An unusual oxidative rearrangement of azabicyclo[2.2.1]heptenes, providing a stereoselective route to 2′- and 3′-hydroxycyclopentylglycines

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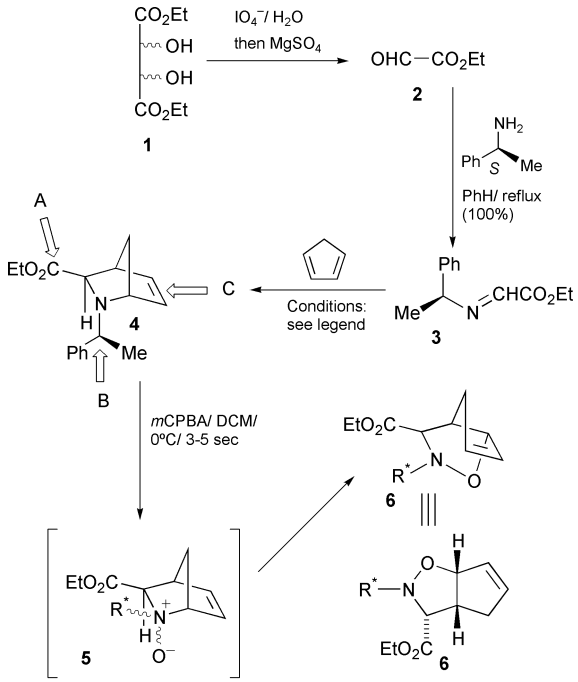
Treatment of the azabicyclo[2.2.1]heptene derivative 4 with *m*CPBA for 3–5 seconds generates the oxazabicyclo-[3.2.1]octene derivative 7 (X-ray structure) *via* rapid Meisenheimer rearrangement of the *N*-oxide 5, whilst heating 7 in MeCN for 4–6 h leads to further rearrangement to the more thermodynamically stable oxazabicyclo[3.3.0]octene isomer 6; 6 and 7 can be readily reduced to enantio-pure hydroxylated cyclopentylglycine derivatives.

Pharmacologically active peptoids can be generated by attaching the side-chains of a parent peptide to carrier moieties such as sugars, steroids, or porphyrins.[1] We have been exploring the use of azabicyclo[2.2.1]heptanes as rigid templates for such systems which, if they can be derivatised appropriately, offer potential as 3D structures on which to construct peptoid libraries. We were also attracted to such systems because we had developed an extremely short, efficient, and highly stereoselective route to these systems some years ago;[2] the aza-Diels–Alder reaction of the imine **3** with cyclopentadiene gives the azabicyclo[2.2.1]heptene **4** as a single stereoisomer, and we wished to explore the derivatisation of this adduct.[3] This communication, however, reports some unexpected results that have instead provided a short, efficient, stereo- and regio-specific route to hydroxylated cyclopentylglycines.

As outlined in Scheme 1, the adduct **4** could be efficiently prepared using ethyl glyoxylate generated using the procedure developed by Roberts' group.[4] After formation of the imine, the cycloaddition reaction was found to be most reliable when conducted in trifluoroethanol in the presence of TFA (1 equiv.). As reported by ourselves[4] and others,[5] this reaction proceeds both with excellent *exo* diastereo-control (in contrast to the *endo* selectivity observed for acyclic dienes[2]), and with extremely high asymmetric induction resulting from the presence of the α-methylbenzyl auxiliary (72% isolated yield, 95:5 *exo*:*endo*, 90% asymmetric induction). After chromatography, **4** was obtained as a single stereoisomer, from which we hoped an epoxidation/nucleophilic ring-opening sequence would allow derivatisation at site **C**, whilst further pharmacophores could be introduced at sites **A** and **B**. However, treatment with *m*CPBA failed to give the desired epoxide (even under acidic conditions whereby the nitrogen would be expected to be protonated), but instead yielded an isomeric oxygenated product which we initially assigned as the *N*-oxide **5**. Small amounts of a by-product were also generated, which was identified as the oxazabicyclo[3.3.0]octene **6** from NMR data.†

We had expected that an X-ray crystal structure of the '*N*-oxide' would confirm its identity and allow us to assign its stereochemistry at the chiral nitrogen, but this surprisingly revealed that the isomeric oxazabicyclo[3.2.1]octene **7** had been formed instead (Fig. 1‡). Optimisation of the reaction conditions established that the highest yield of **7** was obtained when the cyclo-adduct **4** was reacted at room temperature with *m*CPBA for only *3–5 seconds* and, that clean conversion to **6** could be achieved by refluxing **7** in acetonitrile for 24 h. Presumably **7** is formed *via* a Meisenheimer rearrangement,[6–9] but the rapidity and selectivity of the initial reaction, in which



Scheme 1 Formation of the oxazabicyclo[3.3.0]octane system **6**. The aza-Diels–Alder reaction (**3** → **4**) was in TFE, TFA (1 eq.), 0 °C, 3.5 h (72% yield, 95% *exo*, 90% asymmetric induction). See text and Scheme 2 for yields and identification of the products **5** and **6** from *m*CPBA oxidation of **4**. [R* = (*S*)-1-phenylethyl].

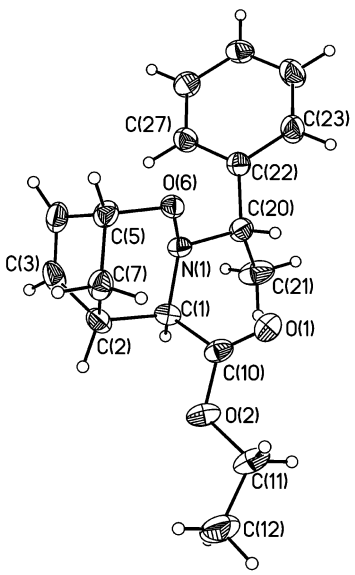
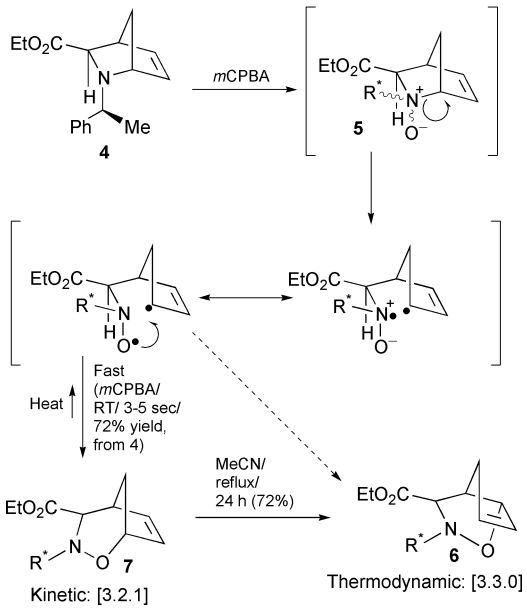
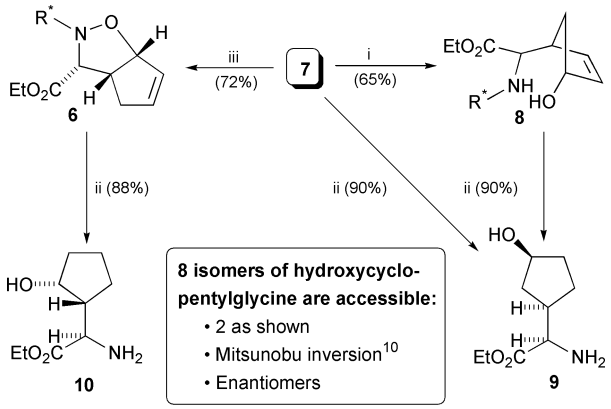


Fig. 1 X-Ray crystal structure of **7** with crystallographic numbering.‡



Scheme 2 Possible mechanism for the formation of **6** and **7**; heterolytic bond cleavage of **7** would also be consistent with its thermolysis to **6**. [R* = (*S*)-1-phenylethyl].



Scheme 3 Conversion of the oxazabicyclooctanes **6** and **7** into hydroxylated cyclopentylglycines such as **9** and **10**. Conditions: (i) Zn–AcOH; (ii) H_2 (50 psi)– $Pd(OH)_2$/C; (iii) MeCN, reflux, 24 h. [R* = (*S*)-1-phenylethyl].

the di-radical must be retained within a solvent cage, is extraordinary. Unprecedented, as far as we are aware, is the establishment of an equilibrium with the Meisenheimer intermediate (or possibly *via* heterolytic bond cleavage of **7**), providing a route by which the thermodynamically more stable adduct **6** can be generated (see Scheme 2).

With an efficient route to two isomeric oxazabicyclooctanes achieved, we wished to explore whether they could be converted into hydroxy-substituted cyclopentylglycines. The key transformations are shown in Scheme 3. In particular, Zn–AcOH treatment of the [3.2.1] isomer **7** allowed selective cleavage of the N–O bond, yielding the 4′-hydroxycyclopent-2′-enyl glycine derivative **8**. Hydrogenation of the double bond (Pearlman's catalyst, 50 psi) resulted in concomitant removal of the α-methylbenzyl auxiliary to afford the 3′-hydroxycyclopentyl glycine **9** as a single (2*R*,1′*R*,3′*S*) stereoisomer; the same hydrogenation conditions also allowed direct conversion of **7** to **9** (90% yield). On the other hand, these hydrogenation conditions enabled us to reduce the [3.3.0] isomer **6** directly to the 2′-hydroxycyclopentyl glycine **10**, also as a single (2*R*,1′*R*,2′*R*) stereoisomer. Closely related analogues of **8** have been used in the synthesis of cyclopentenylglycine,[11] and of carbocyclic analogues of nikkomycin[12] and polyoxin C.[13]

In summary, the asymmetric aza-Diels–Alder adduct **4** reacts with *m*CPBA to generate the Meisenheimer rearranged product **6**, which can be converted into the [3.3.0] system **7** by simple heating. These two isomers can be separately reduced, to provide access to a wide range of cyclopentylglycine derivatives, with complete regio-, diastereo- and enantio-control.

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Notes and references

† Selected data for **6**: $C_{17}H_{21}NO_3$; $\delta_H(CDCl_3)$ 1.1 (3H, t, *J* 7.2), 1.5 (3H, d, *J* 6.6), 2.4 (2H, m), 3.05 (1H, q, *J* 6.6), 3.55 (1H, m), 3.7 (1H, d, *J* 9.1), 3.95 (2H, q, *J* 7.2), 5.3 (1H, dd, *J* 7.4, 0.7), 5.8 (1H, dd, *J* 3.5, 1.7), 5.95 (1H, dd, *J* 1.7, 0.7), 7.2–7.4 (5H, m); $\delta_C(CDCl_3)$ 14.15 (CH_3), 20.47 (CH_3), 34.16 (CH_2), 47.20 (CH), 60.52 (CH_2), 65.68 (CH), 69.85 (CH), 87.35 (CH), 127.66 (CH), 128.25 (2 × CH), 128.30 (2 × CH), 129.49 (CH), 135.17 (CH), 141.91 (C), 169.90 (C).

‡ *Crystal data* for **7**. A single crystal of **7** was grown by slow evaporation of 40–60 pet. ether at rt and coated in Nujol and mounted on a glass fibre covered with vacuum grease for data collection with a Bruker P4 diffractometer[14] at 160 K. Colourless plate, 0.12 × 0.72 × 0.34 mm, $C_{17}H_{21}NO_3$, *M* = 287.35, monoclinic, space group $P2_1$, *a* = 6.0734 (4), *b* = 13.0445 (9), *c* = 10.1045(7) Å , β = 98.280(5)°, *U* = 792.18(13) Å^3, *Z* = 2, μ(Mo–K_α) = 0.082 mm^{-1}. Data measured = 3180, unique data = 1593, *R* = 0.0778 on all data (*wR*2 = 0.0306). Absolute structure parameter = 3.5(19), so the absolute structure could not be confirmed from the X-ray data. Crystallographic computing was performed using the SHELXTL[15] system version 5.1. CCDC 182/1836. See http://www.rsc.org/suppdata/b0/b006683o/ for crystallographic data in .cif format.

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