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Stereoselective synthesis of polyhydroxylated pyrrolidines: a route to novel 3,5-bis(hydroxymethyl)pyrrolidines from 2-azabicyclo[2.2.1]hept-5-enes

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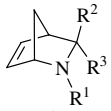
Abstract—An efficient preparation of racemic and chiral 2-functionalized-3,5-bis(hydroxymethyl)pyrrolidines is described. The method uses 2-azabicyclo[2.2.1]hept-5-enes, readily obtained from glyoxylates of aliphatic amines and cyclopentadiene, as starting material. The hydroxylation of the double bond followed by the oxidative cleavage of the six-membered ring and in situ reduction of the dialdehyde intermediate gives the title pyrrolidines.

3-Functionalized 2-azabicyclo[2.2.1]hept-5-enes (**1**) and their derivatives are useful as synthetic intermediates in the preparation of diverse compounds of pharmaceutical and/or biological interest. For example, lactam **2** has been used in the preparation of herbicides,[1] cyclic analogues of GABA,[2] the antibiotic amidomycin[3] and several antiviral and antineoplastic agents.[4]



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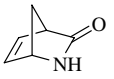

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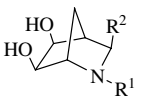

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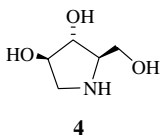
Our research group is, more recently, involved in the synthesis of polyhydroxylated pyrrolidines/piperidines from aza-bicycles (**3**). Many of these 'glycomimetics', also called azasugars or iminosugars, have shown potential useful activity, due to their structural resemblance to sugars and their resultant ability to act as glycosidase inhibitors.[5] This group of inhibitors is now finding application as antiviral[6] (included anti-HIV), antineoplastic[7] and antidiabetic agents.[8]

In particular, the compounds known as DAB1 (**4**), fagomine (**5**) and (2*S*,3*R*,4*R*)-3,4-dihydroxyproline (**6**) have been screened as potential inhibitors of HIV replication[6d,e] as part of a project looking at the potential of amino sugar derivatives in dissecting glycoprotein biosynthesis.[6f]



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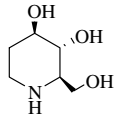

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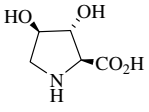

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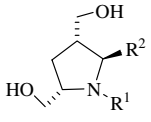

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A look at the recent literature reveals that the synthesis of 3,5-substituted prolines (or pyrrolidines) (**7**) is not a trivial task since there are only a few general routes to enantiomerically pure compounds and all of them are multistep procedures.[9] Previous results have shown that 3,6-bis(hydroxymethyl)piperidinic compounds (pipecolic analogues)[10] could be obtained via the oxidative cleavage of the alkene moiety of 2-azabicyclo[2.2.2]oct-5-enes but the preparation of the pyrrolidinic analogues from 2-azabicyclo[2.2.1]hept-5-enes has not yet been described.

In this work, we describe the synthesis of 2-functionalized 3,5-bis(hydroxymethyl)pyrrolidines (**7**) through

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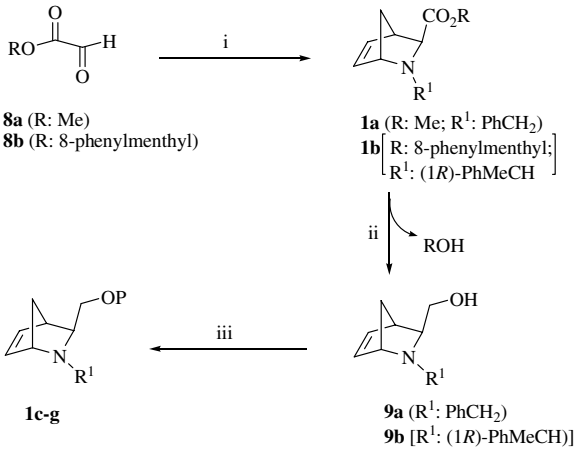


Scheme 1. Reagents and conditions: (i) Amine ($PhCH_2NH_2$ or (1*R*)-phenylethylamine), TFA, $F_3B{\cdot}OEt_2$, cyclopentadiene, CH_2Cl_2, −78 °C, 69–80%. (ii) $LiAlH_4$, Et_2O, 5 h, rt [**9a**, 97%; **9b**, 96% and ROH = (−)-8-phenylmenthol, 97%]. (iii) a: $ClSi^tBuPh_2$, Et_3N, DMAP, CH_2Cl_2, 12 h, rt (**1c**, 89%; **1d**, 91%); b: $BrCH_2Ph$, Et_3N, DMAP, CH_2Cl_2, 12 h, rt (**1e**, 81%); d: Ac_2O, Et_3N, DMAP, CH_2Cl_2, 12 h, rt (**1f**, 89%). Yields determined after purification by flash chromatography.

bis-(hydroxylation) of 2-azabicyclo[2.2.1]hept-5-enes (**1**) followed by the oxidative cleavage of the corresponding diols (**3**) and in situ reduction of the resulting intermediates (dialdehydes).

The synthesis of the starting materials (2-azabicyclo-[2.2.1]hept-5-ene derivatives) is outlined in Scheme 1.

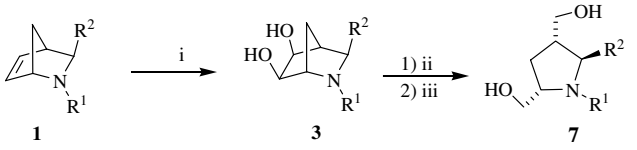
Azabicycloalkenes **1a** and **1b** were synthesised in one-step according to a literature procedure by an aza-Diels–Alder reaction between a primary amine [benzylamine or (1*R*)-phenylethylamine], cyclopentadiene and glyoxylate **8a** or **8b**, respectively.[11]

The transformation of the resulting cycloadducts (racemic *exo*-adduct **1a** and optically pure **1b**) into the corresponding aminoalcohols, **9a**[11b] (racemic) and optically pure **9b**, respectively, was achieved by reduction with $LiAlH_4$ in dry Et_2O.[11b] In the case of adduct **1b**, the yield of the corresponding amino alcohol [(−)-**9b**)][12] and the recovered chiral auxiliary [(−)-8-phenylmenthol] was 97%.[13]

Aminoalcohols **9a** and **9b** were transformed into the *O*-protected (–CH_2OP) azabicycloalkenes (**1c**–**f**) by silylation, benzylation and acetylation. All of these transformations (Scheme 1) were accomplished with retention of the configuration of the azabicycles.[11b,12]

The synthesis of the target 3,5-bis(hydroxymethyl)-pyrrolidines from these azabicycloalkenes is outlined in Scheme 2; the results obtained in Table 1.

Azabicycloalkenes (**1a**–**f**), except **1b**, were transformed into the corresponding vicinal diols using OsO_4 (cat.) and *N*-methylmorpholine *N*-oxide (cooxidant).[10] The vicinal diols **3a**–**f** yielded, upon oxidative cleavage of



Scheme 2. Reagents and conditions: (i) OsO_4/*N*-methylmorpholine *N*-oxide, dioxane/THF/H_2O, rt, 12 h. (ii) $NaIO_4/SiO_2$, CH_2Cl_2/H_2O, 20 min. (iii) $NaBH_4$, MeOH, 30 min.

Table 1. Synthesis of diols **3** and 3,5-bis(hydroxymethyl)pyrrolidines **7** from alkenes **1**

1	R^1	R^2	3 (Yield%)[a]	7 (Yield%)[a]
1a	$PhCH_2$–	–CO_2Me	**3a** (90)	**7a** (84)
1c	$PhCH_2$–	–$CH_2OSi^tBuPh_2$	**3c** (83)	**7c** (90)
1d	(1*R*)-PhMeCH–	–$CH_2OSi^tBuPh_2$	**3d** (81)	**7d** (92)
1e	(1*R*)-PhMeCH–	–CH_2OCH_2Ph	**3e** (87)	**7e** (78)
1f	(1*R*)-PhMeCH–	–CH_2OAc	**3f** (80)	**7f** (72)

[a] Yields determined after purification by flash chromatography.

the C_5–C_6 bond with $NaIO_4$/silica gel[14] in CH_2Cl_2 at room temperature, followed by an in situ reduction of the resulting crude dialdehyde with $NaBH_4$ in MeOH, the target 3,5-bis(hydroxymethyl)pyrrolidines (**7**). The yields are shown in Table 1.

All new compounds gave satisfactory ^1H NMR,[15] ^{13}C NMR and IR data together with either elemental analyses, HRMS or specific rotations.

We also attempted the synthesis of the referred pyrrolidine derivatives (**7a**–**f**) by a direct oxidative cleavage of the corresponding 2-azabicyclo[2.2.1]hept-5-enes (**1**) via ozonolysis or using OsO_4-$NaIO_4$ (2 equiv). Nevertheless we were not able to isolate the desired compounds (dialdehyde or/and bis-hydroxymethyl derivative) from the reaction mixture, most probably due to rearrangements (via rapid Meisenheimer rearrangement) of the *N*-oxides formed in the conditions employed.[16]

The results obtained illustrate the utility of this methodology to afford optically pure 2-functionalized-3,5-bis(hydroxymethyl)pyrrolidines, 'prolino- and prolinol-mimetics', with potential biological activity.

Acknowledgements

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12. Comparison of the spectroscopic data (^{1}H and ^{13}C NMR) and specific rotation of aminoalcohol (−)-**9b** with an authentic sample of (+)-**9b**, whose absolute configuration is well known from its crystallographic X-ray data (CCDC 240700) allowed the determination of its absolute configuration (1*S*, 3*exo*), and therefore the configuration of its derivatives **3d**–**g** (also 1*S*, 3*exo*) and **7d**–**g** (2*S*,3*S*,5*S*) could be established.
13. (a) The recovered alcohol [$[\alpha]_D^{25}$ −25.2 (*c* 0.5, $CHCl_3$)], was identified as (−)-8-phenylmenthol by comparison of its spectroscopic and specific rotation data with those reported in the literature.[13b] (b) Fernández, F.; García-Mera, X.; López, C.; Rodríguez, G.; Rodríguez-Borges, J. E. *Tetrahedron: Asymmetry* **2000**, *11*, 4805.
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15. Selected ^{1}H NMR data [δ_H (300 MHz, $CDCl_3$)]: Compound (**9b**): 1.32–1.40 (m, 1H), 1.39 (d, 3H, $J = 6.5$ Hz), 1.72–1.80 (m, 2H), 2.01 (s, 1H), 2.70–2.76 (m, 2H), 2.99–3.08 (m, 2H), 4.14 (d, 1H, $J = 1.3$ Hz), 6.20 (dd, 1H, $J = 5.6$, 1.7 Hz), 6.46 (dd, 1H, $J = 4.5$, 3.3 Hz), 7.19–7.31 (m, 5H). Compound (**1c**): 0.99 (s, 9H), 1.26 (d, 1H, $J = 8.4$ Hz), 1.57 (d, 1H, $J = 8.4$ Hz), 1.86 (dd, 1H, $J = 9.2$ Hz, 5.1 Hz), 2.93 (s, 1H), 3.12 (d, 1H, $J = 9.3$ Hz), 3.18 (d, 1H, $J = 9.3$ Hz), 3.28–3.44 (m, 2H), 3.66 (s, 1H), 6.09–6.13 (m, 1H), 6.40–6.45 (m, 1H), 7.10–7.50 (m, 15H). Compound (**1d**): 0.89 (s, 9H), 1.19–1.26 (m, 2H), 1.32 (d, 3H, $J = 6.6$ Hz), 1.87–1.92 (m, 1H), 2.98–3.09 (m, 4H), 4.09 (br, 1H), 6.17 (dd, 1H, $J = 5.4$, 2.1 Hz), 6.44–6.48 (m, 1H), 7.10–7.50 (m, 15H). Compound (**1e**): 1.36–1.39 (d, 1H, $J_{anti} = 8.4$ Hz), 1.37 (d, 3H, $J = 6.9$ Hz), 1.64 (d, 1H, $J_{syn} = 8.4$ Hz), 1.87–1.91 (m, 1H), 2.76 (dd, 1H, $J = 9.9$ Hz, 3.6 Hz), 2.91 (s, 1H), 2.94 (d, 1H, $J = 9.9$ Hz), 3.03 (q, 1H, $J = 6.6$ Hz), 4.08 (d, 2H, $J = 4.8$ Hz), 4.13 (s, 1H), 6.20 (dd, 1H, $J = 5.4$ Hz, 2.1 Hz), 6.40–6.42 (m, 1H), 7.08–7.28 (m, 10H). Compound (**1f**): 1.38 (d, 1H, $J = 6.5$ Hz), 1.40 (s, 1H), 1.50–1.45 (m, 1H), 1.70 (d, 1H, $J = 8.8$ Hz), 1.89 (s, 3 H), 2.75 (s, 1H), 3.05 (q, 1H, $J = 6.5$ Hz), 3.33 (dd, 1H, $J = 4.2$ Hz, 11.1 Hz), 3.56 (t, 1H, $J = 10.8$ Hz), 4.19 (s, 1H), 6.21 (d, 1H, $J = 5.1$ Hz), 6.39–6.44 (m, 1H), 7.20–7.50 (m, 5H). Compound (**3a**): 1.74 (s, 1H), 2.28 (s, 1H), 2.44 (s, 1H), 2.62 (s, 1H), 3.27 (d, 1H, $J = 3.8$ Hz), 3.63 (s, 3H), 3.52–4.22 (m, 6H), 7.21–7.34 (m, 5H). Compound (**3c**): 1.02 (s, 9H), 1.49 (d, 1H, $J = 10.6$ Hz), 1.62 (d, 1H, $J = 10.6$ Hz), 2.15 (t, 1H, $J = 6.9$ Hz), 2.39 (s, 1H), 2.93 (s, 1H), 3.31 (d, 2H, $J = 7.1$ Hz), 3.61 (d, 2H, $J = 2.6$ Hz), 3.83 (d, 1H, $J = 5.4$ Hz), 4.23 (d, 1H, $J = 5.7$ Hz), 4.41 (s, 2H), 7.18–7.30 (m, 5H), 7.34–7.69 (m, 10H). Compound (**3d**): 0.88 (s, 9H), 1.34 (d, 3H, $J = 6.6$ Hz), 1.49 (d, 1H, $J = 10.8$ Hz), 1.69 (d, 1H, $J = 10.8$ Hz), 2.14 (dd, 1H, $J = 9.9$ Hz, 4.2 Hz), 2.47 (s, 1H), 2.53 (dd, 1H, $J = 10.1$ Hz, 4.1 Hz), 2.84 (t, 1H, $J = 10.1$ Hz), 2.89 (s, 2H), 3.38 (s, 1H), 3.46 (q, 1H, $J = 6.6$ Hz), 3.87 (d, 1H, $J = 6.0$ Hz), 4.27 (d, 1H, $J = 6.0$ Hz), 7.09–7.45 (m, 15H). Compound (**3e**): 1.38 (d, 3H, $J = 6.6$ Hz), 1.49 (d, 1H, $J = 10.7$ Hz), 1.65 (d, 1H, $J = 10.7$ Hz), 2.50 (s, 1H), 2.64 (m, 1H), 2.78 (dd, 1H, $J = 9.9$ Hz, 4.2 Hz), 2.89 (s, 2H), 2.96 (dd, 1H, $J = 9.9$ Hz, 4.1 Hz), 3.24 (q, 1H, $J = 6.6$ Hz), 3.39 (s, 1H), 3.90 (d, 1H, $J = 6.1$ Hz), 4.11 (d, 2H, $J = 5.0$ Hz), 4.28 (d, 1H, $J = 6.1$ Hz), 7.09–7.31 (m, 10H). Compound (**3f**): 1.37 (d, 1H, $J = 6.5$ Hz), 1.74 (s, 1H), 1.88 (s, 3H), 2.27 (s, 1H), 2.39 (s, 1H), 2.59 (s, 1H), 3.02 (q, 1H, $J = 6.5$ Hz), 3.30 (m, 1H), 3.32–4.21 (m, 6H), 7.23–7.51 (m, 5H). Compound (**7a**): 1.19–1.75 (m, 2H), 2.25–2.36 (m, 2H), 2.43–2.71 (s, 2H), 3.45–3.96 (m, 10H), 7.23–7.30 (m, 5H). Compound (**7c**): 1.05 (s, 9H), 1.99 (s, 2H), 2.18–2.26 (m, 1H), 2.40–2.53 (m, 1H), 2.74 (dd, 1H, $J = 17.1$ Hz, 9.6 Hz), 3.28 (q, 1H, $J = 3.3$ Hz), 3.37–3.55 (m, 2H), 3.61–3.72 (m, 4H), 3.89 (s, 2H), 4.94 (d, 1H, $J = 15$ Hz), 6.95–7.65 (m, 15H). Compound (**7d**): 1.06 (s, 9H), 1.25 (d, 3H, $J = 6.6$ Hz), 1.61–1.67 (m, 1H), 2.21–2.33 (m, 1H), 2.35 (s, 2H), 2.83 (dd, 1H, $J = 11.1$ Hz, 4.2 Hz), 3.01 (dd, 1H, $J = 11.4$ Hz, 2.1 Hz), 3.12 (m, 1H), 3.30 (dd, 1H, $J = 7.0$ Hz, 3.2 Hz), 3.57–3.77 (m, 4H), 3.84 (q, 1H, $J = 6.6$ Hz), 7.18–7.30 (m, 5H), 7.34–7.69 (m, 10H). Compound (**7e**): 1.44 (d, 3H, $J = 6.6$ Hz), 1.55–1.62 (m, 1H), 2.22–2.31 (m, 2H), 2.60 (s, 2H), 2.90 (dd, 1H, $J = 11.2$ Hz, 4.1 Hz), 3.05 (dd, 1H, $J = 11.4$ Hz, 2.4 Hz), 3.10–3.20 (m, 1H), 3.39–3.42 (m, 1H), 3.46–3.68 (m, 4H), 3.94 (q, 1H, $J = 6.6$ Hz), 4.46–4.54 (m, 2H), 7.20–7.40 (m, 10H). Compound (**7f**): 1.45 (d, 3H, $J = 7.4$ Hz), 1.66 (dd, 1H, $J = 14.8$ Hz, 1.9 Hz), 2.05 (s, 3H), 2.10–2.12 (s, 1H), 2.20–2.32 (m, 1H), 2.83 (dd, 1H, $J = 11.1$ Hz, 4.2 Hz), 3.00 (d, 1H, $J = 10.2$ Hz), 3.10–3.15 (m, 1H), 3.36–3.43 (m, 1H), 3.55–3.65 (m, 2H), 3.90–4.10 (m, 2H), 4.25 (dd, 1H, $J = 11.6$ Hz, 3.2 Hz), 4.70 (s, 2H), 7.24–7.30 (m, 5H).
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