# Enantioselective Synthesis of [(1*R*,3-*exo*)-2-Benzyl-2-azabicyclo[2.2.1]hept-5-en-3-yl]methanol via Aza-Diels–Alder Reaction

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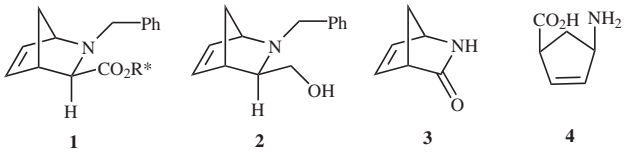
**Abstract:** The asymmetric aza-Diels–Alder reaction of the 8-phenylneomenthyl (or 8-phenylisomenthyl) glyoxylate-derived *N*-benzylimine with cyclopentadiene resulted in the enantioselective synthesis of the corresponding [(1*R*,3-*exo*)-2-benzyl-2-azabicyclo[2.2.1]hept-5-en-3-yl]carboxylate. In both cases, the (1*R*,3-*exo*)-adduct was the main diastereomer and was isolated in 70% and 65% yield, respectively. Reduction of the (1*R*,3-*exo*)-adducts with $LiAlH_4$ afforded [(1*R*,3-*exo*)-2-benzyl-2-azabicyclo[2.2.1]hept-5-en-3-yl]methanol, with recovery of the chiral auxiliaries with retention of configuration.

**Key words:** asymmetric synthesis, chiral auxiliaries, Diels–Alder reactions, induction

2-Azabicyclo[2.2.1]heptane and its derivatives are useful as synthetic intermediates in the preparation of a great variety of compounds of chemical, pharmaceutical and/or biological interest. For example, 2-azabicyclo[2.2.1]hept-5-enyl-3-carboxylates **1** are used in the preparation of the corresponding bicyclic derivatives of 2-azabicyclo[2.2.1]hept-5-enyl-3-methanol **2**, which have been successfully employed as chiral ligands in asymmetric synthesis/catalysis (carbon-carbon bond formation,[1] asymmetric transfer hydrogenation of ketones[2]). Carboxylates **1** have also been used in the enantioselective synthesis of lactam **3** and its saturated analogue,[3] key intermediates in the synthesis of several compounds with biological interest; among them are the four stereoisomers of 4-aminocyclopent-2-ene carboxylic acid (**4**) and the corresponding saturated analogues,[4] which show specific inhibitory activity towards some processes of the action and metabolism of GABA;[5] furthermore, isomer (1*R*,3*S*)-3-aminocyclopentane carboxylic acid is the core structure of the antibiotic amidomycin.[6] These bicyclic compounds containing the 2-azabicyclo[2.2.1]hept-5-ene system represent an important group of synthons useful in the preparation of amino alcohols derived from cyclopentene (or cyclopentane), necessary for the synthesis of carbocyclic analogues of nucleosides which are potential antiviral and antineoplastic drugs.[7]



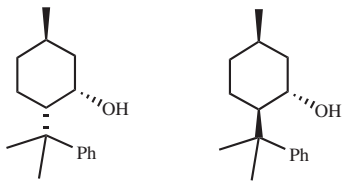

**1** **2** **3** **4**

**1a**: R* = 8-phenylneomenthyl
**1b**: R* = 8-phenylisomenthyl

**Figure 1**

In the course of our work aimed at the enantioselective synthesis of 3-substitued 2-azabyciclo[2.2.1]hept-5-enes and similar species, using asymmetric aza-Diels–Alder reactions, we recently prepared all the diastereomers of the auxiliary 8-phenylmenthol.[8a]

In this communication we report the high asymmetric (1*R*,3-*exo*) induction observed in the aza-Diels–Alder reaction between cyclopentadiene and the iminium ions of the *N*-benzylimines of the glyoxylates of two of the referred chiral auxiliaries, (+)-8-phenyl*neo*menthyl and (+)-8-phenylisomenthyl, leading to the diastereoselective synthesis of two optically pure (2-azabicyclo[2.2.1]hept-5-en-3-yl)carboxylates (**1a**,**b**). Reduction of adducts **1a** and **1b** afforded the aminoalcohol **2**, the chiral alcohols **5a**,**b** being recovered with retention of configuration (Figure 1).




**5a** **5b**

**Figure 2**

The starting pure chiral alcohols, (+)-8-phenylneomenthol [**5a**, prepared by Herbert Brown reduction of (2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexanone with L-Selectride®, Figure 2][8b] and (+)-8-phenylisomenthol [**5b**, prepared by reduction of (1*R*,2*S*,3*R*,6*R*)-1,2-epoxy-3-methyl-6-(1-methyl-1-phenylethyl)cyclohexane with Super-Hydride®],[8c] were converted into the corresponding glyoxylates **7a**,**b** (Scheme 1) by reaction with acryloyl

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chloride in the presence of triethylamine and DMAP, followed by treatment of the resulting acrylates **6a**,**b** either with ozone (with dimethyl sulfide quenching) or with osmium tetroxide. The glyoxylates were characterized by determination of their spectroscopic and physical properties and those of their 2,4-dinitrophenylhydrazone derivatives **8a**,**b**. Although the glyoxylates were isolated initially as a mixture of the glyoxylate and its hydrate, this presented no problem since both compounds react with primary amines to give the desired imines. Treatment of the glyoxylates with equimolar amounts of benzylamine, trifluoroacetic acid and boron trifluoride etherate in dichloromethane generated the corresponding iminium salt (protonated imine), which was reacted in situ with excess cyclopentadiene at –78 °C. Chromatographic purification of the mixture of adducts obtained allowed isolation of the most abundant (1*R*,3-*exo*)-diastereoisomers [**1a** (70% yield) and **1b** (65% yield)].[9,10]

Treatment of the cycloadducts **1a**,**b** with $LiAlH_4$ then afforded aminoalcohol **2**,[11] while allowing recovery of the chiral auxiliaries **5a**,**b** with retention of configuration in both cases.

Comparison of the spectroscopic data ($^1H$ NMR and $^{13}C$ NMR) and specific rotation of aminoalcohol **2** with those of aminoalcohol **9**, the absolute configuration of which has been established by crystallography X-ray of its precursor ester **10**,[12] allowed determination of the absolute configurations of adducts **1a**,**b** (1*R*,3-*exo* in both cases, Figure 3).

The results obtained illustrate the utility of 8-phenylneomenthol and 8-phenylisomenthol as two easily recoverable stereocontrolling auxiliaries, affording optically pure 3-functionalized 2-azabyciclo[2.2.1]hept-5-enes with (1*R*,3-*exo*) induction (majority) by asymmetric aza-

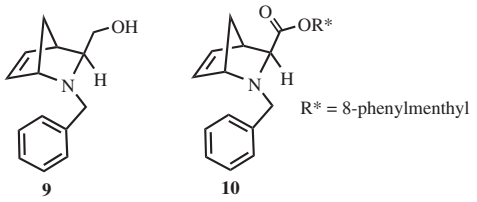


**Figure 3**

Diels–Alder reaction between cyclopentadiene and the imine ion formed in the reaction of benzyl amine with the corresponding glyoxylates of these alcohols.

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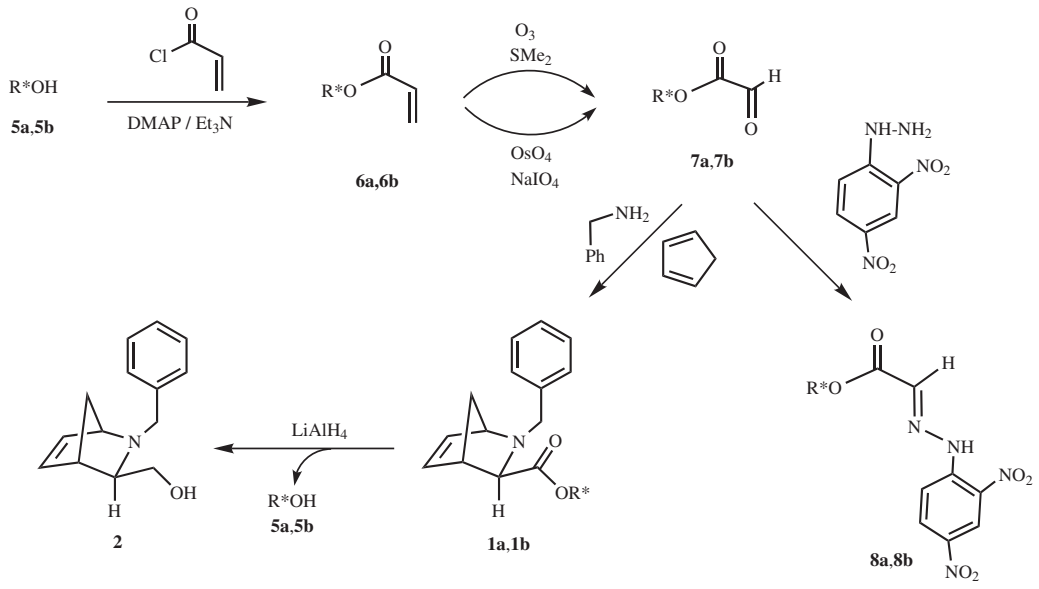


**Scheme 1**

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(9) **General Procedure for the Synthesis of 1a.**
A solution of acryloyl chloride (2.10 mL, 25.8 mmol) in dry $CH_2Cl_2$ (40 mL) was added dropwise under argon to a solution of (+)-8-phenylneomenthol [(**5a**, 3.00 g, 12.9 mmol)], $Et_3N$ (3.6 mL, 26 mmol) and 4-(dimethylamino)pyridine (227 mg, 1.81 mmol) in dry $CH_2Cl_2$ (60 mL) at 0 °C. The mixture was stirred for 2 h at r.t. and was then treated with sat. $NaHCO_3$ solution (125 mL) and extracted with $Cl_2CH_2$ (3 × 100 mL). The pooled organic layers were washed with sat. $NaHCO_3$ solution (2 × 100 mL) and brine (100 mL), and were then dried with $Na_2SO_4$. The solvent was removed in a rotary evaporator, and purification of the resulting residue on a short column of silica gel using $Et_2O$–EtOAc 9:1 as eluent afforded **6a** as a yellow oil. Yield 3.29g (89%).
A mixture of **6a** (2.35 g, 8.21 mmol), $OsO_4$ (20.8 mg, 10 equiv), $H_2O$ (9 mL) and dioxane (30 mL) was stirred at r.t. for 5 min, during which time the mixture became dark brown. Then $NaIO_4$ (3.51 g, 2 equiv) was added in portions over 30 min, and the mixture (now pale brown) was stirred at r.t. for another 2 h and then extracted thoroughly with $Et_2O$. The combined organic extracts were dried ($Na_2SO_4$) and concentrated, affording a yellow oil that upon filtration through a short column of silica gel using hexane–EtOAc 3:1 as eluent afforded **7b** as a mixture of the glyoxylate and its hydrate which was used without further purification. Yield 2.31 g (98%).
A solution of benzylamine (0.57 mL, 5.2 mmol) in dry $Cl_2CH_2$ (10 mL) was added under argon to a stirred suspension of **7b** (1.5 g, 5.2 mmol) and 3 Å molecular sieves (4 g) in dry $Cl_2CH_2$ (30 mL) at 0 °C. When the addition was complete the reaction mixture was cooled to –78 °C and treated successively with TFA (0.4 mL, 1 equiv), $BF_3{\cdot}OEt_2$ (0.65 mL, 1 equiv) and freshly distilled cyclopentadiene (1 mL, ca. 2 equiv). After 6 h a mixture of sat. aq $NaHCO_3$ solution (13 mL) and then solid $NaHCO_3$ (1.3 g) were added. The reaction mixture was allowed to reach r.t. and filtered. The organic layer was separated from the filtrate and washed with $H_2O$ and $CH_2Cl_2$ on a celite pad; the organic layer of the resulting mixture was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 80 mL). The pooled organic layers were washed with sat. $NaHCO_3$ solution (80 mL) and brine (90 mL), and were dried over $Na_2SO_4$.
Removal of the solvent on a rotary evaporator yielded an orange oil (2.3 g) which was purified by column chromatography (silica gel) using hexane–EtOAc 3:1 as eluent. Fractions 7–10 afforded a colorless oil (1.61 g) identified as the pure major adduct (1*R*,3-*exo*) **1a**. Yield 70%.
Compound **1a**: $[\alpha]_D^{25}$ +52.5 (*c* 1, $CHCl_3$). IR (NaCl): ν = 3059, 2948, 1734 (CO), 1601, 1560, 1496, 1455, 1368, 1322, 1170, 1146, 1096, 1031, 978, 919, 846, 761, 733, 699, 661 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ = 0.84 (d, *J* = 6.5 Hz, 3 H, 5′-$CH_3$), 0.88–1.05 (m, 2 H), 1.18 and 1.20 [2 s, 6 H, 8′-$(CH_3)_2$], 1.30–1.49 (m, 2 H), 1.50–1.79 (m, 4 H), 1.82–1.88 (m, 1 H), 1.94 (virtual d, *J* = 8.3 Hz, 1 H, $7_{sin}$-H), 2.29 (br s, 1 H, $3_{endo}$-H), 3.06 (br s, 1 H, 4-H), 3.55 (s, 2 H, $CH_2Ph$), 3.88 (br s, 1 H, 1-H), 5.03 (br s, 1 H, $1'_{eq}$-H), 6.25 (dd, *J* = 5.5 Hz, *J* = 1.8 Hz, 1 H, 5-H), 6.49 (dd, *J* = 5.5 Hz, *J* = 3.4 Hz, 1 H, 6-H), 7.10–7.45 (m, 10 H, $C_6H_5$). $^{13}C$ NMR ($CDCl_3$): δ = 22.57 (5′-$CH_3$), 22.75 (C-3′), 26.11 (C-5′), 27.06 and 27.38 [8′-$(CH_3)_2$], 35.79 (C-4′), 40.14 (C-8′), 40.33 (C-6′), 47.00 (C-7), 48.95 (C-4), 51.63 (C-2′), 59.50 ($NCH_2$-Ph), 64.52 (C-1), 65.96 (C-3), 71.64 (C-1′), 125.95 [aromatic C-4 (Ph)], 126.43 [aromatic C-2 + C-6 (Ph)], 127.47 [aromatic C-4 (Bn)], 128.35 [aromatic C-3 + C-5 (Ph)], 128.68 [aromatic C-2 + C-6 (Bn)], 129.39 [aromatic C-3 + C-5 (Bn)], 134.12 (C-5), 136.76 (C-6), 139.53 [aromatic C-1 (Bn)], 150.34 [aromatic C-1 (Ph)], 173.09 [C(O)O]. HRMS: *m/z* calcd for $C_{30}H_{37}NO_2$: 443.2824. Found: 443.2817.

(10) Compound **1b**: yield 65%; $[\alpha]_D^{25}$ +53.5 (*c* 1, $CHCl_3$). IR (NaCl): ν = 3021, 3062, 2966, 1732 (CO), 1598, 1560, 1494, 1464, 1452, 1386, 1366, 1358, 1324, 1241, 1217, 1202, 1187, 1172, 1078, 1043, 1018, 919, 859, 768, 741, 734, 704 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ = 0.93 (d, *J* = 7.1 Hz, 3 H, 5′-$CH_3$), 1.172 and 1.177 [2 s, 6 H, 8′-$(Me_2)$], 1.20–1.35 (m, 4 H), 1.36–1.50 (m, 2 H), 1.52–1.65 (m, 2 H), 1.82 (virtual d, *J* = 8.3 Hz, 1 H, $7_{sin}$-H), 1.85–1.90 (m, 1 H), 1.95 (s, 1 H, $3_{endo}$-H), 2.84 (br s, 1 H, 4-H), 3.42 and 3.52 (AB system, 2 H, *J* = 13.0 Hz), 3.82 (br s, 1 H, 1-H), 5.02 (td, 1 H, $J_t$ = 10.8 Hz, $J_d$ = 4.18 Hz, $1'_{ax}$-H), 6.20 (dd, 1 H, *J* = 5.6 Hz, *J* = 1.8 Hz, 1 H, 5-H), 6.38 (dd, 1 H, *J* = 5.6 Hz, *J* = 3.3 Hz, 1 H, 6-H), 7.10–7.40 (m, 10 H, $C_6H_5$). $^{13}C$ NMR ($CDCl_3$): δ = 19.52 (5′-$CH_3$), 21.79 (C-3′), 26.45 (C-5′), 27.51 and 27.89 [8′-$(CH_3)_2$], 31.52 (C-4′), 40.40 (C-8′), 38.30 (C-6′), 46.75 (C-7), 49.02 (C-4), 50.74 (C-2′), 59.31 ($NCH_2$-Ph), 64.45 (C-1), 65.50 (C-3), 71.93 (C-1′), 125.53 [aromatic C-4 (Ph)], 126.03 and 126.12 [aromatic C-2 + C-6 (Ph)], 127.36 [aromatic C-4 (Bn)], 128.30 [aromatic C-3 + C-5 (Ph)], 128.54 and 128.60 [aromatic C-2 + C-6 (Bn)], 129.39 [aromatic C-3 + C-5 (Bn)], 134.05 (C-5), 136.80 (C-6), 139.63 [aromatic C-1 (Bn)], 151.32 [aromatic C-1 (Ph)], 173.08 [C(O)O]. HRMS: *m/z* calcd for $C_{30}H_{37}NO_2$: 443.2824. Found: 443.2814.

(11) Compound **2**: yield 92%; colorless oil; $[\alpha]_D^{25}$ +71.5 (*c* 1, $CHCl_3$). IR (NaCl): ν = 3364, 3060, 2985, 2870, 1495, 1452, 1367, 1324, 1208, 1134, 1028, 910, 717 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ = 1.25–1.28 (d, 1 H, *J* = 8.40 Hz, $7_{anti}$-H), 1.68–1.71 (d, 1 H, *J* = 8.40 Hz, $7_{sin}$-H), 1.82–1.86 (t, 1 H, *J* = 5.55 Hz, 3-H), 2.32 (br s, 1 H, OH), 2.69 (s, 1 H, 4-H), 3.32–3.44 (m, 4 H, $CH_2OH$ + $CH_2Ph$), 3.69 (s, 1 H, 1-H), 6.10–6.13 (dd, 1 H, *J* = 5.65, 1.80 Hz, 5-H), 6.41–6.45 (dd, 1 H, *J* = 5.65, 3.24 Hz, 6-H), 7.16–7.28 (m, 5 H, $C_6H_5$). $^{13}C$ NMR ($CDCl_3$): δ = 46.13 (C-7), 47.16 (C-4), 59.34 ($NCH_2Ph$), 64.43 (C-1), 64.98 (C-3), 65.66 ($CH_2OH$), 127.55 (C-4′), 128.80 (C-2′ + C-6′), 129.43 (C-3′ + C-5′), 132.71 (C-5), 138.27 (C-6), 140.11 (C-1′). HRMS: *m/z* calcd for $C_{14}H_{17}NO$: 215.1310. Found: 215.1319.

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