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A highly stereocontrolled route to 2-(2′-oxiranyl)piperidines and pyrrolidines: enantioselective synthesis of (+)-α-conhydrine

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ABSTRACT

The first enantio- and diastereoselective approach to both 2-(2′-oxiranyl)piperidines and to 2-(2′-oxiranyl)pyrrolidines is reported. The method relies on the Sharpless asymmetric epoxidation of allyl alcohols as the sole source of chirality, and involves as the key step the base-mediated cyclization of (α-aminoalkyl)oxiranes functionalized at the ϵ (or δ) position. The asymmetric synthesis of (+)-α-conhydrine illustrates the applicability of this strategy to the preparation of biologically active 2-(1-hydroxyalkyl)piperidine alkaloids.

Alkaloids containing a 2-(1-hydroxyalkyl)piperidine substructural unit (Ia) are ubiquitous in nature and in most instances present strong biological activities.[1] Although they are much less common, 2-(1-hydroxyalkyl)pyrrolidine derivatives (Ib) are also interesting from the biomedicinal point of view.[2] It is therefore not surprising that the preparation of these two types of compounds has been actively pursued in the past years, particularly from the point of view of asymmetric synthesis. Whereas 2-(2′-oxiranyl)piperidines (IIa) and pyrrolidines (IIb) would be obvious precursors of Ia and Ib, respectively, no stereoselective synthetic routes to these deceptively simple structures have been described in the literature. In particular, 2-(2′-oxiranyl)pyrrolidines IIb have been accessed by epoxidation of suitable carbonylic[2b,3] or of olefinic[2c,4] pyrrolidine derivatives, but these reactions invariably lead to diastereomer mixtures (and are accompanied in some cases by racemization[3]); on the other hand, 2-(2′-oxiranyl)piperidines IIa are essentially unknown compounds. We disclose in this Letter an efficient, enantio-, and diastereocontrolled route to IIa and IIb. Our approach, summarized in Scheme 1, implies that these key structures would arise from the cyclization of adequately functionalized 2-(1-aminoalkyl)oxiranes (IIIa,b), whose stereocontrolled preparation from allyl alcohols IVa,b should be easily achieved by means of the synthetic strategy developed a few years ago in our laboratories,[5] using the catalytic asymmetric epoxidation of allyl alcohols[6] as the sole source of chirality.[7]

We report now the initial implementation of this concept that has led to the stereocontrolled preparation of (2*S*,2′*S*)-*N*-Cbz-2-(2′-oxiranyl)piperidine (**1**) and of the pyrrolidine analog **2**, as well as to the conversion of **1** to (+)-α-conhydrine (**3**). The starting material in our route to 2-(2′-oxiranyl)piperidines (depicted in Scheme 2) is the known[8,9] allyl alcohol **4** that was easily prepared in three steps (65% overall yield) from 4-hexyn-1-ol.[8] The catalytic asymmetric epoxidation of **4**, using D-(−)-diisopropyl tartrate as the chiral ligand, afforded the expected (*R*,*R*)-epoxy alcohol **5** in 80% yield and with 97% ee.[10] The regio- and stereoselective ring-opening of **5** with (diazido)titanium diisopropoxide[11] furnished the *anti*-azido diol **6** in 72% yield. When this compound was submitted to catalytic hydrogenation in the presence of di(*tert*-butyl)dicarbonate, the *anti*-*N*-Boc-amino diol **7** was obtained in excellent yield. The conversion of **7** to epoxide **8** took place uneventfully, using reaction conditions previously employed by us[4a] for similar transformations. At this point, the silyl ether was cleaved with fluoride ion, affording the desired alcohol **9** (86% yield). Although at least one precedent for the direct cyclization of **9** under Mitsunobu conditions could be found in the literature,[12] all our attempts along these lines met with failure. On the other hand, several base-mediated cyclization reactions of corresponding mesylate afforded complex reaction mixtures in which the target *N*-Boc-2-(2′-oxiranyl)piperidine **10** was present in low yields. Careful examination of the byproducts accompanying the formation of **10** led us to conclude that a change of the nitrogen protecting group was necessary. Therefore, the azido diol **6** was hydrogenated, and the crude amino diol was treated with benzyl

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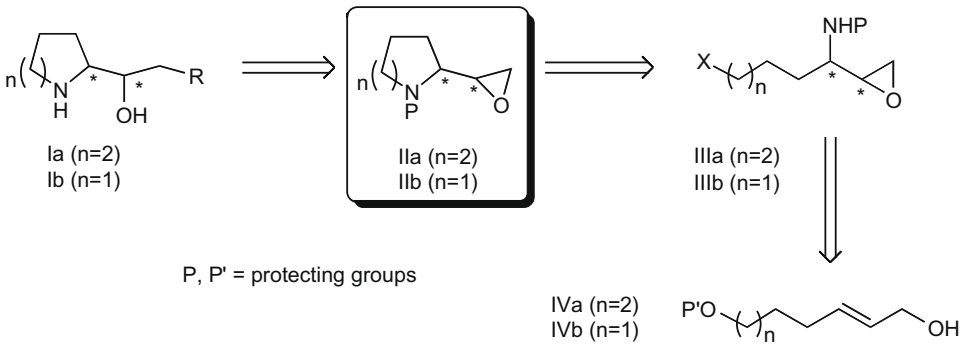
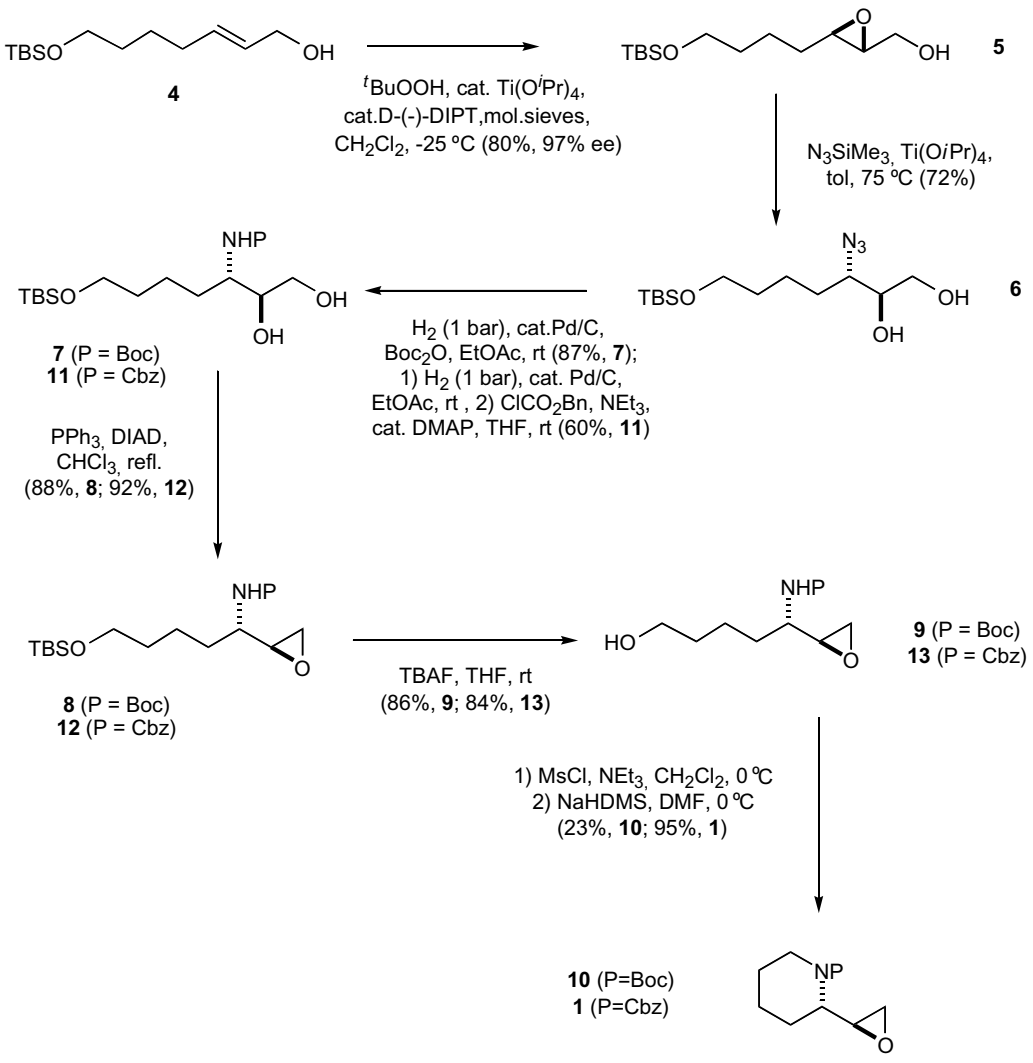


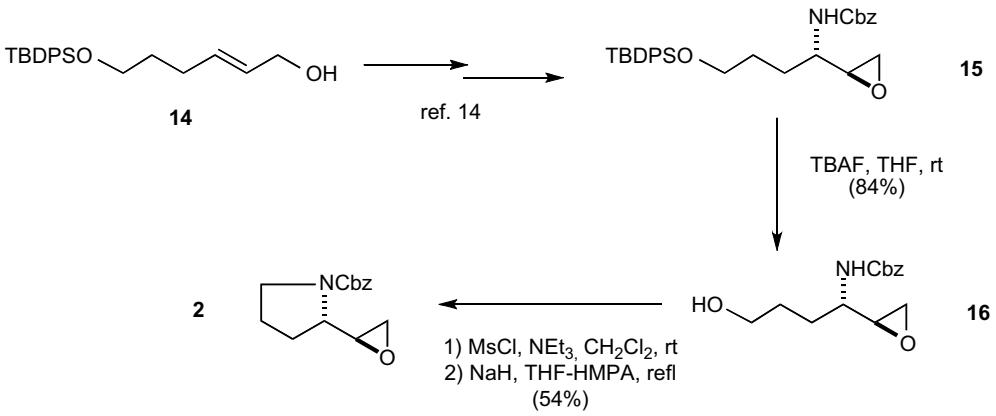
Scheme 1. 2-(2′-Oxiranyl)piperidines (IIa) and pyrrolidines (IIb) as key intermediates in the stereocontrolled synthesis of 2-(1-hydroxyalkyl)piperidines (Ia) and pyrrolidines (Ib).



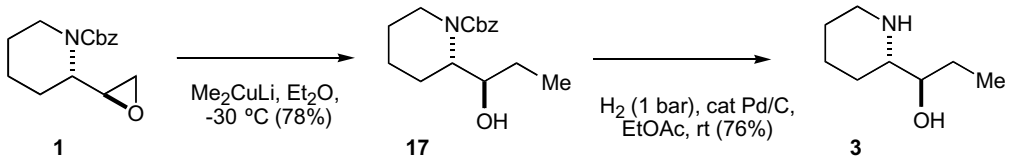
Scheme 2. Synthesis of (*S*,*S*)-2-(2′-oxiranyl)piperidines.

chloroformate in the presence of base to afford the *N*-Cbz-amino diol **11** (66% overall yield from **6** after chromatographic purification). Mitsunobu cyclization of **11** gave the *N*-Cbz-*anti*-epoxide **12** in 92% yield; desilylation of this compound afforded alcohol **13** (84% yield). Gratifyingly, base-mediated cyclization (NaHDMS, DMF, 0 °C, 30 min) of the derived mesylate furnished the target *N*-Cbz-2-(2′-oxiranyl)piperidine **1** in almost quantitative yield and with high purity.

The same strategy can be used for the stereoselective synthesis of 2-(2′-oxiranyl)pyrrolidines IIb (Scheme 3). Thus, the chiral non-racemic (95% ee) epoxide **15** (prepared from the known allyl alcohol **14**[5f,13] by a reaction sequence analogous to that used for the



Scheme 3. Enantioselective synthesis of (2*S*,2*S*′)-*N*-Cbz-2-(2′-oxiranyl)pyrrolidine **2**.



Scheme 4. Synthesis of (+)-α-conhydrine **3**.

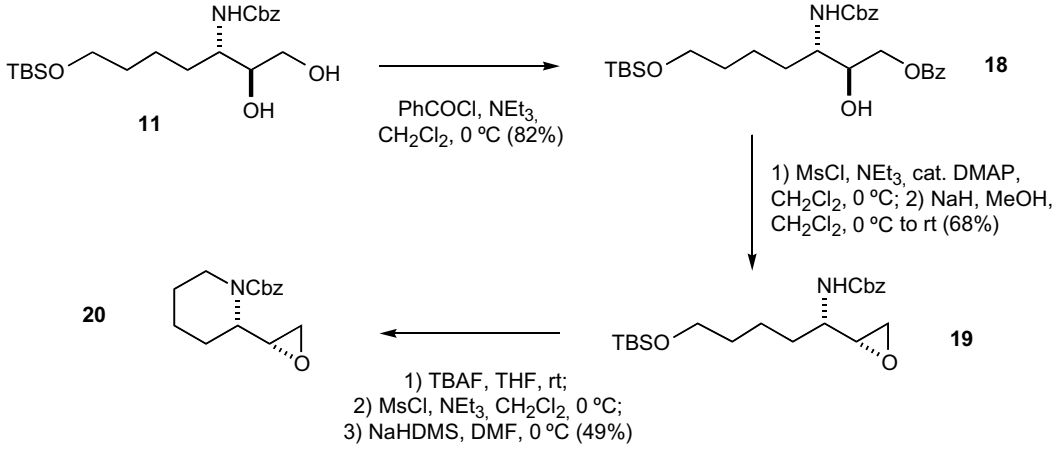
synthesis of **12** in Scheme 2 as described in detail in Ref. 14) was desilylated with TBAF (84% yield), and the resulting alcohol **16** was mesylated and cyclized under basic conditions (NaH, THF–HMPA, reflux) to give the (2*S*,2′*S*)-*N*-Cbz-2-(2′-oxiranyl)pyrrolidine **2** in 54% overall yield, after chromatographic purification.

(+)-α-Conhydrine **3**, a highly bioactive alkaloid first isolated from the poisonous hemlock, *Conium maculatum* L., in 1856,[15] and whose structure was elucidated in 1933,[16] has become (together with its (−)-enantiomer) an increasingly popular target for stereoselective synthesis.[17,18] The efficient two-step conversion of (2*S*,2′*S*)-2-(2′-oxiranyl)piperidine **1** to (+)-α-conhydrine, outlined in Scheme 4, was therefore chosen to illustrate the application of our methodology to the synthesis of alkaloids containing a 2-(1-hydroxyalkyl)piperidine unit.

The treatment of **1** with lithium dimethylcuprate (−30 °C, diethyl ether) cleanly afforded the expected *N*-Cbz-(+)-α-conhydrine **17**[18] in 78% yield. As described, catalytic hydrogenation of this compound gave pure **3**, with spectroscopic and polarimetric data closely corresponding with those reported for natural (+)-α-conhydrine.[18]

It is worth noting that since both the *anti* and the *syn* diastereomers of a given (α-aminoalkyl)epoxide can be accessed from the same epoxy alcohol,[5] the procedure disclosed in this Letter can lead stereoselectively to any of the four possible stereoisomers of a given 2-(2′-oxiranyl)piperidine (or pyrrolidine). Thus, as depicted in Scheme 5, the primary hydroxyl of the *N*-Cbz-aminodiol **11** was selectively benzoylated (82% yield), and the resulting benzoate **18** was mesylated and reacted with sodium methoxide to afford the *syn* epoxide **19** (68% yield); the same reaction sequence described in Scheme 2 for its *anti* isomer **12** (desilylation, mesylation, and base-promoted cyclization) afforded the (2*S*,2′*R*)-*N*-Cbz-2-(2′-oxiranyl)piperidine **20**.[19]

In summary, we have disclosed the efficient, stereocontrolled synthesis of (2*S*,2′*S*)-*N*-Cbz-2-(2′-oxiranyl)piperidine (**1**) and of



Scheme 5. Synthesis of (2*S*,2′*R*)-*N*-Cbz-2-(2′-oxiranyl)piperidine **20**.

the pyrrolidine analog **2**, potentially useful intermediates for the preparation of *N*-heterocyclic natural products such as (+)-α-conhydrine.

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19. *Physical data of representative compounds*: Compound **12**: $[\alpha]_D$ −5.4 (*c* 1.02, CH_2Cl_2). IR (NaCl film) ν_{max} = 3330, 2954, 2931, 2860, 1702, 1534, 1472, 1457, 1389, 1256, 1097, 837, 776 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.35–7.29 (m, 5H), 5.06 (m, 2H), 4.68 (d, *J* = 6.8 Hz, 1H), 3.67–3.37 (m, 3H), 2.89–2.65 (m, 3H), 1.73–1.11 (m, 6H), 0.85 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 156.0 (C), 136.0 (C), 128.5 (CH), 128.0 (CH), 66.9 (CH_2), 62.9 (CH_2), 53.9 (CH), 46.1 (CH_2), 32.4 (CH_2), 31.5 (CH_2), 26.0 (CH_3), 22.0 (CH_2), 18.4 (C), −5.2 (CH_3). MS (CI, NH_3): *m/z* = 411 ($[M+18]^+$, 10%), 394 ($[M+1]^+$, 100%). HRMS (ESI-TOF): *m/z* calcd for $C_{21}H_{36}NO_4Si$: 394.2414; found for $[M+1]^+$: 394.2414. Compound **1**: $[\alpha]_D$ −19.0 (*c* 1.05, CH_2Cl_2). IR (NaCl film) ν_{max} = 2941, 2860, 1700, 1416, 1355, 1310, 1256, 1156, 899, 855 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.40–7.25 (m, 5H), 5.20–5.10 (m, 2H), 4.15 (m, 1H), 3.95 (m, 1H), 3.18–3.15 (m, 1H), 3.00 (td, *J* = 13.2 Hz, *J*′ = 2.4 Hz, 1H), 2.74 (t, *J* = 4.8 Hz, 1H), 2.66 (m, 1H), 1.85–1.82 (m, 1H), 1.72–1.67 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5 (C), 136.6 (C), 128.5 (CH), 128.0 (CH), 127.9 (CH), 67.2 (CH_2), 52.5 (CH), 50.9 (CH), 46.8 (CH_2), 41.3 (CH_2), 25.7 (CH_2), 25.0 (CH_2), 19.6 (CH_2). MS (CI, NH_3): *m/z* = 279 ($[M+18]^+$, 15%), 262 ($[M+1]^+$, 58%), 172 ($[M-72]^+$, 100%). HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{20}NO_3$: 262.1443; found for $[M+1]^+$: 262.1440. Compound **16**: $[\alpha]_D$ −11.6 (*c* 1.10, $CHCl_3$). IR (NaCl film) ν_{max} = 3323, 3064, 2931, 1694, 1538, 1455, 1258, 1050, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.32 (m, 5H), 5.09 (m, 2H), 5.04 (br d, 1H), 3.64 (t, *J* = 5.4 Hz, 2H), 3.54 (m, 1H), 2.89 (m, 1H), 2.76 (m, 2H), 1.99 (br s, 1H), 1.75–1.54 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2 (C), 136.3 (C), 128.5 (CH), 128.2 (CH), 128.1 (CH), 66.9 (CH_2), 62.2 (CH_2), 53.9 (CH), 52.3 (CH), 46.1 (CH_2), 28.3 (CH_2), 28.1 (CH_2). MS (CI, NH_3): *m/z* = 283 ($[M+18]^+$, 20%), 266 ($[M+1]^+$, 63%), 222 ($[M-43]^+$, 100%). HRMS (ESI-TOF): *m/z* calcd for $C_{14}H_{20}NO_4$: 266.1392; found for $[M+1]^+$: 266.1387. **2**: $[\alpha]_D$ −11.7 (*c* 1.00, $CHCl_3$). IR (NaCl film) ν_{max} = 2958, 2881, 1702, 1455, 1411, 1357, 1191, 1106, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.34 (m, 5H), 5.15 (m, 2H), 5.04 (br d, 1H), 3.72 (m, 1H), 3.50 (m, 2H), 3.03–2.50 (m, 3H), 1.95–1.90 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 157.2 (C), 136.8 (C), 128.5 (CH), 128.2/128.1 (CH), 127.9/127.8 (CH), 67.1/66.7 (CH_2), 59.1/58.5 (CH), 52.9/52.5 (CH), 47.6/47.4 (CH_2), 47.2/46.7 (CH_2), 28.6/27.3 (CH_2), 24.1/23.2 (CH_2). MS (CI, NH_3): *m/z* = 265 ($[M+18]^+$, 26%), 248 ($[M+1]^+$, 100%), 204 ($[M-43]^+$, 7%). HRMS (ESI-TOF): *m/z* calcd for $C_{14}H_{18}NO_3$: 248.1287; found for $[M+1]^+$: 248.1281.