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A Convenient, Stereodivergent Approach to the Enantioselective Synthesis of *N*-Boc-Aminoalkyl Epoxides

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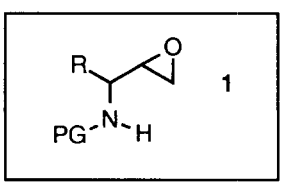
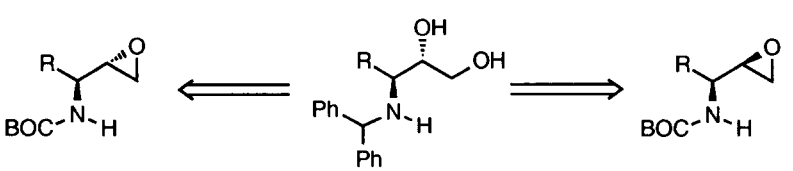
Abstract: An efficient, stereodivergent and enantioselective synthesis of *N*-Boc-aminoalkyl epoxides has been developed. Starting from enantiomerically enriched *anti* *N*-diphenylmethyl-3-amino-1,2-diols, and after a change in the nitrogen protecting group, an intramolecular Mitsunobu reaction leads to the *erythro* aminoalkyl epoxides; a three step sequence consisting of protection of the primary alcohol, activation of the secondary alcohol and simultaneous deprotection/cyclization affords in good yields the corresponding *threo* isomers.

Protected aminoalkyl epoxides ([1-aminoalkyl]oxiranes, **1**) are useful synthetic intermediates, especially in connection with the preparation of several dipeptide isosteres used in the assembly of selective inhibitors of some key aspartic proteases, such as renin[1] and HIV-1 protease.[2]



Previous syntheses of aminoalkyl epoxides have been based on sulfonium ylide addition to protected α-amino aldehydes,[3] on the stereoselective epoxidation of allyl amines (these two methods giving preferentially the *threo* isomers),[2g,4] on the *erythro*-selective reduction of α-amino-α'-halo-[5] or α'-hydroxyketones,[2h] or on the reductive amination of α-ketoepoxides.[6,7] It is worth noting that in all of these approaches, with exception of the last one,[6] the ultimate starting material is an α-amino acid.

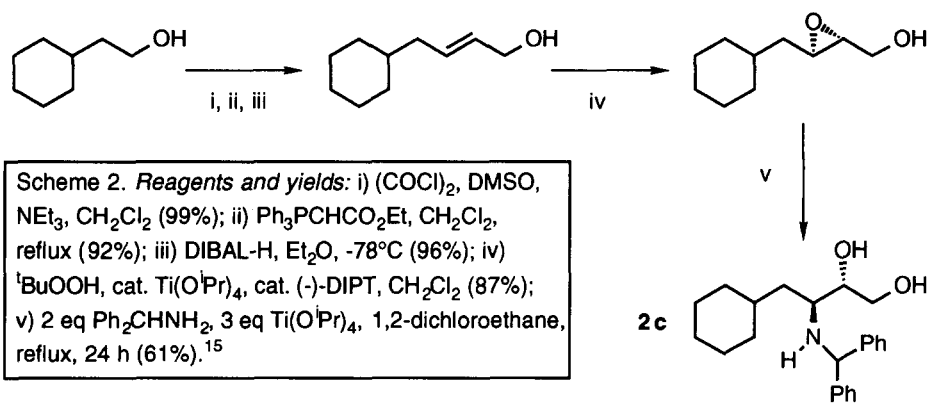
A few years ago, we described a practical approach to scalemic *erythro* *N*-diphenylmethyl-3-amino-1,2-diols (**2**) based on the regio- and stereoselective opening of enantioenriched epoxy alcohols[8] with primary amines.[9] Subsequent research in our laboratory has shown that amino diols **2** are excellent chiral building blocks for the enantioselective preparation of azetidinols,[10] aziridines,[10] *N*-Boc-α-amino acids,[11] allylamines[12] and *N*-Boc-β-amino acids.[12] In the present communication, we report on the successful stereodivergent conversion of amino diols **2** into both *erythro [anti]* (**1E**) and *threo [syn]* (**1T**) *N*-Boc-aminoalkyl epoxides (Scheme 1).



1E **2** **1T**

Scheme 1

In order to ascertain the effect of the nature of the R group of the aminoalkyl glycols **2** in the efficiency of the synthetic process, we selected three *erythro* *N*-diphenylmethyl-3-amino-1,2-diols (**2a-c**) with different alkyl substituents as starting materials. The preparation of **2a** (R=CH_3; 91% e.e.) and **2b** (R=C_6H_5; >99% e.e.) has been previously described;[9] the new[13] amino diol **2c** was obtained in high enantiomeric purity (e.e. > 90%, according to the ^1H NMR spectrum of the Mosher's ester[14] of the intermediate *(2R,3R)* epoxy alcohol) by means of the sequence depicted in Scheme 2.

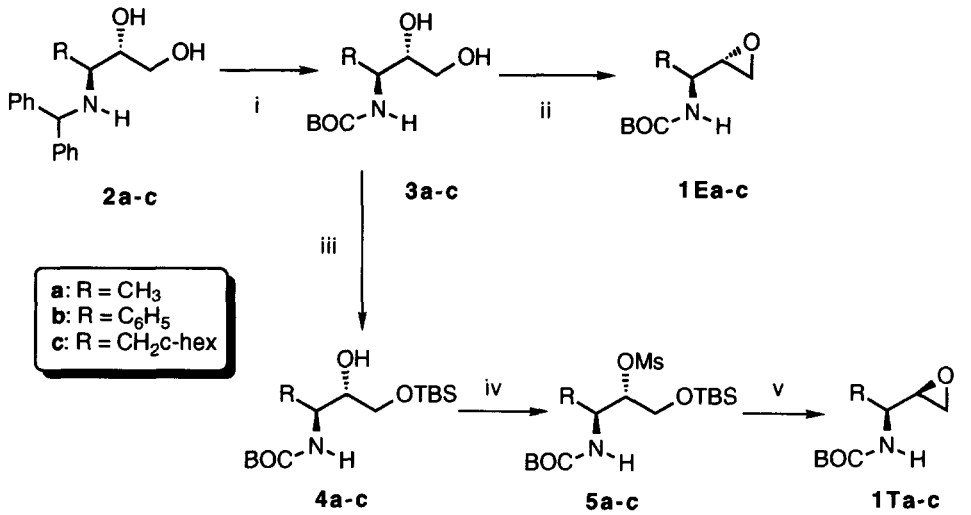


Scheme 2. *Reagents and yields:* i) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2 (99%); ii) Ph_3PCHCO_2Et, CH_2Cl_2, reflux (92%); iii) DIBAL-H, Et_2O, -78°C (96%); iv) ^tBuOOH, cat. $Ti(O^iPr)_4$, cat. (-)-DIPT, CH_2Cl_2 (87%); v) 2 eq Ph_2CHNH_2, 3 eq $Ti(O^iPr)_4$, 1,2-dichloroethane, reflux, 24 h (61%).[15]

Since the conversion of **2a-c** into the epoxides **1T** or **1E** requires the activation of one of the hydroxyl groups, the diphenylmethyl protecting group was changed to the *tert*-butoxycarbonyl[11a] at the beginning of the sequence, in order to avoid competing intramolecular cyclization reactions.[10] Moreover, the resulting *N*-Boc-3-amino-1,2-diols **3a-c** are highly crystalline solids, thus offering the opportunity of further enantiomeric enrichment by recrystallization (from hexane/ether). After some experimentation, we were most pleased to find that a simple procedure for the one-pot transformation of **3** into the *anti* epoxides **1E** consisted in an intramolecular Mitsunobu reaction,[16] which cleanly accomplished the desired conversion of the 1,2-diol to the terminal epoxide with retention of configuration at C-2. In no case were we able to detect products arising from the participation of the *tert*-butoxycarbonylamino neighbouring group (Scheme 3).[17]

On the other hand, the conversion of **3a-c** into *threo* epoxides involves an inversion of configuration at the secondary alcohol, and the intermediate protection of the primary alcohol was thus required. A screening of base-labile hydroxyl protecting groups revealed that a reliable route to the *threo* epoxides **1T** consisted of: a) selective protection of the primary alcohol of **3** as *tert*-butyldimethylsilyl ether; b) mesylation of the secondary alcohol; and c) one-pot deprotection/cyclization effected by successive treatment of the mesylates **5a-c** with tetrabutylammonium fluoride and sodium methoxide (Scheme 3). This sequence gave satisfactory yields of the desired *syn* amino epoxides **1T** with complete inversion of configuration at C-2.[17]

In summary, we have developed efficient and completely stereoselective routes to both enantiomerically pure *erythro* and *threo* *N*-Boc-aminoalkyl epoxides **1** from the *erythro* 3-diphenylmethylamino-1,2-diols **2**. Synthetic applications of chiral *N*-Boc-aminoalkyl epoxides are in development in our laboratories and will be reported in due course.



Scheme 3. *Reagents and yields:* i) $(Boc)_2O$, H_2, cat. $Pd(OH)_2/C$, AcOEt (**3a**: 85%; **3b**: 90%; **3c**: 85%); ii) PPh_3, DEAD, $CHCl_3$, reflux (**1Ea**: 68%; **1Eb**: 84%; **1Ec**: 77%); iii) $^tBuMe_2SiCl$, imidazole, DMF, R. T. (**4a**: 78%; **4b**: 75%; **4c**: 76%); iv) MsCl, NEt_3, cat. 4-DMAP, CH_2Cl_2 (**5a**: 94%; **5b**: 67%; **5c**: 97%); v) 1M TBAF, NaOMe, THF (**1Ta**: 80%; **1Tb**: 56%; **1Tc**: 81%).

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17.- **Representative experimental procedure: *(S)*-1-[*(S)*-1-(*t*-butoxycarbonylamino)-1-phenylmethyl] oxirane, 1Eb:** An stirred mixture of *N*-Boc-amino diol **3b**[11a] (0.50 g, 1.87 mmol), triphenylphosphine (0.52 g, 1.96 mmol) and diethyl azodicarboxylate (0.34 g, 1.96 mmol) in dry chloroform (16 mL) was refluxed for 36 h; after elimination of the solvent at reduced pressure, the crude residue was purified by column chromatography on triethylamine-pretreated silica gel (2.5% v/v), eluting with hexane/ethyl acetate mixtures, to give 0.39 g (84% yield) of the title compound as a white solid of m. p. 90-91°C. $[\alpha]_D^{20}$ = +22.4 (c=2.74, $CHCl_3$). IR (KBr) ν_{max}: 3380, 3040, 3000, 2950, 1695, 1530, 1250, 750, 700 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.42 (s, 9H), 2.50 (dd, J=4.8 Hz, J'=2.6 Hz, 1H), 2.75 (dd, J=4.8 Hz, J'=3.9 Hz, 1H), 3.25 (m, 1H), 4.71 (br s, 1H), 5.20 (br d, 1H, NH), 7.32 ppm (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 28.3 (q), 45.8 (t), 53.8 (d), 55.4 (d), 79.9 (s), 127.1 (d), 127.9 (d), 128.6 (d), 137.9 (s), 155.1 ppm (s). MS (CI-NH_3) *m/e*: 250 (M+1, 33%), 267 (M+18, 100%), 284 (M+35, 4%). Anal. Found: C, 67.49; H, 7.65; N, 5.59. (Calc. for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62).

***(R)*-1-[*(S)*-1-(*t*-butoxycarbonylamino)-1-phenylmethyl]oxirane, 1Tb:** To an ice-cooled, stirred solution of *N*-Boc-amino mesylate **5b**[18] (0.13 g, 0.29 mmol) in 1 mL of anhydrous THF, 0.52 mL of a 1.1 M solution of tetrabutylammonium fluoride in THF (Aldrich, 0.57 mmol) were added dropwise. The solution was stirred at room temperature for 15 min., and treated with solid sodium methoxide (17 mg, 0.32 mmol). The stirring was continued for 30 min., after which time the reaction mixture was poured into water (5 mL) and extracted thrice with diethyl ether (5 mL). After drying ($MgSO_4$) and elimination of the solvent at reduced pressure, the crude residue was purified by column chromatography on triethylamine-pretreated silicagel (2.5% v/v), eluting with hexane/ethyl acetate mixtures, to give 40 mg (56% yield) of the title compound as a white solid of m. p. 80-81°C. $[\alpha]_D^{20}$ = +99.8 (c=2.04, $CHCl_3$). IR (KBr) ν_{max}: 3480, 3060, 3020, 2990, 2940, 1680 (br), 1520, 1250, 880, 750, 700 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.41 (s, 9H), 2.74 (m, 1H), 2.80 (m, 1H), 3.26 (br s, 1H), 4.96 (br signal, 2H, C-1'H and NH), 7.39 ppm (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 28.3 (q), 44.3 (t), 53.1 (d), 54.0 (d), 79.9 (s), 127.0 (d), 127.9 (d), 128.0 (d), 140.2 (s), 155.3 ppm (s). MS (CI-NH_3) *m/e*: 250 (M+1, 34%), 267 (M+18, 100%), 284 (M+35, 6%). Anal. Found: C, 66.85; H, 7.64; N, 5.58. (Calc. for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62).
18.- Prepared from amino diol **3b** according to standard procedures (see Scheme 3).

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