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Indole Alkaloids. Enantiocontrolled Synthesis and Absolute Configuration of (+)-Decarbomethoxy-15,20;16,17-tetrahydrosecodine.

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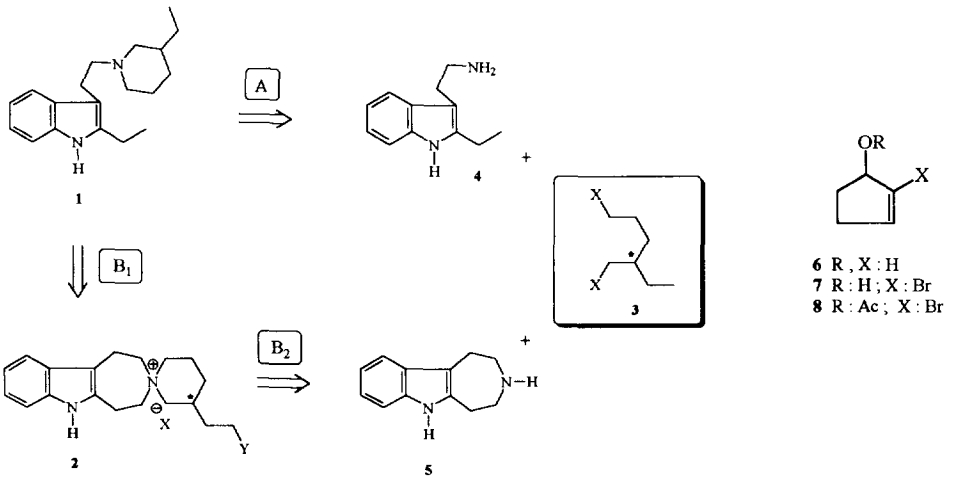
Abstract: Lipase-catalyzed transesterification of 2-bromo-2-cyclopenten-1-ol has been utilized in the asymmetric synthesis and consequent configurational assignment of the title compound.

More than two decades ago Crooks *et al.*[1] succeeded in isolating, from the leaves of *Tabernaemontana cumminsii*, the indole alkaloid **1** (2-ethyl-3[2-(3-ethylpiperidinyl)-ethyl]-1*H*-indole). Since the original isolation, **1** has also been isolated from *Aspidosperma marcgraviamum*,[2] *Haplophyton crooksii* [3] and *Rhazya stricta*,[4] and, only in the last case, a specific rotation of +90 has been reported for this compound.

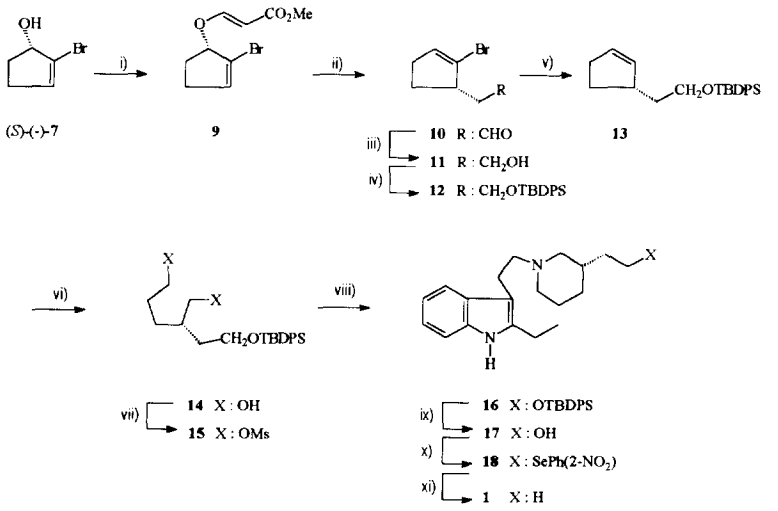
SCHEME I



The spectroscopic data exhibited by this compound support the structure **1**, but, to date, no assignment of absolute configuration has been made. The isolation of (+)-**1** was of particular biogenetic relevance as it is another member of the long-sought secodines and these elusive compounds represent the plausible precursors of dimeric (*e.g.*, secamines) as well as of monomeric alkaloids (*e.g.*, *Hazunta* and *Aspidosperma* alkaloids).[5] Following our interest in the chemistry of indole alkaloids, we carried out the first synthesis of the dextrorotatory enantiomer of **1**, thereby establishing its absolute configuration. It was envisaged that a chiral C_7 building block could be incorporated into **1** following two strategies, a common 1,5-dielectrophilic reagent **3** being recognised as a latent cyclopentene (Scheme I) and being produced upon the [3,3]-allyl vinyl ether-type rearrangement (Claisen reaction)[6] of homochiral 2-cyclopenten-1-ol **6**. By virtue of the [π2s + π2s + σ2s] nature of this process, the strategy inherently permits control of the stereochemistry in the target molecule.[7] The preparation of enantiopure **1** required setting the stereochemistry of **6** (or its synthetic equivalent) and this was achieved through enzyme-mediated reactions.[8] Disappointingly, it can be seen in the literature[9] that enzymatic resolution of 2-cycloalken-1-ols *per se* is generally inefficient.[10] Thus, a sterically demanding group (*i.e.*, Br) was temporarily introduced (in **7**) to attain high enantiodiscrimination. Transesterification of *rac*-**7**[11] with vinyl acetate promoted by porcine pancreatic lipase (PPL; E.C. 3.1.1.3) proceeded stereoselectively (E=133)[12] to give optically active (+)-**8.** A suitable condition for this reaction was to use crude PPL (Sigma, Type II, no. 3126) immobilized on Hyflo Supercel[8] and neat vinyl acetate as solvent and acyl donor.[13] The reaction mixture (0.142 M solution of **7**) was stirred at 45°C for 80 h (at 41% conversion) and purified by silica gel chromatography (hexane-EtOAc, 9:1): acetate (*R*)-(+)-**8** $[\alpha]_D^{20}$ +60.5 (c 2.1,$CHCl_3$) was isolated in 35 % yield and 96.4% ee.[14] The recovered (-)-**7** (52 %) having 79.5% ee[15] was again subjected to the enzymatic reaction under the same conditions. This process, when allowed to proceed to 9% level, returned (-)-**7** in virtually enantiopure form, $[\alpha]_D^{20}$ - 47.5 (c 2.4, $CHCl_3$) and 75 % isolated yield.[16] The absolute configuration (*S*) of (-)-**7** was assigned on the basis of the Cotton dichroic effect of its *p*-nitrobenzoate.[17] We began our synthesis with (*S*)-**7** which subsequently proved to be the correct choice to arrive at the natural stereochemistry. The stereoconservative translocation of the stereogenic center from (*S*)-**7** to the aldehyde **10** was accomplished according to our recently delineated strategy.[7] Thus, (-)-**7** was transformed through the agency of methyl propiolate [*N*-methylmorpholine (NMM), Et_2O, rt]. The resulting acrylate **9** [α]$_D^{20}$ -22.1(c 5.4, $CHCl_3$) in DMF was heated (140°C, sealed tube) in the presence of LiI to yield aldehyde **10.** Initial attempts to isolate **10** were plagued by its volatility, we therefore reduced it ($NaBH_4$, rt) to (*S*)-**11** [α]$_D^{20}$ -4.0 (c 2.5, $CHCl_3$) in 76% overall yield (from **7**). Having served its purpouse, the bromine atom was removed, unmasking a disubstituted cyclopentene fragment. The alcohol **11** was first protected as its *t*-butyldiphenylsilyl (TBDPS) derivative **12** [TBDPSCl, $i Pr_2NEt$ (DIPEA), CH_2Cl_2, rt][18] and then subjected to halogen-lithium exchange (*n*-BuLi, THF, -90° $\rightarrow$ 0°C). Subsequent protodemetallation (1M aq. oxalic acid, 0°C) provided **13** $[\alpha]_D^{20}$ +34.4 (c 3.4, $CHCl_3$) in nearly quantitative yield.[19] Ozonolysis of **13** in MeOH at - 78°C, quenching with Me_2S and immediate *in situ* reduction with $NaBH_4$ led to the monoprotected triol **14.** Upon exposure of 2-

ethyltryptamine **4** [20] to dimesylate **15** (available by standard mesylation of **14**) in refluxing MeCN in the presence of LiI, 12-crown-4 (cat.) and DIPEA, smooth ring formation occurred to generate the (*R*)-piperidine **16** (71%) [α]$_D^{20}$ +9.2 (c 2.5, $CHCl_3$).

SCHEME II



i) HC≡C-COOMe, NMM, Et_2O; ii) LiI, DMF, 140 °C; iii) $NaBH_4$; iv) TDBPSCl, DIPEA, CH_2Cl_2; v) *n*BuLi, THF; then 1M aq $(COOH)_2$; vi) O_3, MeOH, Me_2S; then $NaBH_4$; vii) MsCl, TEA, CH_2Cl_2; viii) **4**, MeCN, LiI, 12-crown-4; ix) 1M Bu_4NF, THF; x) $(2\text{-}NO_2)PhSeCN$, Bu_3P, THF; xi) $NiCl_2$, $NaBH_4$, MeOH-THF.

The synthesis of **1** was completed by deoxygenation of O-protected function in a 3-step sequence which embodied :i) desilylation (1M $Bu_4N^+F^-$, THF, rt] of **16** to **17** [α]$_D^{20}$ +7.4 (c 1.1, $CHCl_3$); ii) selenation according to the Grieco protocol[21] [2-nitrophenyl selenocyanate, Bu_3P, THF, rt] to **18** [α]$_D^{20}$ +20.8 (c 1.3, $CHCl_3$), and iii) hydrogenolysis of C-Se bond with nickel boride ($NaBH_4$, $NiCl_2$, MeOH-THF, 0°C)[22] to give (+)-**1** [α]$_D^{20}$ +11.8 (c 0.35, $CHCl_3$) in 66 % overall yield (from **16**). Once it was established that (+)-**1** could be obtained , we examined the possibility of an alternative approach using **15** to serve in an alternative approach (Scheme I, path B). The crucial azoniaspiro[5,6]dodecane ring formation was accomplished by refluxing (MeCN) the dimesylate **15** (2.1 equiv) and hexahydroazepino[4,5-b]indole **5**[23] yielding **2** (X:OMs, Y:TBDPS) (as a likely mixture of diastereomers at the spirocenter). Mindful of the success enjoyed by Sharkova *et al.*[24] in promoting reductive Emde degradation in akin indolo-azepinium salts, we submitted crude **2** to catalytic hydrogenation (Raney nickel, 1M NaOH, MeOH, 40°C). Since the piperidine **16** was isolated in only 18% yield (from **15**), this route to (+)-**1** proved less fruitful than the preceding one and it was not further pursued. Although we were not able to obtain an authentic sample of the dextrorotatory natural compound, the spectroscopic data (^{1}H-, ^{13}C- NMR) of our compound correlate closely to data reported by Atta-ur-Rahman[4]. However, synthetic material had a specific rotation of +11.8 instead of +90. Since synthetic (+)-**1** appeared to be optically pure (chiral hplc) the difference in the magnitude, as well as the low value of optical rotation, did

not allow to assess - with certainty - the absolute configuration of natural **1** isolated from *Rhazya stricta*. In conclusion, the present approach represents the first stereoselective synthesis of natural decarbomethoxy-15,20;16,17-tetrahydrosecodine, *thereby establishing, beyond any doubt, that* (+)-**1** *has the (R)-configuration.* It follows that (+)-**1** is also topologically related to (20*R*)-cleavamine alkaloids by C(14)-C(15) bond fragmentation and thence can be viewed as (+)-14,15-*seco*-(20*R*)-dihydrocleavamine.

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References and Notes.

1. Crooks, P.A.; Robinson, G.F.; Smith, G.F. *Chem. Commun.* **1968**, 1210
2. Robert, G.M.T.; Ahond, A.; Poupat, C.; Potier, P.; Jolles, C.; Jousselin, A.; Jacquemin, H. *J.Nat.Prod.* **1983**, *46*, 694.
3. Mroue, M.A..; Ghuman, M.A.; Alam, M. *Phytochemistry* **1993**, *33*, 217. Alkaloid **1** showed a complete inhibition of acetylcholinesterase activity (*ca.* 63x less potent of eserine).
4. Atta-ur-Rahman, Zaman, K., Perveen, S.; ur-Rehman, H.; Muzaffar, A.; Choudhary, M.I.; Pervin, A. *Phytochemistry* **1991**, *30*, 1285.
5. For an exhaustive review on secodines, see: Cordell, G.A.; Saxton, J.E. Bisindole Alkaloids; In 'The Alkaloids' Manske, R.H.F.; Rodrigo, R.G.A., Eds.; vol. XX, p. 88-105; Academic Press, N.Y. 1981.
6. a) Ziegler, F.E. *Chem.Rev.* **1988**, *88*, 1423; b) Blechert, S. *Synthesis* **1989**, 71.
7. Palmisano, G.; D'Anniballe, P.; Santagostino, M. *Tetrahedron* **1994**, *50*, 9487.
8. Carrea, G.; Danieli, B.; Palmisano, G.; Riva, S.; Santagostino, M. *Tetrahedron:Asym.* **1992**, *3*, 775.
9. Gupta, A.K.; Kazlauskas, P.J. *Tetrahedron:Asym.* **1993**, *4*, 879 and references quoted.
10. For alternative preparations of optically active 2-cyclopenten-1-ol , see: a) Sato, T.; Gotoh, Y.; Wakabayashi, Y.; Fujisawa, T. *Tetrahedron Lett.* **1993**, *24*, 4123; b) Fujisawa, T.; Yamanaka, K.; Mobele, B.I.; Shimizu, M. *Tetrahedron Lett.* **1991**, *32*, 399; c) Corey, E.J ; Chen, C.-P.; Reichard, G.A. *Tetrahedron Lett.* **1989**, *30*, 5547; d) Fukuzawa, T.; Hashimoto, T. *Tetrahedron Asym.* **1993**, *4*, 2323; e) Ito, S.; Kasai, M.; Ziffer, H.; Silverton, J,V. *Can. J. Chem.* **1987**, *65*, 574.
11. The *rac*-2-bromoderivative **7** was prepared in two steps from 2-cyclopenten-1-one by bromination in the presence of TEA, followed by reduction with $NaBH_4$ / $CeCl_3$ (see Ref. 10e).
12. Chen, C.; Fujimoto, Y.; Girdaukas, G.; Sih, C.J. *J.Am.Chem.Soc.* **1982**, *104*, 7294.
13. Screening experiments were carried out using several commercially available preparations: lipase P from *Ps. fluorescens* (Amano), lipase CE-5 from *Humicola lanuginosa* (Amano), lipase G from *Geotrichum candidum* (Amano), lipase from *Candida cylindracea* (Sigma), lipase from *Mucor miehei* (Biocatalyst), lipase from *Candida antarctica* (Novo), lipase from *Chromobacterium viscosum* (Finnsugar).
14. The ee of acetate was determined by chiral GLC on a CP-cyclodextrin-β-2,3,6-M-19 column (50 m, 0.25 mm i.d.; Chromopack) using H_2 as carrier gas.
15. Ee of (-)-**7** was determined by GLC on permethylated β-cyclodextrin column after derivatization as acetate
16. In our hands, enantioselective reduction of 2-bromo-2-cyclopentenone with BH_3 in the presence of the oxazaborolidine of (+)-1*S*,5*R*,8*S*-8-phenyl-2-azabicyclo[3.3.0]octan-8-ol according to Corey protocol gave the (*R*)-alcohol in only 75% ee (see Ref. 10c).
17. Harada, N.; Inabuchi, J.; Yokota, Y.; Uda, H.; Nakanishi, K. *J.Am.Chem.Soc.* **1981**, *103*, 5590.
18. Hanessian, S.; Lavalleee, P. *Can.J.Chem.* **1975**, *53*, 2975.
19. Attempts to directly debrominate **12** by thermal or photochemical radical-mediated protocol gave poorer results.
20. Fleming, I.; Harley-Mason, J. *J.Chem.Soc.* **1965**, 425).
21. Grieco, P.A.; Gilman, S.; Nishizawa, M. *J.Org.Chem.* **1976**, *41*, 1485.
22. Back, T.G. *J.Chem.Soc., Chem.Commun.* **1984**, 1417.
23. Hester, J.B.; Tang, A.H.; Keasling, H.H.; Veldkamp, W. *J.Med.Chem.* **1968**, 101.
24. Sharkova, N.M.; Kucherova, N.F.; Portnova, S.L.; Zagorevskii, V.A. *Khim. Geterotsikl.Soedin* **1968**, 131 (*J.Heterocycl. Comp. USSR* **1968**, 101; *Chem.Abstr.***1968**, *69*, 86857u).
25. In the IR spectrum ($CHCl_3$) of natural **1** isolated by Atta-ur-Rahman (see Ref. 4) is present an inexplicable (carbonyl?) band at 1710 cm^{-1}.

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