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SYNTHESIS OF NOVEL CHIRAL BISAZETIDINES BY THE HYDROALANE REDUCTION OF BIS-BETA-LACTAMS

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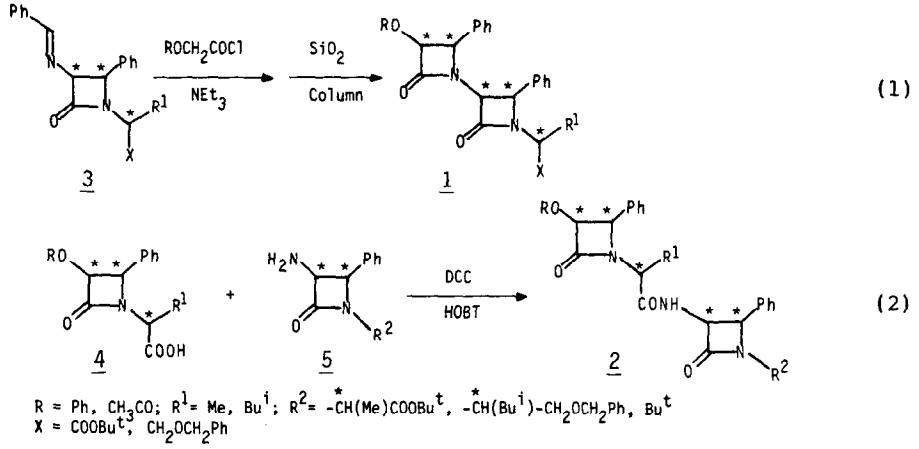
Summary: A series of novel chiral bisazetidines in which two azetidine rings are either directly connected or coupled in tandem style, are synthesized in good yields by the hydroalane reduction of the corresponding bis-beta-lactams.

The azetidine skeleton has been one of the most difficult amines to synthesize because of its ring strain. Recently, however, we and Sammes' research group have developed two effective methods for the synthesis of azetidines from the corresponding monocyclic beta-lactams.[1,2] Our method is the direct and selective reduction of beta-lactam by using hydroalanes[1] whereas Sammes' method is a two step synthesis consisting of the diborane reduction of a beta-lactam to a beta-amino alcohol by using a modified Mitsunobu reaction.[2]

Although it has been shown that a variety of azetidines exhibit various biological activities,[3] there have not been reported any studies on the use of chiral azetidines as chiral reagents or building blocks for organic synthesis. Based on our hydroalane reduction method, we have been exploring new chemistry of chiral azetidines and polyazetidines and their use as reagents or synthetic building blocks. We would like to describe here a facile synthesis of a novel series of chiral bisazetidines by the one step reduction of bis-beta-lactams with chlorodihydroalane, AlH_2Cl, as specific reducing agent.

We employed two types of bis-beta-lactams, viz., bis-beta-lactams (1) in which two beta-lactam rings are directly connected and tandem style bis-beta-lactams (2). The bis-beta-lactams (1) were prepared by the [2+2] cycloaddition of a ketene in situ generated to a 3-benzylideneamino-beta-lactam (3) followed by chromatographic separation of two diastereomers (eq. 1) and the bis-beta-lactams (2) were prepared by the coupling of a chiral beta-lactam carboxylic acid (4) with a chiral 3-amino-beta-lactam (5) (eq. 2) in a manner similar to that reported previously from our laboratory.[5,7]



A typical procedure for the synthesis of chiral bisazetidines by the reduction of bis-beta-lactams with chlorohydroalane is described as follows, and typical results are summarized in Table 1.[6]

(3R,4S)-[(S)-1-(t-Butoxycarbonyl)ethyl]-3-[(3S,4R)-3-acetoxy-4-phenylazetidin-2-onyl]-4-phenylazetidin-2-one (1d)[7] (182 mg, 0.38 mmol) in dry ether (10 ml) was added to the suspension of chlorodihydroalane at ambient temperature, which was prepared in situ by mixing aluminum trichloride (387 mg, 2.90 mmol) with lithium aluminum hydride (110 mg, 2.90 mmol) in refluxing dry ether (10 ml) for 30 min. The mixture was heated under reflux for 2 hrs with stirring. The completion of the reaction was monitored by TLC. Then, water (50 ml) was added to the reaction mixture at ice-cooled temperature, and the reaction mixture was extracted with dichloromethane (90 ml) by using a centrifuge, dried over anhydrous sodium sulfate and concentrated in vacuo to give (2R,3R)-1-[(S)-1-(hydroxymethyl)ethyl]-2-phenyl-3-[(2S,3S)-2-phenyl-3-hydroxyazetidinyl]-azetidine (6d) (92.6 mg, 72% yield) as a viscous oil.

The obtained novel chiral bisazetidines are unique chiral polyamines bearing rigid azetidine rings as stereo-controlling factor, and are expected to serve as effective optical resolution reagents, chiral catalysts for asymmetric Michael addition, chiral ligands for metal complexes and chiral liquid phase or modifier for chiral columns for chromatography. Also, these novel chiral bisazetidines can readily be converted to the corresponding open chain chiral polyamino alcohols and polyamino ethers by hydrogenolysis on palladium catalyst,[8] which will serve as versatile chiral building blocks for the synthesis of biologically active compounds containing polyamines.

Further studies along this line are actively underway and the use of these novel chiral bisazetidines and their derivatives as chiral reagents will be reported elsewhere shortly.

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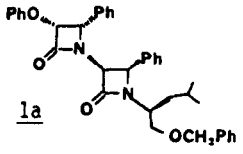
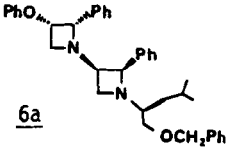
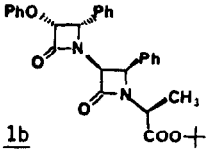
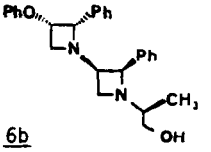
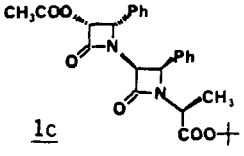
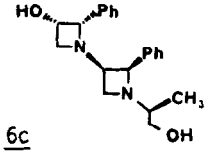
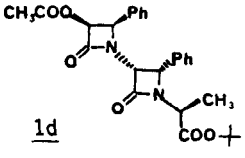
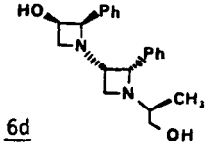
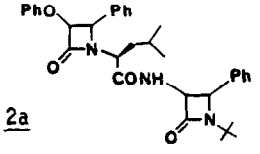
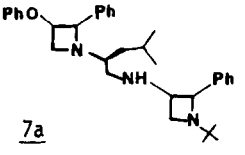
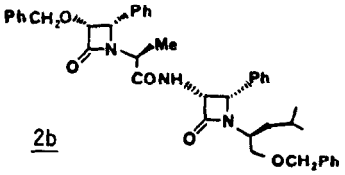
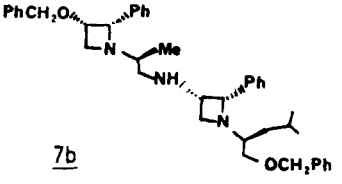
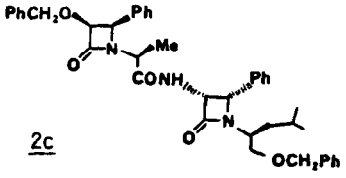
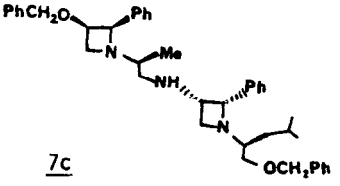
Table 1. Synthesis of Novel Bisazetidines

Bis-β-lactams	Conditions	Bisazetidines	Isolated Yield(%)
 1a	AlH_2Cl (7.2 eq.) Ether reflux 1.5 h	 6a	88
 1b	AlH_2Cl (7.2 eq.) Ether reflux 2 h	 6b	66
 1c	AlH_2Cl (7.2 eq.) Ether reflux 2 h	 6c	63
 1d	AlH_2Cl (7.2 eq.) Ether reflux 2 h	 6d	72
 2a	AlH_2Cl (7.2 eq.) Ether reflux 2 h	 7a	80
 2b	AlH_2Cl (7.2 eq.) Ether reflux 5 h	 7b	50
 2c	AlH_2Cl (7.2 eq.) Ether reflux 5 h	 7c	40

References and Notes

1. M. Yamahita and I. Ojima, J. Am. Chem. Soc., 105, 6339 (1983).
2. P. G. Sammes and S. Smith, J. Chem. Soc., Chem. Commun., 682 (1983).
3. (a) E. Testa, A. Wittigens, G. Maffii and G. Bianchi In "Research Progress in Organic, Biological and Medicinal Chemistry", U. Gallo and L. Santamaria Eds., North-Holland Pub. Co., Amsterdam, 1964, Vol. 1, pp 477-583. (b) K. Masuda, Yuki Gosei Kagaku Kyokaishi, 30, 271 (1972). (c) E. Bellasio and G. Cristiani, J. Med. Chem., 12, 196 (1969). (d) D. D. Miller, J. Fowble and P. N. Patil, ibid., 16, 177 (1973). (e) T. Okutani, T. Kaneko and K. Masuda, Chem. Pharm. Bull., 22, 1490 (1974). (f) J. N. Wells and O. R. Tarwater, J. Pharm. Sci., 60, 156 (1971).
4. All new compounds gave satisfactory spectral (IR, 300 MHz NMR) data and microanalyses. The specific optical rotations for the chiral bis-beta-lactams are as follows (2a is racemic): 1a, $[\alpha]_D^{20}$-24.1° (c 1.00, $CHCl_3$); 1b, $[\alpha]_D^{20}$-40.8° (c 1.00, $CHCl_3$); 1c, $[\alpha]_D^{20}$+56.5° (c 1.01, $CHCl_3$); 2b, $[\alpha]_D^{20}$+ 20.8° (c 1.00, $CHCl_3$); 2c, $[\alpha]_D^{20}$-16.0° (c 1.00, $CHCl_3$).
5. (a) N. Hatanaka and I. Ojima, J. Chem. Soc., Chem. Commun., 344 (1981). (b) H. Hatanaka, R. Abe and I. Ojima, Chem. Lett., 445 (1982). (c) I. Ojima In "Asymmetric Reactions and Processes in Chemistry", E. L. Eliel and S. Otsuka, Eds., ACS Symp. Ser., 185, American Chemical Society, Washington, D. C., 1982, pp 109-138.
6. All new compounds gave satisfactory spectral (IR, 300 MHz NMR) data and elemental analyses. The specific optical rotations for the chiral bisazetidines are as follows (7a is racemic); 6a, $[\alpha]_D^{20}$-53.1° (c 1.00, $CHCl_3$); 6b, $[\alpha]_D^{20}$-74.9° (c 0.79, $CHCl_3$); 6c, $[\alpha]_D^{20}$-57.5° (c 0.73, $CHCl_3$); 6d, $[\alpha]_D^{20}$+61.3° (c 0.93, $CHCl_3$); 7b $[\alpha]_D^{20}$+2.0° (c 1.53, $CHCl_3$); 7c $[\alpha]_D^{20}$-54.1° (c 0.98, $CHCl_3$).
7. The preparation of the bis-beta-lactams, 1d and 2b, are typically described.
(a) The preparation of 1d

The solution of 3b [R^1=Me, X=$COOBu^t$; (3S,4R,1'S)] (1.076g) and Et_3N (2.20ml) in dry CH_2Cl_2 (50ml) was added dropwise acetoxyacetyl chloride (2.10g) at -15°C and the mixture was stirred overnight at 0°C∿ambient temperature. After washing with 5% $NaHCO_3$aq, water, 10% aqueous citric acid and brine, drying over anhydrous $MgSO_4$ and removal of solvent, a crude mixture of the bis-beta-lactams (1d and 1d') was obtained, which was submitted to a column chromatography on silica gel (eluant: n-hexane/AcOEt=2/1) to give 1d [(3S",4S")-isomer, 724 mg] and the other diastereomer (1d') [(3R",4R")-isomer, 228mg] as colorless crystals (total yield: 70%)

1d: mp. 151-152°C. NMR ($CDCl_3$,TMS) δ 1.17(d, J=7Hz, 3H), 1.43(s, 9H), 1.54(s, 3H), 4.06(d, J=5Hz, 1H), 4.51(d, J=5Hz, 1H), 4.55(q, J=7Hz, 1H), 5.04(d, J=5Hz, 1H) and 7.00-7.60(m, 10H). IR (KBr disk) 1775, 1750, 1730(s) (νc=o) cm^{-1}.

1d': mp. 143-144°C. NMR ($CDCl_3$,TMS) δ 1.17(d, J=7Hz, 3H), 1.43(s, 9H), 1.54(s, 3H), 4.22 (d, J=5Hz, 1H), 4.38(q, J=7Hz, 1H), 5.04(d, J=5Hz, 1H), 5.22(d, J=5Hz, 1H), 5.40(d, J=5Hz, 1H), and 6.70-7.60(m, 10H). IR (KBr disk) 1790, 1750, 1740(s) (νc=o) cm^{-1}.

(b) The preparation of 2b

To a solution of 4b' [R=$PhCH_2$, R^1=Me; (3R,4S)][9] (618mg), 5a [R^2= $-CH(Bu^i)CH_2OCH_2Ph$; (1S)][5b] (670mg) and 1-hydroxybenzotriazole(HOBT) (282mg) in DMF (15ml) was added DCC (392mg) in DMF (5ml) at 0°C with stirring and the mixture was stirred at ambient temperature overnight. After the removal of solvent, AcOEt (50ml) was added and the resulting white precipitates were filtered off. The filtrate was washed with 10% aqueous citric acid, water, 5% $NaHCO_3$aq, water and brine, and dried over anhydrous $MgSO_4$. After the removal of solvent in vacuo, the residue was submitted to chromatographic purification on a short silica gel column (eluant: n-hexane/AcOEt=1/1) to give 2c (752mg, 60%).

2b: mp. 187-188°C. NMR ($CDCl_3$,TMS) δ 0.79(d, J=6.5Hz, 3H), 0.92(d, J=7.5Hz, 3H), 0.94(d, J=6.5Hz, 3H), 1.38-1.48(m, 1H), 1.58-1.79(m, 2H), 3.27(dd, J=4,10Hz, 1H), 3.40(dd, J=7.5,10Hz, 1H), 3.79-3.88(m, 1H), 4.03(d, J=5Hz, 1H), 4.11(s, 2H), 4.13(q, J=7.5Hz, 1H), 4.27(d, J=12Hz, 1H), 4.33(d, J=12Hz, 1H), 4.36(d, J=5Hz, 1H), 4.98(d, J=5.5Hz, 1H), 5.39(dd, J=5.5,8.5Hz, 1H), 6.95-7.38(m, 20H) and 7.15(d, J=8.5, 1H). IR (KBr disk) 1750, 1650 (νc=o) cm^{-1}.

8. As for the conversion of an azetidine to the corresponding open chain amine by hydrogenolysis on Pd/C, see Reference 1.
9. The precursor of 4b', (3R,4S)-1-[(S)-1-(t-butoxycarbonyl)ethyl]-3-benzyloxy-4-phenylazetidin-2-one (8b'), was prepared by the cycloaddition of benzyloxyketene in situ generated from benzyloxyacetyl chloride and Et_3N to t-butyl (S)-N-benzylidenealaninate in the same manner as that reported previously from our loboratory [I. Ojima, S. Suga and R. Abe, Tetrahedron Lett., 21, 3907 (1980)], followed by chromatographic separation on silica gel: 8b' [(3R,4S)-isomer], 33%, mp. 129.5-130°C, $[\alpha]_D^{20}$+117.9° (c 0.95, MeOH); 8b [(3S,4R)-isomer], 40.5%, mp. 102-103°C, $[\alpha]_D^{20}$-100.0° (c 0.95, MeOH). Then, 8b' was treated with CF_3COOH in anisole at 0-25°C for 12 hrs to give 4b' in 92% yield: 4b', mp. 134-135°C, $[\alpha]_D^{20}$ +105.9° (c 1.01, MeOH).

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