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Enantioselective Syntheses of the Indole Alkaloid (+)-*R*-Decarbomethoxytetrahydrosecodine and Its Enantiomer

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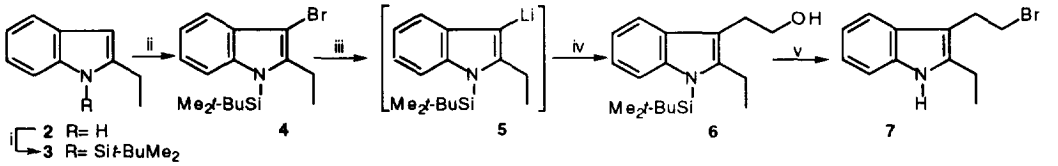
Abstract: The alkaloid (+)-*R*-decarbomethoxytetrahydrosecodine (+)-**1** has been synthesized by alkylation of (*R*)-3-ethylpiperidine with 3-(2-bromoethyl)-2-ethylindole (**7**). The required enantiopure piperidine was prepared by alkylation of the chiral non-racemic oxazolopiperidone (+)-*trans*-**8** followed by reduction of the lactam carbonyl group and removal of the chiral auxiliary, whereas tryptophyl bromide **7** was obtained by reaction of *N*-silyl-3-lithioindole **5** with ethylene oxide followed by treatment with PBr_3. The enantiomer of the natural product was prepared in a similar way, starting from (-)-*trans*-**8**.

(+)-*R*-Decarbomethoxy-15,16,17,20-tetrahydrosecodine (+)-**1** is the simplest secodine-type alkaloid occurring in nature.[1] It was isolated for the first time in 1968 from *Tabernaemontana cuminsii*,[2,3] although its absolute configuration was not established until 1995,[4] when the alkaloid was synthesized in enantiopure form for the first time.[5] A second enantiocontrolled synthesis of (+)-**1** has been recently reported.[6] In both cases, the stereogenic center was created by lipase mediated kinetic transesterification of a racemic precursor, either a 2-cyclopentenol[4] or a 3-hydroxy-1,2,3,6-tetrahydropyridine[6] derivative.

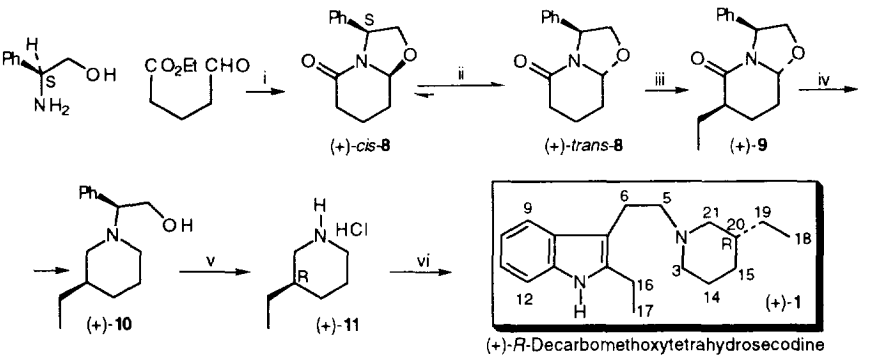
We present here enantioselective syntheses of (+)-*R*-decarbomethoxytetrahydrosecodine (+)-**1** and its enantiomer (-)-**1**. Our approach involves the alkylation of each enantiomer of 3-ethylpiperidine with 3-(2-bromoethyl)-2-ethylindole **7** and takes advantage of two methodologies recently developed in our laboratory: a) the use of stable *N*-silyl-3-lithioindole derivatives for the regioselective preparation of 3-substituted indoles[7], and b) the use of chiral non-racemic oxazolopiperidones for the stereoselective synthesis of diversely substituted enantiopure piperidines.[8]

The required tryptophyl bromide **7** was prepared as outlined in Scheme 1. 2-Ethylindole was protected as a *tert*-butyldimethylsilyl derivative and then allowed to react with *N*-bromosuccinimide at -78°C to give the 3-bromoindole derivative **4** in 90% overall yield.[9] Treatment of a THF solution of **4** with *t*-BuLi (2.0 equiv) at -78°C, followed by reaction of the resulting 3-lithio species **5**[10] with ethylene oxide, provided tryptophol **6** in 75% yield. This reaction not only further demonstrates the usefulness of bulky silyl groups as indole protecting groups in the generation and reactions of 3-lithioindoles but also constitutes an efficient method for the synthesis of 2,3-disubstituted indoles. Finally, treatment of tryptophol **6** with PBr_3 afforded tryptophyl bromide **7** in 85% yield.



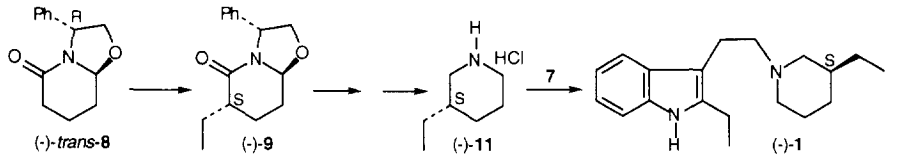
Scheme 1. *Reagents and conditions*: (i) NaH, *t*-BuMe2SiCl, THF, 25°C; (ii) NBS, THF, -78°C; (iii) *t*-BuLi, THF, -78°C; (iv) ethylene oxide, THF, -78°C; (v) PBr_3, CH_2Cl_2, 25°C.

On the other hand, (*R*)-3-ethylpiperidine was prepared from the enantiopure oxazolopiperidone (+)-*trans*-**8**, which, in turn, was obtained by reaction of ethyl 5-oxopentanoate with (*S*)-phenylglycinol followed by equilibration with TFA of the initially formed mixture (8:2 ratio) of (+)-*cis*-**8** and (+)-*trans*-**8** (Scheme 2). In this manner, a 15:85 mixture of *cis* and *trans* isomers, which were easily separated by column chromatography, was obtained. Generation of the enolate derived from (+)-*trans*-**8** by treatment with lithium hexamethyldisilazide, followed by alkylation with ethyl iodide, afforded (+)-**9**[11] with high stereoselectivity (the 3*S*,6*R* diastereomer was the only isomer observed by NMR) and excellent chemical yield (83%).[12] $LiAlH_4$ reduction of the lactam carbonyl group of (+)-**9** took place with simultaneous reductive cleavage of the oxazolidine ring to give (+)-**10**[13] in 95% yield. Finally, removal of the chiral auxiliary by hydrogenolysis gave (*R*)-3-ethylpiperidine hydrochloride (+)-**11**[14] (76% yield), which was then alkylated with tryptophyl bromide **7** to give the target alkaloid (+)-**1**,[15] $[\alpha]_D^{22}$ +10.5 (*c* 0.45, $CHCl_3$),[16] in 64% yield.



Scheme 2. *Reagents and conditions*: (i) toluene, reflux, Dean-Stark; (ii) TFA, CH_2Cl_2, 25°C; (iii) LiHMDS, EtI, THF, -78°C; (iv) $LiAlH_4$, THF, 25°C; (v) HCl/C_6H_6, then H_2, Pd-C, MeOH; (vi) **7**, $NaHCO_3$, CH_3CN, 80°C.

Following a reaction sequence identical to that depicted in Scheme 2, (-)-*trans*-**8**[8a] was converted to (*S*)-3-ethylpiperidine hydrochloride (-)-**11** by way of (-)-**9** (Scheme 3) and then alkylated with tryptophyl bromide **7** to give (-)-**1**, $[\alpha]_D^{22}$ -10.8 (*c* 0.45, $CHCl_3$), the enantiomer of natural decarbomethoxy-tetrahydrosecodine. In this enantiomeric series, the configuration of the stereogenic center at the piperidine 3-position was determined as *S* by X-ray diffraction analysis of (-)-**9**,[17] thus confirming the *R* configuration of the alkaloid (+)-**1**.



Scheme 3

The above results illustrate the potential of the easily accessible bicyclic lactams (+)-*trans*-**8** and (-)-*trans*-**8** for the enantioselective synthesis of 3-substituted piperidines. Using either (*R*)- or (*S*)-phenylglycinol, both of them commercially available, as source of chirality, (*S*)- or (*R*)-3-alkylpiperidines can be easily obtained. It is worth mentioning that (*R*)- and (*S*)-3-ethylpiperidine had previously been obtained only by resolution of the racemate.[18]

Acknowledgments

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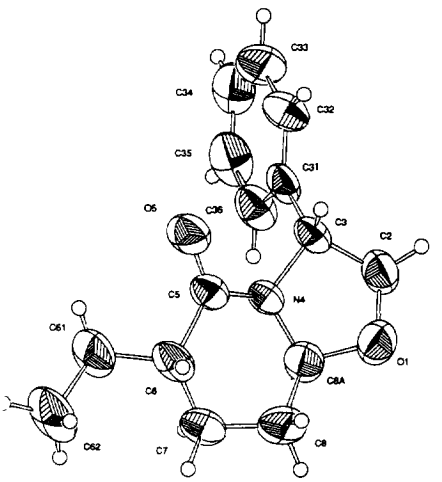
9. All yields are from material purified by column chromatography. Satisfactory analytical and/or spectral data were obtained for all new compounds. ^{1}H-^{1}H COSY and HETCOR spectra were used to assign individual NMR signals.
10. There are no studies about 2-alkyl-3-lithioindoles. However, see: Bauta, W. E.; Wulff, W. D.; Pavkovic, S. F.; Zaluzec, E. J. *J. Org. Chem.* **1989**, *54*, 3249. For leading references concerning 3-lithioindoles, see reference 7a.
11. (+)-**9**: $[\alpha]_D^{22}$ +102.9 (*c* 1.0, EtOH); mp 91.5ºC (ether-hexane); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.93 (t, *J*= 7.5 Hz, 3H, CH_3), 1.50-1.60 (m, 2H, H-7, H-8), 1.66 and 1.90 (2m, 2H, CH_2), 2.04 (m, 1H, H-7), 2.32 (m, 1H, H-6), 2.40 (m, 1H, H-8), 3.73 (dd, *J*= 9.0, 8.0 Hz, 1H, H-2), 4.51 (dd, *J*= 9.0, 8.0 Hz, 1H, H-2), 5.02 (dd, *J*= 8.6, 4.8 Hz, 1H, H-8a), 5.28 (t, *J*= 8.0 Hz, 1H, H-3); 7.20-7.38 (m, 5H, C_6H_5); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 10.7 (CH_3), 22.2 (C-7), 25.4 (CH_2), 28.1 (C-8), 42.8 (C-6), 58.2 (C-3), 72.7 (C-2), 88.8 (C-8a), 125.7 (C-*o*), 127.4 (C-*p*), 128.7 (C-*m*), 139.7 (C-*ipso*), 171.7 (C-5).
12. a) Previous attempts to alkylate the enantiomeric oxazolopiperidone (-)-*trans*-**8**, derived from (*R*)-phenylglycinol, with LDA had resulted either in failure[12b] or in moderate success (~40% yield).[8b] b)

Micouin, L.; Varea, T.; Riche, C.; Chiaroni, A.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1994**, *35*, 2529.

13. (+)-**10**: $[\alpha]_D^{22}$ +28.1 (*c* 0.38, EtOH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.72 (qd, *J*= 11.6, 3.0 Hz, 1H, H-4), 0.88 (t, *J*= 7.5 Hz, 3H, CH_3), 1.23 (m, 2H, CH_2), 1.47 (m, 1H, H-3), 1.52-1.56 (m, 4H, H-4, 2H-5, H-6), 1.95 (t, *J*= 10.5 Hz, 1H, H-2), 2.79 (m, 2H, H-2, H-6), 3.60 (dd, *J*= 10.2, 5.0 Hz, 1H, CH_2O), 3.70 (dd, *J*= 10.2, 5.0 Hz, 1H, NCH), 3.98 (t, *J*= 10.2 Hz, 1H, CH_2O), 7.18 (m, 2H, Ar), 7.34 (m, 3H, Ar); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 11.4 (CH_3), 25.6 (C-5), 27.0 (CH_2), 30.5 (C-4), 38.5 (C-3), 46.8 (C-6), 58.7 (C-2), 59.7 (CH_2O), 70.1 (NCH), 127.7 (C-*p*), 128.0 (C-*o*), 128.9 (C-*m*), 135.4 (C-*ipso*).
14. (+)-**11**: Mp 158ºC (ether); $[\alpha]_D^{22}$ +3.2 (*c* 1.0, EtOH). ^{1}H-NMR (300 MHz, CD_3OD) δ 1.06 (t, *J*= 7.7 Hz, 3H, CH_3), 1.30 (m, 1H, H-4ax), 1.45 (m, 2H, CH_2), 1.76 (m, 1H, H-3ax), 1.85 (m, 1H, H-5ax), 1.98-2.10 (m, 2H, H-4eq, H-5eq), 2.71 (t, *J*= 12.0 Hz, 1H, H-2ax), 2.99 (td, *J*= 12.8, 2.7 Hz, 1H, H-6ax), 3.38-3.48 (m, 2H, H-2eq, H-6eq); ^{13}C-NMR (CD_3OD, 75 MHz) δ 11.2 (CH_3), 23.3 (C-5), 27.5 (CH_2), 29.4 (C-4), 36.5 (C-3), 45.4 (C-6), 49.9 (C-2).
15. The ^{13}C-NMR (75 MHz, $CDCl_3$) data of (+)-**1** were identical to those previously reported.[3bc,6] ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.85 (qd, *J*= 12.0, 5.0 Hz, 1H, H-15ax), 0.90 (t, *J*= 7.5 Hz, 3H, H-18), 1.24 (m, 2H, H-19), 1.27 (t, *J*= 7.5 Hz, 3H, H-17), 1.54 (m, 1H, H-20ax), 1.62-1.74 (m, 3H, H-21ax, 2H-14), 1.80 (dm, *J*= 12.0 Hz, 1H, H-15eq), 1.96 (td, *J*= 11.0, 2.5 Hz, 1H, H-3ax), 2.56 (m, 2H, H-5), 2.75 (q, *J*= 7.5 Hz, 2H, H-16), 2.92 (m, 2H, H-6), 3.02-3.10 (m, 2H, H-3eq, H-21eq), 7.05 (td, *J*= 7.0, 1.0 Hz, 1H, H-10), 7.09 (td, *J*= 7.0, 1.0 Hz, 1H, H-11), 7.26 (dm, *J*= 7.0 Hz, 1H, H-12), 7.51 (dm, *J*= 7.0 Hz, 1H, H-9), 7.79 (br s, 1H, NH).
16. The reported[3b] specific rotation for the natural product is $[\alpha]_D^{22}$ +90 ($CHCl_3$). However, the reported [α] values for synthetic *R*-(+)-**1** are $[\alpha]_D^{22}$ +11.8 (*c* 0.35, $CHCl_3$)[4] and $[\alpha]_D^{30}$ +11.3 (*c* 0.17, $CHCl_3$).[6]
17. Crystal structure of (-)-**9**:



Crystal data: $C_{15}H_{19}NO_2$, orthorhombic, space group $P2_12_12_1$, *a*= 6.063(1) Å, *b*= 11.585(1) Å, *c*= 19.347(3) Å, V= 1358.9(3) Å^3, μ (MoKα)= 0.08 mm^{-1}, D_c= 1.20 g cm^{-3}. A set of 25 reflections were randomly measured on an Enraf Nonius CAD4 diffractometer using graphite monochromated MoKα radiation. The crystal had approximate dimensions of 0.51x0.47x0.11 mm. Data collection was up to a resolution of 2θ= 50º producing 1411 reflections. The structure was solved by direct methods (MULTAN 11/84) after applying Lorentz, polarization and absorption (empirical PSI scan method: maximum and minimum absorption corrections were 0.984 and 0.866, respectively) corrections. Full-matrix least squares refinement (SHELXL-93) using anisotropic thermal parameters for non-H atoms and a global isotropic thermal parameters for H-atoms (positioned at calculated positions) converged to a R factor of 0.072 (calculated for the reflections with I>2σ(I)). The extinction coefficient was 0.052(10). Maximum and minimum heights at the final difference Fourier synthesis were 0.253 and -0.288 eÄ$^{-3}$. Complete data have been deposited at the Cambridge Crystallographic Data Centre.

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