 3193−3328.
(5) Blair, L. M.; Sperry, J. *Synlett* **2013**, *24*, 1931−1936.
(6) For noteworthy examples of catalytic enantioselective Pictet−Spengler reactions, see: (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558−10559. (b) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086−1087. (c) Wanner, M. J.; van der Haas, R. N. S.; de Cuba, K. R.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7485−7847.
(7) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136.
(8) For selected reviews on the Friedel−Crafts reaction, see: (a) Sartori, G.; Maggi, R. *Chem. Rev.* **2006**, *106*, 1077−1104. (b) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903−2915. (c) Rueping, M.; Nachtsheim, B. J. *Beilstein J. Org. Chem.* **2010**, *6*, 6−29.
(9) For selected reviews on chiral phosphoric acids, see: (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999−1010. (b) You, S.-L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190−2201. (c) Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2010**, *8*, 5262−5276. (d) Schenker, S.; Zamfir, A.; Freund, M.; Tsogoeva, S. B. *Eur. J. Org. Chem.* **2011**, *2011*, 2209−2222.
(10) For recent examples of use of chiral phosphoric acids in the Friedel−Crafts reaction, see: (a) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804−11805. (b) Wang, Y.-Q.; Song, J.; Hong, R.; Li, H.; Deng, L. J. *J. Am. Chem. Soc.* **2006**, *128*, 8156−8157. (c) Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5565−5567. (d) Zhuo, M.-H.; Jiang, Y.-J.; Fan, Y.-S.; Gao, Y.; Liu, S.; Zhang, S. *Org. Lett.* **2014**, *16*, 1096−1099.
(11) See the SI for details.

DOI: 10.1021/acs.orglett.6b02718
Org. Lett. 2016, 18, 5990−5993