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An Enantioselective Entry to Linear, C_2-Symmetrical and Pseudosymmetrical 1,6-Diamino-2,5-diols

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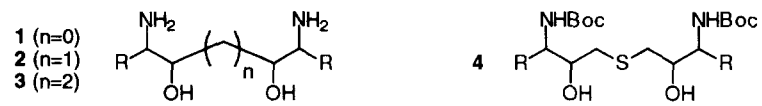
Abstract: An enantioselective synthesis of C_2-symmetrical and pseudosymmetrical acyclic 1,6-diamino-2,5-diols has been accomplished for the first time by employing a Ramberg-Bäcklund reaction as the key step.

Key words: *Amino alcohols; asymmetric synthesis; enzyme inhibitors; sulfides*

The enantioselective synthesis of organic compounds with C_2 symmetry, particularly those containing amino and hydroxyl groups, is receiving much attention, due to the promising applications of these structures both as chiral ligands[1] and as core units of pseudopeptide HIV protease inhibitors and other bioactive molecules.[2] In particular, several synthetic routes to C_2-symmetrical 1,4-diamino-2,3-diols (**1**) have been described in the literature.[3] On the other hand, the closely related homologous systems **2** and **3** remain practically unexploited, there being a lack of efficient synthetic methods for their construction. We wish to report here a regio- and stereoselective approach to the synthesis of 1,6-diamino-2,5-diols (**3**), which uses the easily available, enantiopure *anti-N*-Boc-3-amino-1,2-diols as starting materials.[4]



A retrosynthetic analysis of the general structure **3** revealed that these compounds can in principle be accessed, using a Ramberg-Bäcklund reaction[5] as the carbon-carbon bond forming step, from the sulfur-tethered bis(amino alcohols) **4**, whose synthesis has been recently completed in our laboratories.[6] The actualization of these ideas for the preparation of C_2-symmetrical 1,6-diamino-2,5-diols is shown in Scheme 1. First, the vicinal amino and hydroxy groups in sulfides **4a,b** were converted into the corresponding dimethyloxazolidines (2,2-dimethoxypropane or 2-methoxypropene, cat. *p*-toluenesulfonic acid)[4c] in order to avoid interferences with the strongly basic conditions required for the Ramberg-Bäcklund reaction. The protected compounds **5a,b** were then oxidized with *m*-chloroperbenzoic acid in dichloromethane to afford the sulfones **6a,b** in nearly quantitative yields. After some experimentation, we found that the optimal reaction conditions for the Ramberg-Bäcklund reaction of **6a,b** involved the use of potassium hydroxide on alumina as a base and dibromodifluoromethane as the brominating agent, in *tert*-butyl alcohol at room temperature.[7] The resulting olefins **7a,b** (obtained as *ca.*

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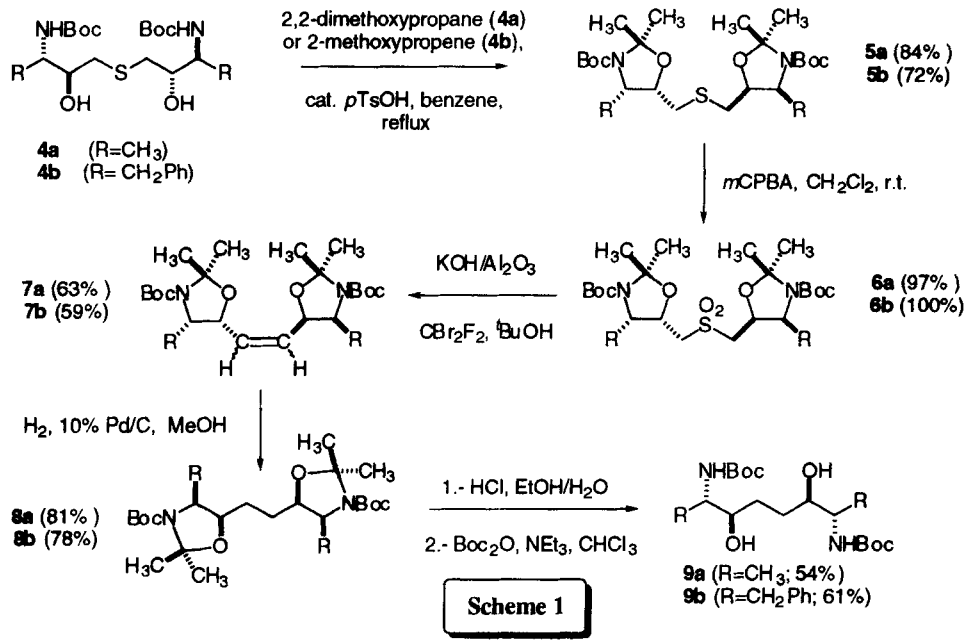
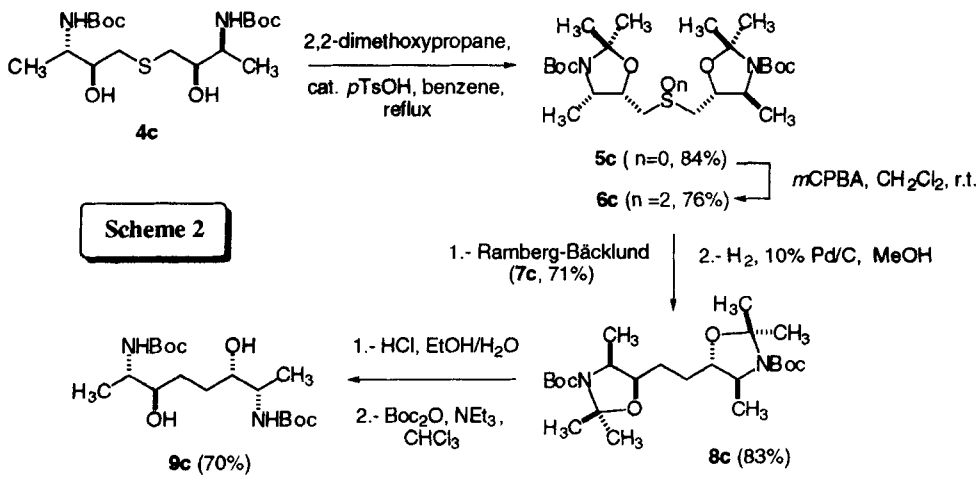
70:30 mixtures of the *E* and *Z* isomers) were hydrogenated to afford the protected 1,6-diamino-2,5-diols **8a,b** in good overall yields. Finally, acid-catalyzed hydrolysis (HCl, EtOH/H_2O) of the oxazolidine and carbamate groups provided the free 1,6-diamino-2,5-diols, which were most conveniently purified and characterized after their conversion to the corresponding bis(*N*-Boc) derivatives **9a,b**.



The above methodology can also be applied to the synthesis of pseudosymmetrical 1,6-diamino-2,5-diols Thus, the sulfur-tethered bis(amino alcohol) **4c**[6] was efficiently converted into (2*S*,3*R*,6*S*,7*S*)-2,7-bis(*t*-butoxycarbonylamino)-3,6-octanediol (**9c**) by means of the reaction sequence summarized in Scheme 2.



In summary, both C_2-symmetrical and pseudosymmetrical 1,6-diamino-2,5-diols can be prepared in a totally regio- and stereocontrolled way by means of a synthetic procedure in which the assembly of two enantiopure β-amino alcohol moieties is achieved by a Ramberg-Bäcklund reaction.[8] It is worth noting that, from the retrosynthetic point of view, this procedure provides a novel disconnective transform that can be useful in the synthetic analysis of stereochemically complex acyclic chains.[9,10] The application of this novel strategy to the construction of other acyclic systems with stereogenic centers having a 1,4-spatial relationship is currently being evaluated in our laboratories.

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temperature, the reaction mixture was diluted with methylene chloride and filtered through Celite. Elimination of solvents at reduced pressure and chromatographic purification (SiO_2, hexane/diethyl ether) gave 8 mg of pure *(Z)* isomer, 21 mg of pure *(E)* isomer and 25 mg of a 2:1 (*E*:*Z*) mixture of **7a**. The overall yield of **7a** (70:30 *E*/*Z* isomer mixture) was 63%. (*E*)-**7a**: $[\alpha]_D$= -17.6 (*c* = 1.80, $CHCl_3$). IR (NaCl film) : ν_{max} 2980, 2930, 1690, 1390, 1370 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 55°C): δ = 1.08 (d, *J* = 6.6 Hz, 6H), 1.47 (s, 18H), 1.52 (s, 6H), 1.60 (s, 6H), 3.85-4.02 (m, 2H), 4.54-4.60 (m, 2H), 5.80 (dd, *J*=1.35 Hz, *J'*=3.15 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 55°C): δ = 15.6 (CH_3), 24.7 (br, CH_3), 26.7 (CH_3), 27.5* (CH_3), 28.5 (CH_3), 56.2 (CH), 76.6 (CH), 79.8 (Cq), 93.2 (Cq), 128.6 (CH), 151.7 (Cq) ppm. MS (CI-NH_3) *m/e* = 455 ($M+1^+$, 11%), 472 ($M+18^+$, 49%). HRMS (CI-NH_3): Calcd. for $C_{24}H_{42}N_2O_8$+H, 455.3121; found, 455.3102. *b) Catalytic hydrogenation.* A solution of the olefin mixture **7a** (81 mg, 0.18 mmol) in dry methanol (3.5 mL) was stirred at room temperature under hydrogen (atmospheric pressure) in the presence of 10% Pd/C (8 mg, 0.018 mmol) during 24 h. At this point, an equivalent amount of catalyst was added and the stirring was continued for 24 h. The reaction mixture was diluted with dichloromethane, filtered through Celite and evaporated at reduced pressure to give the crude product. Chromatographic purification (NEt_3-pretreated SiO_2, hexane/diethyl ether) afforded 66 mg (81% yield) of the protected diamino diol **8a.** $[\alpha]_D$= -6.5 (*c* = 1.70, CHCl3). IR (NaCl film): ν_{max} 2970, 2930, 2850, 1695, 1385, 1320, 1310 cm^{-1}. ^1H NMR (300 MHz, CDCl3): δ = 1.10 (two overlapping d, 6H), 1.47 (s, 18H), 1.50-1.60 (m, 16H), 3.80-4.05 (m, 4H) ppm. ^{13}C NMR (75 MHz, CDCl3): δ = 13.8 (CH_3), 14.5* (CH_3), 23.8 (CH_3), 24.9* (CH_3), 25.6 (CH_2), 27.3 (CH_3), 28.2* (CH_3), 28.5 (CH_3), 55.3 (CH), 75.8 (CH), 79.2 (Cq), 79.9* (Cq), 92.4 (Cq), 92.6* (Cq), 151.6 (Cq), 151.8* (Cq) ppm. MS (CI-NH3) *m/e* = 457 ($M+1^+$, 22%), 474 ($M+18^+$, 100%). HRMS (CI-NH_3): Calcd. for $C_{24}H_{44}N_2O_8$+H, 457.3278; found, 457.3289. Signals marked with an asterisk correspond to a rotamer.

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