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Enantioselective Synthesis of 3-Functionalized 2-Azabicyclo[2.2.1]hept-5-enes by Hetero Diels-Alder Addition to Cyclopentadiene

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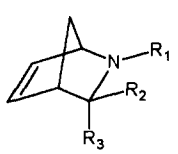
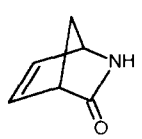
Abstract: Diels-Alder cycloaddition of *N*-benzyl imine of (1*R*)-8-phenylmenthyl glyoxylate to cyclopentadiene gave the mixture of adducts **3a-d**. Major diastereoisomer, the (1*S*,*exo*)-adduct (**3a**), was isolated in 57% yield and transformed in 74% overall yield into (+)-(1*S*)-*N*-benzoyl-2-azabicyclo-[2.2.1]heptan-3-one (**8**), which was compared with an authentic sample of its enantiomer. In the course of this transformation sequence, the chiral auxiliary (1*R*)-8-phenylmenthol was recovered in 90% yield.

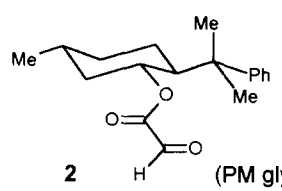
3-Functionalized 2-azabicyclo[2.2.1]hept-5-enes (**1a**) are useful as synthetic intermediates in the preparation of diverse compounds of pharmaceutical and/or biological interest. For example, lactam **1b** (or in some cases its enantiomer) has been used in the preparation of herbicides,[1] cyclic analogues of GABA,[2] the antibiotic amidomycin,[3] and several anti-viral agents, including the anti-HIV agent (–)-carbovir.[4]



1a



1b



2 (PM glyoxylate)

Currently, the most efficient route to (±)-**1b** is addition of a sulfonyl cyanide to cyclopentadiene (CPD), followed by hydrolysis.[5] Hitherto, attempts at developing enantioselective variants of this approach have afforded only modest enantiomeric excesses.[6] This is attributable to the C_∞ local symmetry of the cyanide group, which makes its approach to the diene less susceptible to the asymmetric effects of the rest of the azadienophile molecule. We reasoned that planar azadienophiles would have more demanding stereoelectronic requirements and would thus be more susceptible to the asymmetric effects of a chiral auxiliary. From among the various azadienophiles known to react well with CPD,[7] we chose iminium ions derived from glyoxylates because they are easily prepared and undergo cycloaddition to dienes under mild conditions.[8] This type of approach has previously been proposed to prepare compounds of type **1**, using the iminium ion generated from (+)- or (–)-α-phenylethylamine as active substrate.[8a] However, the drawback of this approach is that subsequent transformation into the above mentioned synthetic targets would require the destruction of the chiral auxiliary.

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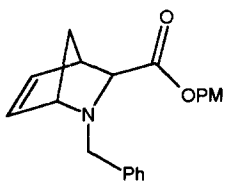
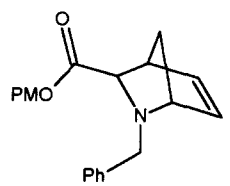
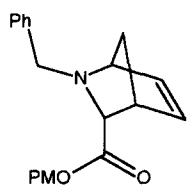
In the approach described here, the iminium ion is generated by reaction of an achiral amine with the glyoxylate of a chiral alcohol, and the latter chiral auxiliary is recovered in the course of subsequent synthetic manipulation of the adduct. Briefly, the iminium salt (generated *in situ* from equimolar amounts of benzylamine, (1*R*)-8-phenylmenthyl glyoxylate (**2**),[9] trifluoroacetic acid and boron trifluoride etherate in dichloromethane) was reacted at -78°C with an excess of cyclopentadiene. The resulting mixture of at least three of the four possible stereoisomeric adducts **3a-d** solidified on standing (89% yield).[10]



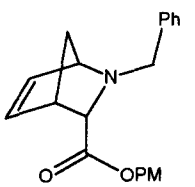
3a (1*S*, 3*exo*)



3b (1*R*, 3*exo*)



3c (1*S*, 3*endo*)



3d (1*R*, 3*endo*)

Fractional crystallization from hexane of the mixture of adducts allowed isolation of the most abundant diastereoisomer, **3a**,[11] in 57% overall yield. X-ray diffraction analysis of crystalline **2a** confirmed its structure to be that shown in Figure 1.

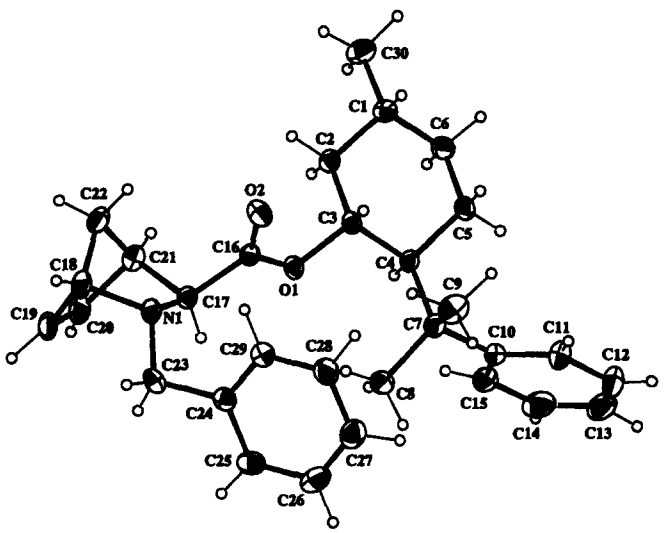
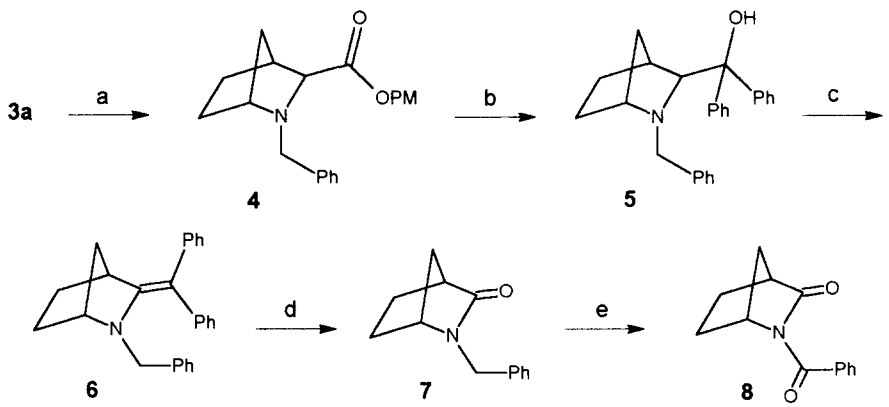


Figure 1. Molecular structure of **3a**

To confirm that preparation of target compounds as those mentioned above from **3a** would allow recovery of the chiral auxiliary, **3a** was transformed into (1*S*)-*N*-benzoyl-2-azabicyclo[2.2.1]heptan-3-one (**8**) using a reaction sequence based on the Barbier-Wieland degradation (Scheme 1). Firstly, to prevent rearrangement of the norbornene-type structure of **3a**, it was catalytically hydrogenated to **4**.[12] Then, treatment of **3** with an excess of phenylmagnesium bromide,[13] followed by hydrolysis and chromatography (silica gel; eluant, 9:1 hexane/EtOAc) of the crude product, gave tertiary amino alcohol **5**,[14] and the recovered chiral

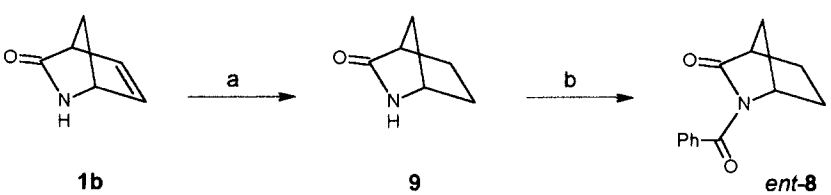
auxiliary (90%). Amino alcohol **5** was easily dehydrated by heating it with HMPA,[15] to give enamine **6**;[16] and Cu(I)-catalysed oxidation of **6** with molecular oxygen[17] gave a mixture of products from which benzophenone and lactam **7**,[18] were easily separated by chromatography (silica gel; eluent, 2:1 hexane/EtOAc). Finally, oxidation of **7** with potassium permanganate gave imide **8** (74% overall yield from **3a**).[19]



Reagents and conditions: a) H_2, 10% Pd/C, 99:1 EtOAC/AcOH, 40 psi, rt, 3 h, 96%. b) PhMgBr (10 equiv), THF, 55°C, 12 h, 91%. c) HMPA (2 equiv), 210°C, 2 h, 95%. d) O_2 (air stream), Cu_2Cl_2 (cat.), $CHCl_3$, 0°C, 6 h, 93%. e) $KMnO_4$ (4 equiv), 18-crown-6 (cat.), 85:15 Me_2CO/AcOH, 60°C, 15 h, 96%.

Scheme 1

Imide **8** had identical melting point and spectroscopic properties (except that its $[\alpha]_D^{22}$ was positive) to a sample of *ent*-**8**,[20] prepared from authentic (1*R*)-2-azabicyclo[2.2.1]hept-5-en-3-one (**1b**)[21] by hydrogenation to **9**,[22] followed by benzoylation (Scheme 2).



Reagents and conditions: a) H_2, 10% Pd/C, EtOAc, 40 psi, rt, 1.5 h, 98%. b) 1) NaH, Et_2O; 2) BzC, Et_2O, 14 h, 85%.

Scheme 2

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9. a) Glyoxylate was prepared according to: Fernández, F.; García, G.; Rodríguez, J. E. *Synthetic Commun.*, **1990**, *20*, 2837. b) (1*R*)-8-phenylmenthol: Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.*, **1975**, *97*, 6908.
10. An *exo*/*endo* ratio of 91:9, and a **3a**/**3b** ratio of 88:12, were evaluated by comparing the integrals of the most cleanly observed, characteristic ^{1}H NMR ($CDCl_3$) signals [**3a**, 2.78 δ (s, 4-H); **3b**, 2.84 δ (s, 4-H); **3c** and/or **3d**, 3.25 δ (s, 4-H)].
11. **3a**. M.p. 125-126°C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: δ: 7.38 (2H, d, *J* 7.1 Hz), 7.31-7.09 (8H, m), 6.35 (1H, dd, *J* 5.6, 2.3 Hz), 6.20 (1H, dd, *J* 5.6, 1.6 Hz), 4.74 (1H, td, J_t 10.7, J_d 4.3 Hz), 3. 84 (1H, s), 3.56 and 3.38 (2H, AB system, J 13.1 Hz), 2.78 (1H, s), 1.97-1.84 (2H, m), 1.87 (1H, s), 1.79 (1H, d, *J* 8.3 Hz), 1.60-1.39 (3H, m), 1.28 (1H, d, *J* 8.3 Hz), 1.09 (3H, s), 1.08 (3H, s), 1.06-0.73 (3H, m), 0.85 (3H, d, *J* 6.5 Hz). The X-ray data for **3a** will be presented in a separate, full paper.
12. **4**. M.p. 121-122°C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.42 (2H, d, *J* 7.0 Hz), 7.32-7.12 (8H, m), 4.71 (1H, td, J_t 10.7, J_d 4.3 Hz), 3.70 and 3.67 (2H, AB system, J 13.0 Hz), 3.28 (1H, s), 2.21 (1H, d, *J* 3.7 Hz), 2.14 (1H, s), 1.99-1.82 (3H, m), 1.76 (1H, dd, *J* 9.5, 1.7 Hz), 1.69-0.75 (10H, m), 1.13 (3H, s), 1.10 (3H, s), 0.85 (3H, d, *J* 6.5 Hz).
13. Use of an excess of commercial 2M phenyllithium in cyclohexane/Et_2O led to similar results.
14. **5**. M.p. 179-180°C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.74 (2H, dd, *J* 7.5, 1.2 Hz), 7.60 (2H, dd, *J* 7.3, 1.2 Hz), 7.36-7.08 (11H, m), 5.17 (1H, bs, D_2O exch.), 3.32 (1H, d, *J* 13.0 Hz), 3.25 (1H, s), 3.11 (1H, s), 2.98 (1H, d, *J* 13.0 Hz), 2.22 (1H, s), 2.07-1.98 (1H, m), 1.94 (1H, d, *J* 9.8 Hz), 1.61-1.38 (2H, m), 1.33-1.22 (1H, m), 0.97 (1H, d, *J* 9.8 Hz).
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16. **6**. M.p. 139-140°C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.27-7.07 (14H, m), 6.98 (1H, tt, *J* 7.3, 1.3 Hz), 4.03 (1H, d, *J* 15.2Hz), 3.50 (1H, d, *J* 15.2Hz), 3.35 (1H, s), 3.11 (1H,d, *J* 1.9Hz), 2.03-1.74 (4H, m), 1.48 (1H, tdd, J_t 11.7 Hz, J_d 4.5), 1.26 (1H, d, *J* 9.0 Hz).
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18. **7**. Oil. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.35-7.24 (5H, m), 4.68 (1H, d, *J* 15.1 Hz), 3.93 (1H, d, *J* 15.1 Hz), 3.68 (1H, s), 2.85 (1H, dd, *J* 3.8, 1.5 Hz), 1.90-1.82 (1H, m), 1.82 (1H, dd, *J* 9.4), 1.72-1.47 (3H, m), 1.33 (1H, d, *J* 9.4 Hz).
19. **8**. M.p. 180-181°C. $[\alpha]_D^{22}$ +284 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.65-7.61 (2H, m), 7.54-7.49 (1H, m), 7.42-7.37 (2H, m), 4.81 (1H, s), 2.94 (1H, t, *J* 1.6 Hz), 2.06 (1H, dt, J_d 10.0 Hz, J_t 1.8 Hz), 2.03-1.95 (3H, m), 1.80-1.73 (1H, m), 1.59 (1H, dt, J_d 10.0 Hz, J_t 1.1 Hz).
20. *ent*-**8**. $[\alpha]_D^{22}$ –287 (*c* 1, $CHCl_3$).
21. Prof P.M. Cullis kindly supplied us with a sample of **1b** obtained by enzymatic resolution of racemic lactam. See: Taylor, S. J. C.; McCague, R.; Wisdom, R.; Lee, C.; Dickson, K.; Ruecroft, G.; O'Brien, F.; Littlechild, J.; Bevan, J.; Roberts, S. M.; Evans, C. T. *Tetrahedron: Asymmetry*, **1993**, *4*, 1117).
22. **9**. $[\alpha]_D^{22}$ –160 (*c* 1, $CHCl_3$). Evans, C.; McCague, R.; Roberts, S. M.; Sutherland, A. G. *J. Org. Chem. Soc Perkin Trans. 1*, **1991**, 656, give $[\alpha]_D^{30}$ –133 (*c* 0.26, MeOH)].