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A novel synthesis of chiral cyclopentyl- and cyclohexyl-amines

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A new route to multifunctionalised chiral cyclopentyl- and cyclohexyl-amines was developed by means of a new reaction involving the ring opening of a 2-azabicyclo-[2.2.1] or -[2.2.2] structure in high yields.

Functionalised chiral cyclopentylamines are of extreme importance in medicinal chemistry since this structural unit is present in a large number of antibiotics. The most interesting are amidomycin[1] and aristeromycin,[2] which have been shown to have antiviral properties, and carbovir[3] which is a promising antibiotic used for the treatment of AIDS[4] (Fig. 1).

We have previously reported our work on 2-azanorbornyl derivatives and their use in various reactions, *i.e.* copper-catalyzed allylic oxidation of olefins,[5a] ruthenium-catalyzed transfer hydrogenation of ketones,[5b] diethylzinc addition to both imines and aldehydes,[5c] borane reduction of ketones,[5d] rearrangement of *meso*-epoxides[5e] and preparation of cyclopentylglycine analogues.[5f] During research to modify the ligand structure, an interesting reaction was discovered that opens up a new, rapid route to substituted enantiomerically pure cyclopentylamines *via* a ring opening reaction of the bicyclic structure **A** [reaction (1)].

When attempting the preparation of the corresponding Grignard reagent of the bicyclic bromide **A**, an unexpected ring opening of the bicyclic structure occurred. Initially **C** was formed with the concurrent formation of another compound which was assigned to structure **B**. The 1 : 1 mixture of products (**B** : **C**) was inseparable by flash chromatography, but the compounds were assigned the structures displayed in reaction (1) by analysis of the spectral data of the mixture.

Despite the low selectivity, the novelty and usefulness of the ring opened product prompted us to optimize the conditions in order to favour its formation. Better results were obtained when the *N*-protecting PhEt group attached to the nitrogen in **A** was replaced by tosyl to give the corresponding tosylate **3** (Scheme 1). The electron-withdrawing properties of this group facilitate the ring opening reaction and the desired compound **4** was obtained in high yield as a single product.

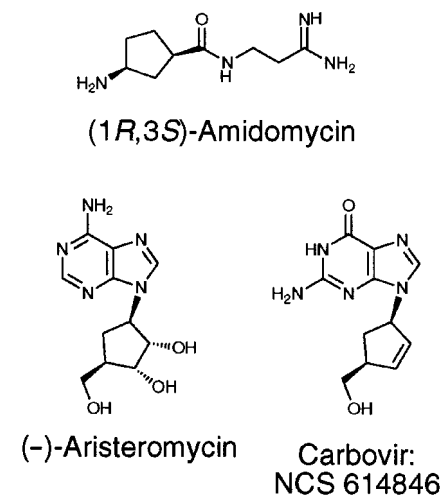
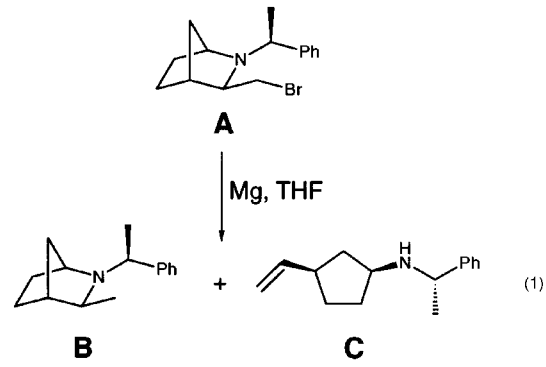


Fig. 1 Some examples of pharmaceutically active cyclopentylamines.

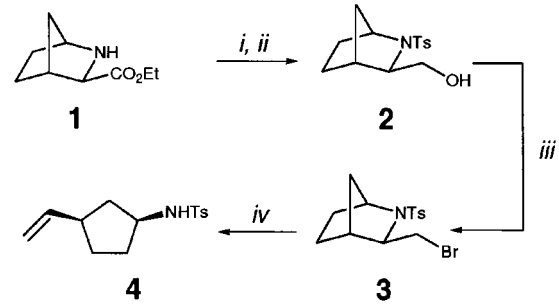


The synthetic route to the key intermediate **3** is outlined in Scheme 1. Compound **1** was obtained *via* a diasteroselective aza-Diels–Alder reaction between cyclopentadiene and the *in situ* generated imine ion of ethyl glyoxylate and (*S*)-1-phenylethylamine,[6,7] followed by simultaneous hydrogenation and hydrogenolysis to the corresponding free amino ester.[5c]

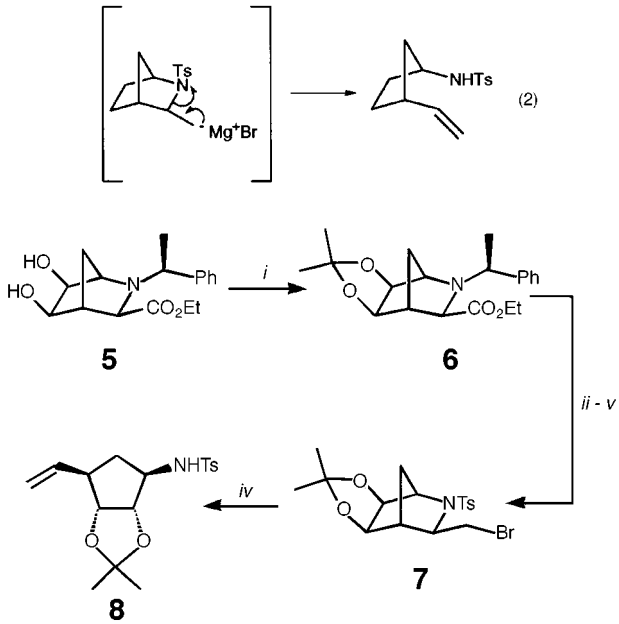
N-Tosylation and subsequent $LiAlH_4$ reduction of the ester functionality led to the alcohol **2**. The alcohol was then treated with CBr_4 and Ph_3P in CH_2Cl_2 to afford the key intermediate **3**. When treated with magnesium and tetrahydrofuran at reflux, the bicyclic bromide ring opened to give compound **4** *via* the mechanism outlined in reaction (2). Acid hydrolysis of the reaction mixture and purification of the crude residue by flash chromatography furnished the desired ring opened product in high yield.

This new methodology could also be extended to other derivatives of the 2-azanorbornyl structure. Catalytic dihydroxylation of the Diels–Alder adduct (used for the synthesis of **1**) with OsO_4 in the presence of NMO as a co-oxidant in *tert*-butyl alcohol at room temperature afforded diol **5** (Scheme 2).

Protection of diol **5** as the corresponding ketal was achieved by treatment with 2,2-dimethoxypropane and toluene-*p*-sulfonic acid in warm MeOH. Formation of product **6** required the use of slightly more than one equivalent of the acid probably due to protonation of the amine functionality, and under these conditions the reaction was completed in *ca.* 15 minutes. Solvent evaporation followed by addition of 20% aqueous NaOH and extractive work-up afforded the pure protected diol **6**. This product was treated with ammonium formate in EtOH at



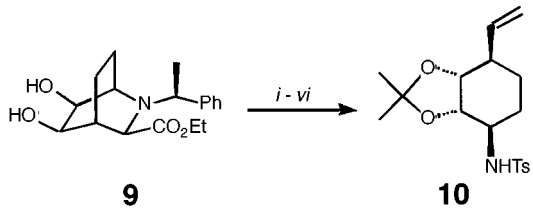
Scheme 1 *Reagents and conditions*: (i) TsCl, Et_3N, CH_2Cl_2 rt, overnight, 92%; (ii) $LiAlH_4$, THF, rt, 2 h, 95%; (iii) CBr_4, Ph_3P, CH_2Cl_2, rt, 24 h, 60%; (iv) Mg, $BrCH_2CH_2Br$, THF, reflux, 24 h, 90%.



Scheme 2 *Reagents and conditions*: (i) $(MeO)_2C(CH_3)_2$, TsOH, warm MeOH, 15 min, 87%; (ii) ammonium formate, Pd/C (10%), EtOH, reflux, 1 h, 99%; (iii) TsCl, Et_3N, CH_2Cl_2, rt, overnight, 90%; (iv) $LiAlH_4$, THF, rt, 2 h, 92%; (v) CBr_4, Ph_3P, CH_2Cl_2, rt, 24 h, 59%; (vi) Mg, $BrCH_2CH_2Br$, THF, reflux, 32 h, 89%.

reflux in the presence of Pd/C (10%) to afford the corresponding free amino ester, and then submitted to the same synthetic sequence as described for **1** to yield the corresponding bromide **7**. Compound **7** ring opened to give product **8** under the conditions described for **3**, albeit in a slightly slower reaction.

By simply using cyclohexa-1,3-diene in the aza-Diels–Alder reaction, a bicyclic [2.2.2] structure was obtained.[6] Dihydroxylation of the purified adduct under the conditions described earlier yielded compound **9** (Scheme 3) which, when submitted to the same synthetic sequence as **5**, yielded the ring opened product **10**.[8] The yields for the transformation of **9** into **10** were similar to those obtained in the transformation of **5** into **8**.[9]



Scheme 3 *Reagents and conditions*: (i) $(MeO)_2C(CH_3)_2$, TsOH, warm MeOH, 15 min, 87%; (ii) ammonium formate, Pd/C (10%), EtOH, reflux, 1 h, 99%; (iii) TsCl, Et_3N, CH_2Cl_2, rt, overnight, 91%; (iv) $LiAlH_4$, THF, rt, 2 h, 94%; (v) CBr_4, Ph_3P, CH_2Cl_2, rt, 24 h, 62%; (vi) Mg, $BrCH_2CH_2Br$, THF, reflux, 32 h, 85%.

This work opens up a new route to cyclopentyl- and cyclohexyl-amines *via* a novel ring opening reaction of [2.2.1] and [2.2.2] azabicyclic structures. The fact that the [2.2.2] structure ring opens without increased difficulty indicates that the reaction is not only a consequence of ring strain on the [2.2.1] system.

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Notes and references

1 S.-Y. Sung and A. W. Frahm, *Arch. Pharm. Pharm. Med. Chem.*, 1996, **329**, 291; S. Nakamura, K. Karasawa, N. Tanaka, H. Yonehara and H. Umezawa, *J. Antibiot., Ser. A*, 1960, 392; H. Nagata T. Taniguchi and K. Ogasawara, *Tetrahedron: Asymmetry*, 1997, **8**, 2679.

2 T. Kusaka, H. Yamamoto, M. Shibata, M. Muroi, T. Kishi and K. Mizuno, *J. Antibiot.*, 1968, 255; M. Arita, K. Adachi, H. Sawai and M. Ohno, *Nucleic Acids Res. Symp. Ser.*, 1983, **12**, 25.

3 E. L. White, W. B. Parker, L. J. Macy, S. C. Shaddix, G. McCaleb, J. A. Secrist III, R. Vince and W. M. Shannon, *Biochem. Biophys. Res. Commun.*, 1989, **161**, 393; R. Vince, M. Hua, J. Brownell, S. Daluge, F. Lee, W. M. Shannon, G. C. Lavelle, J. Qualls, O. S. Weislow, R. Kiser, P. G. Canonico, R. H. Schultz, V. L. Narayanan, J. G. Mayo, R. H. Showmaker and M. R. Boyd, *Biochem. Biophys. Res. Commun.*, 1988, **156**, 1046.

4 Other related biologically active compounds. Neplanocin A: M. Arita, K. Adachi, H. Sawai and M. Ohno, *Nucleic Acids Res. Symp. Ser.*, 1983, **12**, 25; M.-I. Lim, J. D. Moyer, R. L. Cysyk and V. E. Marquez, *J. Med. Chem.*, 1984, **27**, 1536; M.-I. Lim and V. E. Marquez, *Tetrahedron Lett.*, 1983, **24**, 5559. Guanine derivatives: A. B. Reitz, M. G. Goodman, B. L. Pope, D. C. Argentieri, S. C. Bell, L. E. Burr, E. Chourmouzis, J. Come, J. H. Goodman, D. H. Klaubert, B. E. Maryanoff, M. E. McDonnell, M. S. Rampulla, M. R. Schott and R. Chen, *J. Med. Chem.*, 1994, **37**, 3561. Adenosine analogues: Y. F. Shealy and J. D. Clayton, *J. Am. Chem. Soc.*, 1966, **88**, 3885. Tubercidin analogues: J. A. Montgomery and K. Hewson, *J. Med. Chem.*, 1967, **10**, 665. Noraristeromycin: S. M. Siddiqi, F. P. Oertel, X. Chen and S. W. Schneller, *J. Chem. Soc., Chem. Commun.*, 1993, 708. Adenosine deaminase inhibitors: H. J. Schaeffer, D. D. Godse and G. Liu, *J. Pharm. Sci.*, 1964, **53**, 1510. γ-Aminobutyric acid analogue: M. J. Milewska and T. Polonski, *Tetrahedron: Asymmetry*, 1994, **5**, 359. Carboxylic sugars and nucleosides: S. Ranganathan and K. S. George, *Tetrahedron*, 1997, **53**, 3347; M. J. Mulvihill, M. D. Surman and M. J. Miller, *J. Org. Chem.*, 1998, **63**, 4874.

5 (*a*) M. J. Södergren and P. G. Andersson, *Tetrahedron Lett.*, 1996, **37**, 7577; (*b*) D. A. Alonso, D. Guijarro, P. Pinho, O. Temme and P. G. Andersson, *J. Org. Chem.*, 1998, **63**, 2749; (*c*) D. Guijarro, P. Pinho and P. G. Andersson, *J. Org. Chem.*, 1998, **63**, 2530; (*d*) P. Pinho, D. Guijarro and P. G. Andersson, *Tetrahedron*, 1998, **54**, 7897; (*e*) M. J. Södergren and P. G. Andersson, *J. Am. Chem. Soc.*, 1998, **120**, 10760; (*f*) D. A. Alonso, S. K. Bertilsson, S. Y. Johnsson, S. J. M. Nordin, M. Södergren and P. G. Andersson, *J. Org. Chem.*, 1999, in the press.

6 L. Stella, H. Abraham, J. Feneu-Dupont, B. Tinant and J. P. Declercq, *Tetrahedron Lett.*, 1990, **31**, 2603; H. Abraham and L. Stella, *Tetrahedron*, 1992, **48**, 9707.

7 The absolute configuration of the aza-Diels–Alder adduct has been determined by means of X-ray analysis of a derivative, see: H. Nakano, N. Kumagai, C. Kabuto, H. Matsuzaki and H. Hongo, *Tetrahedron: Asymmetry*, 1995, **6**, 1233.

8 For interesting compounds containing this structure unit, see for example: G. E. Keck and S. A. Fleming, *Tetrahedron Lett.*, 1978, **48**, 4763; T. Hudlicky and H. F. Olivo, *Tetrahedron Lett.*, 1991, **32**, 6077; F. Chretien, S. I. Ahmed, A. Masion and Y. Chapleur, *Tetrahedron*, 1993, **49**, 7463; S. Grabowski, J. Armbruster and H. Prinzbach, *Tetrahedron Lett.*, 1997, **38**, 5485; H. Noguchi, T. Aoyama and T. Shioiri, *Tetrahedron Lett.*, 1997, **38**, 2883.

9 Representative spectroscopic and analytical data. (1*R*,3*S*)-1-Tosylamino-3-vinylcyclopentane (4). Magnesium metal (3.0 g, 123 mmol) was placed in a 50 mL two-neck round-bottom flask loaded with a magnetic bar. To one neck a condenser was adapted and to the other a septum. The system was evacuated and placed under argon, after which the magnesium was suspended in dry THF (3 mL). The stirring suspension was then set to reflux and a solution of compound **3** (6.0 g, 17 mmol) in dry THF (20 mL) was added in one portion *via* syringe. After stirring for 15 min a small amount of 1,2-dibromoethane was added to activate the magnesium and the mixture was heated at reflux for 24 h. The reaction was then cooled to 0 °C and quenched by addition of saturated NH_4Cl solution. After separation of the phases and extraction of the water phase with CH_2Cl_2, the combined organic layers were dried with magnesium sulfate. Solvent evaporation afforded a residue that was purified by flash chromatography to yield compound **4** (4.1 g, 15 mmol, 90%) as a white solid; mp 65–66 °C; R_f 0.11 (silica gel, pentane–ether: 80 : 20); $[\alpha]_D^{24} = -8.9$ (c = 1.0, CH_2Cl_2); $\nu(CH_2Cl_2)/cm^{-1}$ 3623, 3369, 2870, 1641, 1599, 1345, 1092, and 1047; $\delta_H(CDCl_3$, 400 MHz) 1.14–1.24 (1H, m), 1.38–1.45 (2H, m), 1.62–1.79 (1H, m), 1.80–1.90 (1H, m), 1.99–2.10 (1H, m), 2.34–2.42 (1H, m), 2.41 (3H, s), 3.57–3.63 (1H, m), 4.83–4.94 (2H, m), 5.65–5.75 (1H, m), 7.28 (2H, app. d, *J* 8.0), and 7.76 (2H, app. d, *J* 8.0); $\delta_C(CDCl_3$, 100 MHz) 21.5, 29.9, 32.6, 40.2, 41.8, 54.5, 113.1, 127.1, 129.6, 137.8, 141.9, and 143.2; *m/z* (EI) (rel. intensity) 264 (M^+, < 1%), 236 (25), 210 (13), 172 (14), 155 (62), 133 (44), 132 (36), 110 (41), 106 (17), 97 (12), 96 (43), 94 (13), 93 (25), 92 (35), 91 (100), 80 (21), 79 (17), and 65 (20) (Anal. Calcd. for $C_{14}H_{19}NO_2S$: C, 63.37; H, 7.22; N, 5.28. Found: C, 63.10; H, 7.07; N, 5.20%). The relative stereochemistry of this compound was determined by means of NOESY experiments.

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