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An Expedient Route to the Calabar Bean Alkaloids (–)-Physovenine and (–)-Physostigmine

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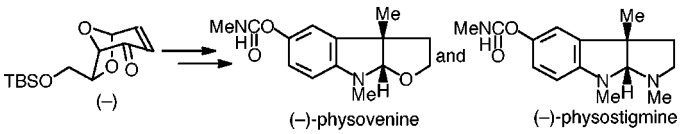
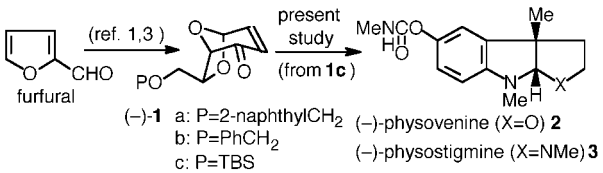
ABSTRACT



An expedient route to the Calabar bean alkaloids (–)-physovenine and (–)-physostigmine has been devised using a chiral building block which was originally designed for diastereocontrolled construction of aldohexoses.

Recently, we developed a systematic diastereo- and enantiocontrolled route to all of the eight possible aldohexoses utilizing a single common chiral block,[1,2] **1a**, containing a dioxabicyclo[3.2.1]octane framework. The block **1a** as well as its two congeners **1b**,**c** bearing different *O*-protecting groups can be obtained very efficiently from furfural in both enantiomeric forms by employing either a catalytic[1] or an enzymatic[3] procedure. The high functionality of **1** and inherent convex-face selectivity allowed enantio- and diastereocontrolled construction of all of the eight aldohexoses[2] and the sugar moiety of the antibiotic novobiocin (+)-noviose.[4] In this Letter, we report utilization of (−)-**1c** for the preparation of nonsugar molecules, the anticholinergic Calabar bean alkaloids[5] (−)-physovenine[6,7] (**2**) and (−)-physostigmine[8,9] (**3**), to extend its utility as a versatile chiral building block (Scheme 1).

Scheme 1



Enantiopure (−)-**1c**[1,3] was first converted into ketone **4**, $[\alpha]^{26}_{D}$ +20.9 (*c* 1.2, $CHCl_3$), by catalytic hydrogenation. Monomethylation of **4** was carried out with iodomethane in the presence of lithium hexamethyldisilazide (LHMDS) in THF containing hexamethylphosphoric triamide (HMPT) to give **5** as an epimeric (5:2) mixture. Refluxing the mixture with 4-methoxyphenylhydrazine hydrochloride in 90% aque-

(1) Takeuchi, M.; Taniguchi, T.; Ogasawara, K. *Synthesis* **1999**, 341.
(2) Takeuchi, M.; Taniguchi, T.; Ogasawara, K. *Chirality* **2000**, 12, 338.
(3) Taniguchi, T.; Takeuchi, M.; Kadota, K.; ElAzab, A. S.; Ogasawara, K. *Synthesis* **1999**, 1325.
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(5) For reviews of the Calabar bean alkaloids, see: (a) Marion, L. *The Alkaloids* **1952**, *2*, 438. (b) Coxworth, E. *The Alkaloids* **1967**, *10*, 383. (c) Robinson, B. *The Alkaloids* **1971**, *13*, 213. (d) Takano, S.; Ogasawara, K. *The Alkaloids* **1989**, *36*, 225.
(6) For a most recent chiral synthesis, see: Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500.
(7) For a previous chiral synthesis by the present group, see: Takano, S.; Moriya, M.; Ogasawara, K. *J. Org. Chem.* **1991**, *56*, 872.
(8) For a most recent chiral synthesis, see: Kawahara, M.; Nishida, A.; Nakagawa, M. *Org. Lett.* **2000**, *2*, 675.
(9) For previous syntheses by the present group, see: (a) Takano, S.; Goto, E.; Hirama, M.; Ogasawara, K. *Chem. Pharm. Bull.* **1982**, *30*, 2641. (b) Takano, S.; Sato, T.; Inomata, K.; Ogasawara, K. *Heterocycles* **1990**, *31*, 411. (c) Takano, S.; Moriya, M.; Iwabuchi, Y.; Ogasawara, K. *Chem. Lett.* **1990**, 109. (d) Reference 7.

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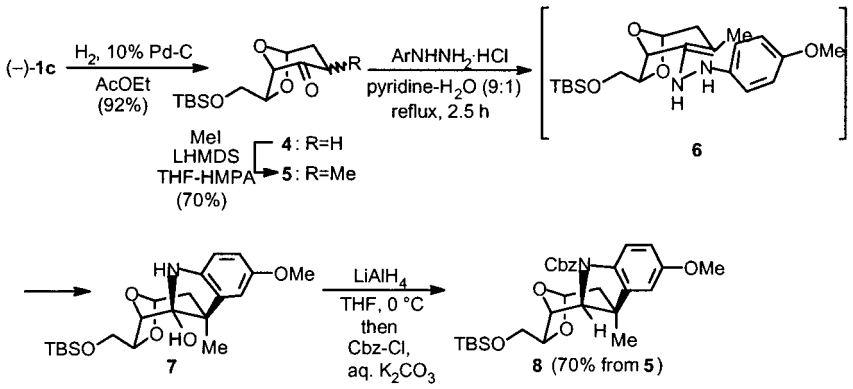
Scheme 2

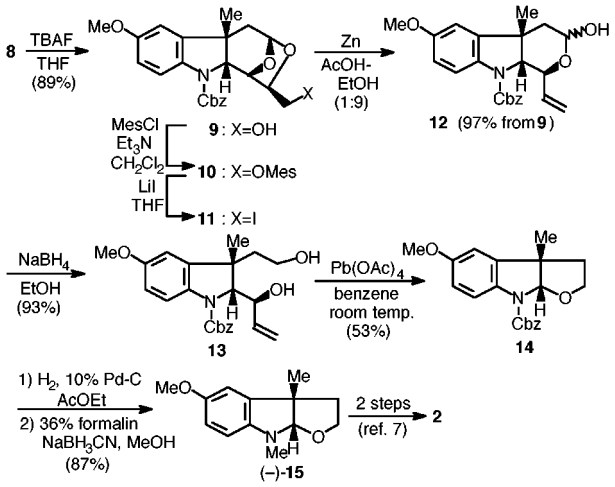


ous pyridine[7,10] led to a diastereoselective formation of the single carbinolamine **7**, $[\alpha]^{25}_D$ −104.1 (*c* 0.7, $CHCl_3$), in 70% yield without affecting the siloxy protecting group. On reduction with lithium aluminum hydride followed by alkaline workup in the presence of carbobenzoxy chloride, **7** furnished the indoline *N*-carbamate **8**, $[\alpha]^{26}_D$ +1.5 (*c* 1.2, $CHCl_3$), as a single diastereomer. The overall yield of **8** from (−)-**1** was 45% in four steps. Although the stereochemistry of **8** could not be determined at this stage, the key Fischer indolization sequence involving a [3.3]-sigmatropic rearrangement was confirmed to proceed diastereoselectively from the convex-face through diaza-1,5-diene intermediate **6** by acquisition of the known tricyclic aminoacetal[7] (−)-**15** at a later stage (Scheme 2).

Employing the same technology as that developed in the sugar synthesis,[1,2] the acetal functionality in **8** was next cleaved in a sequence of four reactions. Thus, alcohol **9**, $[\alpha]^{26}_D$ +22.9 (*c* 1.0, $CHCl_3$), obtained from **8** by desilylation, was transformed sequentially, under standard conditions, into mesylate **10**, $[\alpha]^{26}_D$ +12.7 (*c* 1.1,$CHCl_3$), and iodide **11**, $[\alpha]^{25}_D$ −45.8 (*c* 1.0, $CHCl_3$), which was exposed to zinc in hot ethanol containing acetic acid to initiate reductive cleavage of the internal acetal linkage to give rise to vinylhemiacetal **12** as an epimeric mixture. The overall yield of **12** from **8** was 86%. The mixture **12** was used as the common intermediate for both (−)-physovenine (**2**) and (−)-physostigmine (**3**).

To obtain (−)-physovenine (**2**), **12** was first reduced with sodium borohydride to give the diol **13**, $[\alpha]^{30}_D$ +28.5 (*c* 0.4, $CHCl_3$). After extensive examination, it was found that the removal of an extra three-carbon moiety from **13** was best carried out in one step with lead(IV) acetate.[11] Thus, on exposure to 3 equiv of lead(IV) acetate in benzene at room temperature, **13** afforded tricyclic carbamate **14**, $[\alpha]^{24}_D$ −45.2 (*c* 0.4, $CHCl_3$), in 53% yield by concurrent oxidative removal of the three-carbon allylic alcohol moiety and cyclization. Since an attempted one-step conversion of **14** into the known tricyclic *N*-methyl aminoacetal[7] **15** under catalytic hydrogenolysis conditions in the presence of formalin[12] brought about concurrent hydrogenolysis of the aminoacetal functionality, **14** was first converted into the secondary amine **14** (Cbz = H), $[\alpha]^{24}_D$ −120.7 (*c* 0.4, $CHCl_3$), under standard palladium-mediated hydrogenolysis conditions, which then was treated with formalin in the presence of sodium cyanoborohydride to give **15**, $[\alpha]^{28}_D$ −94.9 (*c* 0.4, $CHCl_3$) [lit.[7] $[\alpha]^{32}_D$ −96 (*c* 0.35, $CHCl_3$)]. At this point it was confirmed that the key Fischer indolization had occurred diastereoselectively from the convex-face of the intermediate **6** as anticipated. The overall yield of the *N*-methylaminoacetal (−)-**15** from **12** was 43% in four steps. Since the aminoacetal (−)-**15** has been transformed into (−)-physovenine (**2**) in two steps,[7] the present acquisition of (−)-**15** constitutes a formal synthesis of the alkaloid (Scheme 3).

Scheme 3



To obtain (−)-physostigmine (**3**), **12** was first heated with methylamine hydrochloride in methanol in a sealed tube in the presence of sodium cyanoborohydride at 90 °C for 12 h to afford the *N*-methylaminoalcohol **16**, $[\alpha]^{26}_D$ +10.5 (*c* 0.5, $CHCl_3$), which was converted into the bis-carbamate **17**,

(10) Welch, W. M. *Synthesis* **1977**, 645.
(11) Suginome, H.; Umeda, H.; Masamune, T. *Tetrahedron Lett.* **1970**, 4571.
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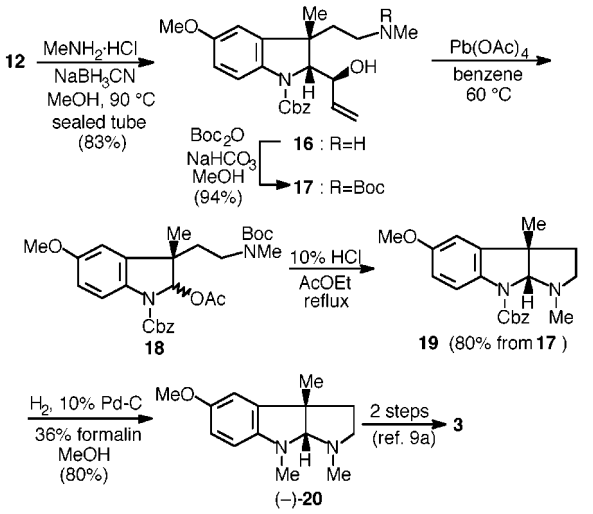
Scheme 4



$[\alpha]^{26}_{D}$ +25.5 (*c* 0.6, $CHCl_3$), under standard conditions. Removal of the extra three-carbon moiety was carried out at this stage as above by treating **17** with lead(IV) acetate in benzene to afford the crude acetate **18** which, on reflux with 10% hydrochloric acid in hot ethyl acetate,[13] gave the tricyclic carbamate **19**, $[\alpha]^{29}_{D}$ −7.7 (*c* 0.3, $CHCl_3$), by concurrent chemoselective decarbamoylation, deacetoxylation, and internal aminalization. On reductive *N*-methylation under catalytic hydrogenolysis conditions in the presence of formalin,[12] **19** afforded the *N*,*N*′-dimethylaminal **20**, $[\alpha]^{26}_{D}$ −129.5 (*c* 0.2, benzene) [lit.[7] $[\alpha]^{34}_{D}$ −134 (*c* 0.41, benzene)], known as esermethol, by concurrent decarbamoylation and reductive *N*-methylation without affecting the aminal linkage. The overall yield of **20** from **12** was 50% in five steps. Transformation of (−)-**20** into (−)-physostigmine (**3**) has also been carried out by the present group in two steps[7,9a] (Scheme 4).

In summary, we have demonstrated an alternative utilization of the chiral building block developed for the construction of the aldohexoses for the synthesis of the two Calabar bean alkaloids (−)-physovenine and (−)-physostigmine. Efforts to extend utilization of the chiral building block **1** and its congeners is presently under investigation on the basis of high functionality and inherent convex-face selectivity.

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