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The use of (−)-8-phenylisoneomenthol and (−)-8-phenylmenthol in the enantioselective synthesis of 3-functionalized 2-azabicyclo[2.2.1]heptane derivatives via aza-Diels–Alder reaction

Maria Luísa Cardoso do Vale,[a] José Enrique Rodríguez-Borges,[a,*] Olga Caamaño,[b] Franco Fernández[b] and Xerardo García-Mera[b,*]

[a]*CIQ-Departamento de Química, Faculdade de Ciências, Universidade do Porto, Rua do Campo Alegre, 687, 4169-007 Porto, Portugal*
[b]*Departamento de Química Orgánica, Facultade de Farmacia, Universidade de Santiago de Compostela, E-15782 Santiago de Compostela, Spain*

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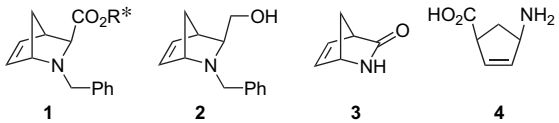
Abstract—The asymmetric aza-Diels–Alder reaction of the (1*R*)-8-phenylmenthyl or (1*R*)-8-phenylisoneomenthyl glyoxylate-derived *N*-benzylimine with cyclopentadiene resulted in the enantioselective synthesis of the corresponding pure [(1*S*,3-*exo*)-2-benzyl-2-azabicyclo[2.2.1]hept-5-ene]-3-carboxylates (80 or 69% yield, respectively). Reduction of these cycloadducts with $LiAlH_4$ afforded pure (−)-[(1*S*,3-*exo*)-2-benzyl-2-azabicyclo[2.2.1]hept-5-en-3-yl]methanol. Furthermore, a reaction sequence based on Barbier–Wieland degradation of both (1*S*,3-*exo*)-adducts afforded pure (+)-(1*R*)-2-benzoyl-2-azabicyclo[2.2.1]heptan-3-one. In the course of the two transformation sequences referred, the chiral auxiliaries were recovered in a virtually quantitative way.

1. Introduction

Chiral nitrogen containing heterocycles are versatile structures, which often occur in natural products and frequently show biological activity;[1] therefore, the development of efficient and stereoselective methods for their preparation is of great interest for organic chemists. The aza-Diels–Alder reaction is a well-known method for the preparation of such nitrogen containing monocyclic and bicyclic molecules,[2] like 2-azabicyclo[2.2.1]heptane and its derivatives, which can be transformed into a variety of compounds of great interest. For example, [2-azabicyclo[2.2.1]hept-5-ene]-3-carboxylates (**1**) are used in the preparation of the corresponding bicyclic derivatives of [2-azabicyclo[2.2.1]-hept-5-en-3-yl]methanol (**2**), which have been successfully employed as chiral ligands in asymmetric synthesis or catalysis (carbon–carbon bond formation,[3] asymmetric transfer hydrogenation of ketones[4]). Carboxylates of type **1** have been used in the enantioselective synthesis of lactam **3** and its enantiomer and of their saturated analogues,[5] 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,[6] which show specific inhibitory activity toward some processes of the action and metabolism of GABA (Fig. 1).[7] On the other hand, isomer (1*R*,3*S*)-3-aminocyclopentane carboxylic acid is the core structure of the antibiotic amidomycin.[8]

These bicyclic compounds containing the 2-azabicyclo-[2.2.1]hept-5-ene system are, through cleavage of the N–C_3 bond, the precursors of an important group of synthons useful in the preparation of chiral amino alcohols derived from cyclopentene or cyclopentane, necessary for the synthesis of carbocyclic nucleosides with antiviral and antineoplastic properties.[9] On the other side, oxidation of the double bond and reduction or hydrolysis of the ester functionality would lead to a great number of chiral nonnatural amino alcohols and α-aminoacids (pyrrolidine derivatives), which,



1 2 3 4

Figure 1.

Keywords: Asymmetric synthesis; Aza-Diels–Alder reaction; Induction; Chiral alcohols.
* Corresponding authors. Fax: +34 981 594912 (X.G.-M.); fax: +351 22 6082959 (J.E.R.-B.); e-mail addresses: qoxgmera@usc.es; jrborges@fc.up.pt

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in turn, are potential nonnucleosidic inhibitors of HIV replication.[10]

In what concerns the aza-Diels–Alder reaction, imines are the most commonly used aza-dienophiles and generally require activation by an electron-withdrawing group and a Lewis acid to participate in these [4+2] cycloaddition reactions.[2c–g] In order to perform the enantioselective synthesis of the referred adducts (**1**), chiral imines must be used. The use of glyoxylates as precursors of chiral electron deficient imines allows the introduction of chirality either through the use of chiral amines[2e,g] or chiral alcohols. Among the latter, (−)-8-phenylmenthol (**5a**) is one of the most widely employed, being used to achieve enantioselectivity in numerous syntheses.[11] Its popularity is due, both to the good enantiomeric excesses it affords (specially in face differentiation processes, in which its capacity for face selective π-stacking interactions is decisive) and to its ready availability (it can be prepared in good yields from the inexpensive (*R*)-(+)-pulegone).[12] Nevertheless, much less is known about the chiral induction behavior of its isomers; for example, its enantiomer, (+)-8-phenylmenthol,[13] which seems just as attractive as **5a** as a chiral auxiliary from a structural point of view, has rarely been used as such due to its high cost.

Whitesell[14] reported that the region C_1–C_2 in 8-phenylmenthol is the one responsible for chiral induction; this led us to the conclusion that we could have similar induction results using diastereomers of (−)-8-phenylmenthol without necessity to use (+)-8-phenylmenthol. Based on this hypothesis, our group has been optimizing various methods of synthesis of the isomers of (−)-8-phenylmenthol from inexpensive, readily available materials.[11a–d] In a recent work,[15] we reported the use of (+)-8-phenylneomenthol and (+)-8-phenylisomenthol in the synthesis of [2-azabicyclo[2.2.1]-hept-5-ene]-3-carboxylates by an aza-Diels–Alder reaction, where a high asymmetric (1*R*,3-*exo*) induction was observed.

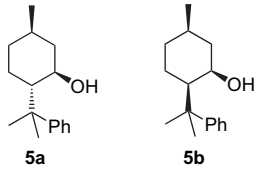
We now report the high asymmetric (1*S*,3-*exo*) induction observed in the same reaction using cyclopentadiene and the iminium ions of the *N*-benzylimines of the glyoxylates of the two diastereomeric alcohols (−)-8-phenylmenthol (**5a**) and (−)-8-phenylisoneomenthol (**5b**).

2. Results and discussion

The chiral auxiliaries (Fig. 2), (−)-8-phenylmenthol [(1*R*,3*R*,4*S*)-8-phenylmenthan-3-ol; **5a**] and (−)-8-phenylisoneomenthol [(1*R*,3*R*,4*R*)-8-phenylmenthan-3-ol; **5b**] were prepared by Bouveault–Blanc reduction of (1*R*,4*S*)-8-phenyl-*p*-menthan-3-one,[11a] which was easily obtained by conjugate addition of phenylmagnesium bromide to (+)-(*R*)-pulegone.[12] Alcohols **5a** and **5b** were straightforwardly separated by flash chromatography on silica gel.

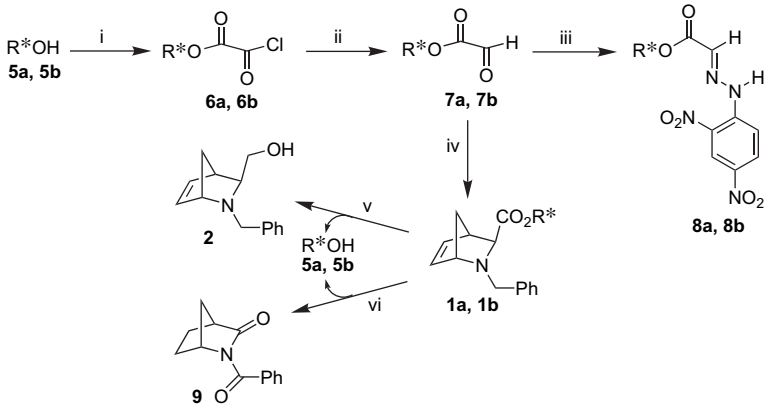
Conversion of the alcohols into their glyoxylates[16] was achieved by reaction with excess oxalyl chloride in chloroform, followed by treatment of the resulting alkyloxy oxalyl chlorides (**6a**, **6b**)[17] with excess tributyltin hydride in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0), at room temperature (Scheme 1). Once reaction was complete, the excess hydride was destroyed by heating in anhydrous chloroform, yielding tributyltin chloride as the only tin co-product. The glyoxylates (**7a**, **7b**) were separated from the reaction mixture by column chromatography on silica gel. Compounds **7a** and **7b** were characterized by the determination of their spectroscopic and physical properties and those of their 2,4-dinitrophenylhydrazone derivatives (**8a**, **8b**).[16] Although, **7a** and **7b** were each isolated initially as a mixture of the anhydrous glyoxylate and of its hydrate, this presented no problem since both forms react with primary amines to give the desired imines.

Treatment of **7a** or **7b** with equimolar amounts of benzylamine, trifluoroacetic acid, and boron trifluoride etherate in dichloromethane generated the corresponding iminium salt (protonated imine), which reacted in situ with excess cyclopentadiene at −78 °C to give mixtures of diastereomeric adducts. Chromatographic purification of each mixture of



5a **5b**

Figure 2.

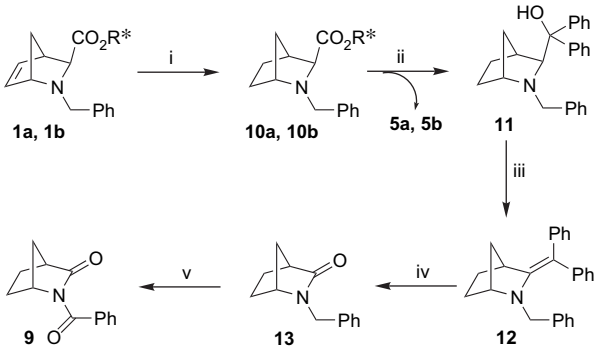


Scheme 1. Reagents and conditions: (i) oxalyl chloride, $CHCl_3$, 0 °C, 1 h; (ii) Bu_3SnH, $Pd(PPh_3)_4$, PhH, 85–89% (overall yield from **5a**, **5b**); (iii) 2,4-dinitrophenyl hydrazine, H_2SO_4, MeOH, 89–92%; (iv) $PhCH_2NH_2$, TFA, $F_3B{\cdot}OEt_2$, cyclopentadiene, CH_2Cl_2, −78 °C, 69–80%; (v) $LiAlH_4$, Et_2O, 5 h, rt, 96–97%; (vi) See Scheme 2 (74–76% overall yield from **1a**, **1b**).

adducts allowed isolation of the most abundant (1*S*,3-*exo*)-diastereoisomer, **1a** (80%yield) or **1b** (69% yield).

Both bicyclic adducts **1a** and **1b** were converted into the same amino alcohol, (−)-[(1*S*,3-*exo*)-2-benzyl-2-azabicyclo[2.2.1]-hept-5-en-3-yl]-methanol (**2**), by treatment with $LiAlH_4$, and into the same lactam, (+)-(1*R*)-2-benzoyl-2-azabicyclo[2.2.1]heptan-3-one (**9**), through a longer reaction sequence based on Barbier–Wieland degradation (Scheme 1). The transformations into these two target compounds were accomplished with a virtually quantitative recovery of the chiral auxiliaries **5a** (98%) and **5b** (97%). Since the absolute configuration of the bicyclic system of adduct **1a** had already been established by X-ray crystallography as being (1*S*,3-*exo*),[18] this outcome allowed to determine the absolute configuration of adduct **1b** (also 1*S*,3-*exo*).

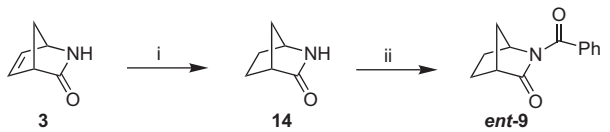
Transformations of **1a** and **1b** into (1*R*)-2-benzoyl-2-azabicyclo[2.2.1]heptan-3-one (**9**) began with their catalytic hydrogenation to **10a** and **10b**, respectively, in order to prevent rearrangements of the norbornene-type (Scheme 2). Treatment of **10a** or **10b** with an excess phenylmagnesium bromide,[19] followed by hydrolysis of the crude product, gave tertiary amino alcohol **11**, with high recovery of the chiral auxiliary (94–96%).



Scheme 2. Reagents and conditions: (i) H_2, 10% Pd/C, 99:1 EtOAc/AcOH, 40 psi, rt, 3 h, 95–97%; (ii) PhMgBr (10 equiv), THF, 12 h, 90–91%; (iii) HMPA (2 equiv), 210 °C, 2 h, 94–95%; (iv) O_2 (air stream), Cu_2Cl_2 (cat.), $CHCl_3$, 0 °C, 6 h, 92–93%; (v) $KMnO_4$ (4 equiv), 18-crown-6 (cat.), 85:15 Me_2CO/AcOH, 60 °C, 15 h, 95–96%.

Amino alcohol **11**[20] was easily dehydrated to enamine **12** by heating with HMPA;[21] Cu(I)-catalyzed oxidation of **12** with molecular oxygen[22] gave a mixture of products from which benzophenone and lactam **13** were easily separated by chromatography on silica gel. Finally, oxidation of **13** with potassium permanganate afforded imide **9** (76 and 74% overall yield from **1a** and **1b**, respectively). Imide **9** had identical melting point and spectroscopic properties, differing only in its $[\alpha]_D$, which was positive, as a sample of *ent*-**9**,[18] prepared from authentic (1*R*)-2-azabicyclo[2.2.1]hept-5-en-3-one (**3**)[18,23] by catalytic hydrogenation to **14**, followed by reaction with benzoyl chloride (Scheme 3).

In an attempt to explain the stereochemical outcome of the aza-Diels–Alder reaction, we present in Figure 3 a model for the approach of diene and dienophile. The high *exo*-selectivity observed in these cases may be explained considering that:



Scheme 3. Reagents and conditions: (i) H_2, 10% Pd/C, AcOEt, 40 psi, rt, 1.5 h, 98%; (ii) (a) NaH, Et_2O; (b) BzCl, Et_2O, 14 h, 85%.

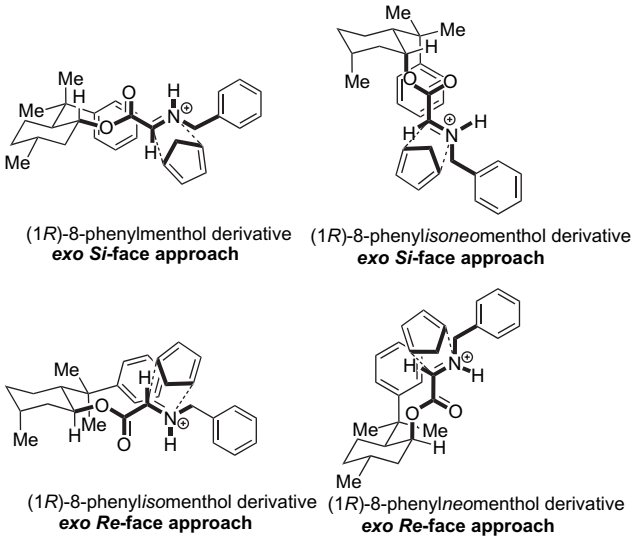


Figure 3.

* the iminium ion, which is the species that acts as dienophile in the reaction, should have an *E* configuration, more stable for both stereochemical (bulky groups far apart) and polar (hydrogen bonding N^+–H···O=C) reasons.
* in the close vicinity of the C=N bond, the (C_{sp^3}) benzyl group exerts a larger steric hindrance than the (C_{sp^2}) ester group.

Consequently, in order to minimize stereochemical interactions in the transition state between the (C_{sp^3}) methylene group of the diene and the bulkier substituents of the dienophile, the approach of diene/dienophile must occur in a manner that places the (C_{sp^3}) benzyl group in an *endo* position and therefore, given the *E* configuration of the dienophile, the ester group in an *exo* position. That is, to say that the stereochemical factors are more important than the secondary orbital interactions between the π systems of cyclopentadiene and the ester group in the dienophile. The configuration of the nitrogen atom in the final adduct is irrelevant, since it exists as a tertiary amine capable of undergoing inversion of the lone pair of electrons to achieve the most stable conformation.

In what concerns the preference observed in the approach of the diene to the diastereotopic faces (due to the presence of the chiral auxiliary) of the dienophile, it is more difficult to suggest a hypothesis, since the geometry of the fragment that connects the chiral auxiliary to the reacting dienophilic site (C=N) in the transition state (diene/dienophile) is not fully known. This fragment consists of three single bonds a, b, and c; for each one, two extreme conformations, *syn* and *anti*, are depicted in Figure 4.

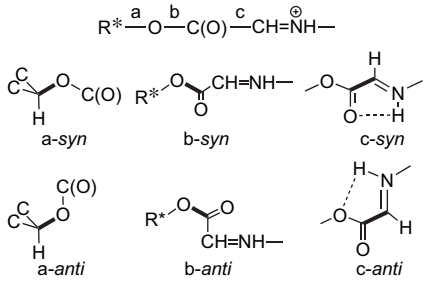


Figure 4.

Some plausible qualitative considerations may be taken into account to offer a rationale for the observed results:

* the $-C(Me)_2Ph$ group of the chiral auxiliary necessarily has to lie in an *equatorial* position with regard to the cyclohexane ring. Given the configurations of the different stereoisomers of the chiral auxiliary, this means that the $C_{(sp^3)}$–O bond will be in an *equatorial* position for 8-phenylmenthol and 8-phenylisomenthol derivatives, and in an *axial* position for 8-phenylneomenthol and 8-phenylisoneomenthol ones.
* π-stacking interactions are supposed to be established between the phenyl group and the aza-diene system, in order to account for the improved results obtained with 8-phenylmenthol derivatives compared to the simple menthol derivatives in achieving better facial diastereoselectivity, which is the base for their use as chiral auxiliaries. This means that the C–Ph bond should lie almost parallel to the $C_{(sp^3)}$–O bond, which determines the conformations of the C–C(Ph) and $C_{(sp^3)}$–O bonds, as is shown in Figures 3 and 4 (a-*syn* bond).
* On the other hand, eclipsing between C═O and $C_{(sp^3)}$–O bonds is the most favored conformation for esters (b-*syn* bond), while preference for c-*syn* conformation in the aza-diene system is justified by the establishment of a stronger hydrogen bond in N^+–H···O═C than in N^+–H···O<.

In consequence, taking into account simultaneously all polar, steric, and electronic prevailing interactions in the system, which includes the *syn*-*syn*-*syn*-alignment of the $C_{(sp^3)}$–O–$C_{(sp^2)}$–$C_{(sp^2)}$ fragment, the geometrical approaches depicted in Figure 3 are the ones, which best explain the stereochemical outcome of these reactions, i.e., formation of the major adducts (1*S*,3-*exo*) as a result of the predominant attack on the *si*-face of the dienophile when using (1*R*)-8-phenylmenthol and (1*R*)-8-phenylisoneomenthol derivatives as chiral auxiliaries, and of the major adducts (1*R*,3-*exo*) as a result of the predominant attack on the *re*-face of the dienophile when using (1*R*)-8-phenylneomenthol and (1*R*)-8-phenyl*iso*menthol derivatives.

3. Conclusion

The results obtained illustrate the utility of (1*R*)-8-phenylmenthol (**5a**) and (1*R*)-8-phenylisoneomenthol (**5b**) as two easily recoverable stereo controlling auxiliaries, affording optically pure 3-functionalized 2-azabicyclo[2.2.1]hept-5-enes with (1*S*,3-*exo*) configuration, by means of an asymmetric aza-Diels–Alder reaction between cyclopentadiene and the protonated imine formed from benzylamine and the glyoxylates of these alcohols. It is noteworthy that a common rationale may be advanced to explain this outcome as well as the opposite asymmetric induction that leads to the corresponding optically pure adducts with (1*R*,3-*exo*) configuration observed when using as chiral auxiliaries the diastereomeric alcohols (1*R*)-8-phenylneomenthol and (1*R*)-8-phenylisomenthol.[15]

From a practical point of view, it is of major importance that the chiral auxiliaries used (isomers of 8-phenylmenthol) to obtain the two enantiomeric families of these azabicyclic compounds (1*S*,3-*exo* and 1*R*,3-*exo*) can be obtained from the same inexpensive starting material, (*R*)-pulegone, with no need to use (+)-(1*S*)-8-phenylmenthol (derived from the prohibitively expensive (*S*)-pulegone).

4. Experimental

4.1. General

Silica gel was purchased from Merck. All other chemicals used were of reagent grade and were obtained from Aldrich Chemical Co. Flash column chromatography was performed on silica gel (Merck 60, 230–240 mesh) and analytical thin-layer chromatography (TLC) on pre-coated silica gel plates (Merck 60 GF_{254}) using iodine vapor and/or UV light for visualization. Melting points were determined on a Reichert Kofler Thermopan or in capillary tubes on a Büchi 510 apparatus, and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 1640-FT spectrophotometer and the main bands are given in cm^{-1}. ^1H NMR (300 MHz) and ^{13}C NMR spectra (75.47 MHz) were recorded on a Bruker WM AMX spectrometer using TMS as an internal standard (chemical shifts (δ) in parts per million, *J* in hertz). Elemental analyses were obtained on a Perkin–Elmer 240B microanalyser by the Microanalysis Service of the University of Santiago de Compostela. Mass spectra were performed on a Hewlett–Packard HP5988A mass spectrometer by electron impact (EI), or on a Finnigan Trace-MS mass spectrometer by chemical ionization (CI). Optical rotations at the sodium D-line were determined using a Perkin–Elmer 241 thermostated polarimeter. GLC analyses were carried out on a Hewlett–Packard 5890 II apparatus provided with a flame ionization detector, using a semi-capillary column (5 m× 0.53 mm i.d., film thickness 2.65 μm) and helium as carrier gas. The hydrogenations were carried out using a Parr 3915 hydrogenator.

4.1.1. (−)-(1*R*)-8-Phenylmenthyl (1*S*,3-*exo*)-2-benzyl-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate, 1a. A solution of benzylamine (877 mg, 0.89 mL, 8.18 mmol) in dry CH_2Cl_2 (16 mL) was added under argon to a stirred suspension of **7a**[16] (2.36 g, 8.18 mmol) and 3 Å molecular sieves (6 g) in dry CH_2Cl_2 (48 mL) at 0 °C. When the addition was complete the reaction mixture was cooled to −78 °C and treated successively with TFA (933 mg, 0.63 mL, 8.18 mmol), $BF_3{\cdot}OEt_2$ (1.16 g, 1.04 mL, 8.18 mmol), and freshly distilled cyclopentadiene (ca. 2 equiv, 1.3 mL). After 6 h, a mixture of saturated aqueous $NaHCO_3$ solution (20 mL) and then solid $NaHCO_3$ (2 g) were added. The

reaction mixture was allowed to reach room temperature and filtered. The organic layer was separated from the filtrate and washed with H_2O (50 mL) and CH_2Cl_2 (50 mL) on a Celite pad; the organic layer of the resulting mixture was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The pooled organic layers were washed with saturated $NaHCO_3$ solution (128 mL) and brine (130 mL), and were dried over Na_2SO_4. Removal of the solvent on a rotary evaporator yielded an orange oil (ca. 3.7 g), which was purified by chromatography on silica gel (105 g), using hexane/EtOAc 7:1 as eluent affording a white solid identified as the pure major adduct (1*S*,3-*exo*)-**1a** (2.90 g, 6.54 mmol; yield 80%). Mp 125–126 °C. $[\alpha]_D^{25}$ −56.7 (*c* 1, $CHCl_3$). IR (neat): ν=2992, 2965, 2927, 2880, 2855, 2801, 1736, 1598, 1541, 1495, 1457, 1235, 1187, 1161, 1094, 1082, 1007, 736, 698 cm^{-1}. ^1H NMR ($CDCl_3$): δ=0.73–1.06 (m, 3H), 0.86 (d, *J*=6.5 Hz, 3H, 1′-CH_3), 1.08 and 1.09 [2s, 6H, 8′-$(CH_3)_2$], 1.28 (d, *J*=8.3 Hz, 1H, 7_{anti}-H), 1.39–1.60 (m, 3H), 1.79 (d, *J*=8.3 Hz, 1H, 7_{syn}-H), 1.87 (s, 1H), 1.84–1.97 (m, 2H), 2.79 (s, 1H, 4-H), 3.38–3.56 (AB system, *J*=13.1 Hz, 2H, NCH_2Ph), 3.84 (br s, 1H, 1-H), 4.74 (td, J_t= 10.7 Hz, J_d=4.3 Hz, 1H, $3'_{ax}$-H), 6.20 (dd, *J*=5.6, 1.6 Hz, 1H, 5-H), 6.35 (dd, *J*=5.6, 2.3 Hz, 1H, 6-H), 7.09–7.38 (m, 10H, 2×C_6H_5). ^{13}C NMR ($CDCl_3$): 22.20 (1′-CH_3), 26.56 and 27.12 [8′-$(CH_3)_2$], 27.20 (C-5′), 31.63 (C-1′), 35.00 (C-6′), 40.20 (C-8′), 41.88 (C-2′), 46.68 (C-7), 49.18 (C-4), 50.78 (C-4′), 59.43 (NCH_2Ph), 64.91 (C-1), 65.53 (C-3), 75.02 (C-3′), 125.39 [aromatic C-4 (Ph)], 125.88 [aromatic C-2+C-6 (Ph)], 127.37 [aromatic C-4 (Bn)], 128.28 [aromatic C-3+C-5 (Ph)], 128.61 [aromatic C-2+ C-6 (Bn)], 129.40 [aromatic C-3+C-5 (Bn)], 134.09 (C-5), 136.76 (C-6), 139.52 [aromatic C-1 (Bn)], 151.98 [aromatic C-1 (Ph)], 173.11 [C(O)O]. MS (EI, *m*/*z*): 443 (M^+). Anal. Calcd for $C_{30}H_{37}NO_2$: C 81.22, H 8.41, N 3.16; found: C 81.47, H 8.61, N 3.09.

4.1.2. (−)-(1*R*)-8-Phenylisoneomenthyl (1*S*,3-*exo*)-2-benzyl-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate, 1b. Prepared from **7b**[16] by the same procedure used to prepare **1a** from **7a**. Yield: 69%. Mp 94–96 °C. $[\alpha]_D^{22}$ −60.4 (*c* 0.23, $CHCl_3$). IR (KBr): ν=2974, 2935, 2897, 2843, 1735, 1601, 1495, 1456, 1150, 1116, 1003, 738, 702 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.06 (d, *J*=7.4 Hz, 3H, 1′-CH_3), 1.18 and 1.19 [2s, 6H, 8′-$(CH_3)_2$], 1.23–1.28 (m, 1H), 1.39 (d, *J*=8.2 Hz, 1H, 7_{anti}-H), 1.46 (dt, J_d=12.9 Hz, J_t=4.3 Hz, 1H), 1.52–1.62 (m, 3H), 1.67–1.80 (m, 2H), 1.87–1.92 (m, 1H), 1.94 (d, *J*=8.2 Hz, 1H, 7_{syn}-H), 2.28 (s, 1H, 3_{endo}-H), 3.20 (s, 1H, 4-H), 3.50 and 3.65 (AB system, *J*=13.0 Hz, 2H, NCH_2Ph), 3.88 (d, *J*=1.2 Hz, 1H, 1-H), 5.04 (br s, $w_{1/2}$= 7.4 Hz, 1H, $3'_{eq}$-H), 6.23 (dd, *J*=5.6, 1.8 Hz, 1H, 5-H), 6.48 (ddd, *J*=5.6, 3.3, 1.0 Hz, 1H, 6-H), 7.15–7.42 (m, 10H, 2×C_6H_5). ^{13}C NMR ($CDCl_3$): 17.75 (1′-CH_3), 21.49 (C-5′), 25.90 (C-1′), 26.61 and 26.84 [8′-$(CH_3)_2$], 32.62 (C-6′), 36.89 (C-8′), 40.49 (C-2′), 46.90 (C-7), 48.41 (C-4), 51.80 (C-4′), 59.60 (NCH_2Ph), 64.26 (C-1), 66.13 (C-3), 72.36 (C-3′), 125.97 [aromatic C-4 (Ph)], 126.45 [aromatic C-2+C-6 (Ph)], 127.48 [aromatic C-4 (Bn)], 128.35 [aromatic C-3+C-5 (Ph)], 128.71 [aromatic C-2+C-6 (Bn)], 129.37 [aromatic C-3+C-5 (Bn)], 134.31 (C-5), 136.58 (C-6), 139.42 [aromatic C-1 (Bn)], 150.37 [aromatic C-1 (Ph)], 173.23 [C(O)O]. MS (EI, *m*/*z*): 443 (M^+). Anal. Calcd for $C_{30}H_{37}NO_2$: C 81.22, H 8.41, N 3.16; found: C 81.44, H 8.64, N 3.07.

4.1.3. (−)-[(1*S*,3-*exo*)-2-Benzyl-2-azabicyclo[2.2.1]hept-5-en-3-yl]methanol, 2. A solution of adduct **1a** (or **1b**) (1.20 g, 2.70 mmol) in dry Et_2O (20 mL) was added dropwise under argon to a suspension of $LiAlH_4$ (607 mg, 16 mmol) in dry Et_2O (20 mL) at 0 °C. The reaction mixture was stirred for 12 h at room temperature and a mixture of MeOH (30 mL) and H_2O (100 mL) was added dropwise at 0 °C; the resulting mixture was extracted with AcOEt (4×100 mL) and the pooled organic layers were washed with H_2O (2×100 mL) and brine (100 mL), and dried with Na_2SO_4. Removal of solvent in a rotary evaporator left a residue that when chromatographed on silica gel with hexane/EtOAc 3:1 as eluent afforded the chiral auxiliary **5a**[25] (615 mg, 98%) [or **5b**[24] (609 mg, 97%)] in the early fractions and compound **2** (563 mg, 97% yield from **1a** and 557 mg, 96% yield from **1b**), as a colorless oil, in the later fractions. $[\alpha]_D^{25}$ −71.3 (*c* 1, $CHCl_3$). IR (neat): ν=3364, 3060, 2985, 2870, 1495, 1452, 1367, 1324, 1208, 1134, 1028, 910, 717 cm^{-1}. ^1H NMR ($CDCl_3$): 1.25–1.28 (d, 1H, *J*=8.40 Hz, 7_{anti}-H), 1.68–1.71 (d, 1H, *J*=8.40 Hz, 7_{syn}-H), 1.82–1.86 (t, 1H, *J*=5.55 Hz, 3-H), 2.32 (br s, 1H, OH), 2.69 (s, 1H, 4-H), 3.32–3.44 (m, 4H, CH_2OH+CH_2Ph), 3.69 (s, 1H, 1-H), 6.10–6.13 (dd, 1H, *J*=5.65, 1.80 Hz, 5-H), 6.41–6.45 (dd, 1H, *J*=5.65, 3.24 Hz, 6-H), 7.16–7.28 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$): 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′). MS (EI, *m*/*z*): 215 (M^+). Anal. Calcd for $C_{14}H_{17}NO$: C 78.10, H 7.96, N 6.51; found: C 77.99, H 8.11, N 6.38.

4.1.4. (−)-(1*R*)-8-Phenylmenthyl [(1*R*,3-*exo*)-2-benzyl-2-azabicyclo[2.2.1]heptane]-3-carboxylate, 10a. To a solution of **1a** (1.00 g, 2.25 mmol) and 99.5% AcOH (0.13 mL, 2.30 mmol) in AcOEt (15 mL) was added 10% Pd–C (ca. 34 mg). The reaction mixture was hydrogenated at room temperature for 3 h under a hydrogen pressure of 40 psi. Then a saturated aqueous $NaHCO_3$ solution (10 mL) was added, the reaction mixture was filtered, and the organic solvents were removed in a rotary evaporator. The resulting mixture (aqueous layer/oil) was extracted with CH_2Cl_2 (3×20 mL), the pooled organic layers were washed with 3% $NaHCO_3$ solution (20 mL) and brine (30 mL), and were then dried with Na_2SO_4. The solvent was removed in a rotary evaporator yielding **10a** as white solid, which was crystallized from hexane (0.95 g; Yield 95%). Mp 121–122 °C. $[\alpha]_D^{22}$ −21.1 (*c* 1, $CHCl_3$). IR (KBr): ν=2971, 1734, 1600, 1540, 1496, 1304, 1195, 1154, 1046, 993, 750, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ=0.85 (d, *J*=6.5 Hz, 3H, 1′-CH_3), 1.10 and 1.13 [2s, 6H, 8′-$(CH_3)_2$], 0.75–1.69 (m, 8H), 1.19–1.33 (m, 2H), 1.76 (dt, J_d=9.5 Hz, J_t=1.80 Hz, 1H), 1.82–1.99 (m, 3H), 2.14 (s, 1H, 3_{endo}-H), 2.21 (d, *J*=3.7 Hz, 1H, 4-H), 3.28 (s, 1H, 1-H), 3.67 and 3.70 (AB system, *J*=13.0 Hz, 2H, NCH_2Ph), 4.71 (td, J_t=10.7 Hz, J_d=4.3 Hz, 1H, $3'_{ax}$-H), 7.12–7.42 (m, 10H, 2×C_6H_5). ^{13}C NMR ($CDCl_3$): δ=22.23 (1′-CH_3), 22.79 (C-5′), 26.67 and 27.02 [(8′-$(CH_3)_2$], 27.14 (C-1′), 29.56 (C-5), 31.62 (C-6′), 35.02 (C-6), 36.62 (C-7), 40.14 (C-8′), 41.88 (C-2′), 42.95 (C-4), 50.67 (C-4′), 55.94 (NCH_2Ph), 60.11 (C-1), 70.01 (C-3), 74.62 (C-3′), 125.38 [aromatic C-4 (Ph)], 125.87 [aromatic C-2+C-6 (Ph)], 127.29 [aromatic C-4 (Bn)], 128.31 [aromatic C-3+C-5 (Ph)], 128.58 [aromatic C-2+C-6 (Bn)], 129.45 [aromatic

C-3+C-5 (Bn)], 139.78 [aromatic C-1 (Bn)], 152.17 [aromatic C-1 (Ph)], 172.91 [C(O)O]. MS (EI, *m/z*): 445 (M^+). Anal. Calcd for $C_{30}H_{39}NO_2$ C 80.85, H 8.82, N 3.14, found C 80.69, H 8.96, N 3.08.

4.1.5. (−)-(1*R*)-8-Phenylisoneomenthyl [(1*R*,3-*exo*)-2-benzyl-2-azabicyclo[2.2.1]heptane]-3-carboxylate, 10b. Prepared from **1b** by the same procedure used to prepare **10a** from **1a**. Yield: 96%. Mp 60–61 °C. $[\alpha]_D^{22}$ −25.0 (*c* 0.5, $CHCl_3$). IR (KBr): ν=2971, 1734, 1654, 1636, 1559, 1496, 1457, 1172, 1115, 758, 694 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.03 (d, *J*=7.4 Hz, 3H, 1′-CH_3), 1.18 and 1.21 [2s, 6H, 8′-$(CH_3)_2$], 1.24–2.05 (m, 14H), 2.62 (br s, 2H, 3_{endo}-H+4-H), 3.31 (s, 1H, 1-H), 3.71 and 3.99 (AB system, *J*=13.2 Hz, 2H, NCH_2Ph), 4.97 (br s, $w_{1/2}$=8.6 Hz, 1H, $3'_{eq}$-H), 7.14–7.45 (m, 10H, 2×C_6H_5). ^{13}C NMR ($CDCl_3$): δ=17.80 (1′-CH_3), 21.44 (C-5′), 22.80 (C-1′), 26.04 (C-6′), 26.59 and 26.85 [8′-$(CH_3)_2$], 29.61 (C-5), 32.62 (C-6), 36.79 (C-7), 36.85 (C-8′), 40.48 (C-2′), 42.26 (C-4), 51.73 (C-4′), 56.12 (NCH_2Ph), 59.45 (C-1), 71.16 (C-3), 72.14 (C-3′), 125.94 [aromatic C-4 (Ph)], 126.42 [aromatic C-2+C-6 (Ph)], 127.31 [aromatic C-4 (Bn)], 128.33 [aromatic C-3+C-5 (Ph)], 128.61 [aromatic C-2+C-6 (Bn)], 129.37 [aromatic C-3+C-5 (Bn)], 129.68 [aromatic C-1 (Bn)], 150.32 [aromatic C-1 (Ph)], 172.83 [C(O)O]. MS (EI, *m/z*): 445 (M^+). Anal. Calcd for $C_{30}H_{39}NO_2$: C 80.85, H 8.82, N 3.14; found: C 80.64, H 8.94, N 3.04.

4.1.6. (+)-(1*R*,3-*exo*)-2-Benzyl-3-[(hydroxy)diphenylmethyl]-2-azabicyclo[2.2.1]heptane, 11. A solution of **10a** (or **10b**) (800 mg, 1.80 mmol) in dry THF (5 mL) was added dropwise under argon to a solution of PhMgBr [prepared, under argon, from Mg (470 mg, 19.4 mmol) and PhBr (1.9 mL, 18 mmol) in dry THF (25 mL)] at room temperature. The reaction mixture was refluxed overnight. Then the mixture was cooled to 0 °C and saturated aqueous NH_4Cl solution (16 mL) was added dropwise, the resulting mixture was filtered and the organic solvents were removed in a rotary evaporator. The remaining mixture was then extracted with CH_2Cl_2 (3×20 mL). The pooled organic layers were washed with saturated aqueous NH_4Cl solution (16 mL) and brine (20 mL), and dried with Na_2SO_4. The solvent was removed in a rotary evaporator and the resulting residue was treated with MeOH (12 mL) yielding **11** as a white solid (591 mg, 89% from **10a** and 578 mg, 87% from **10b**).[20] Removal of the solvent from the mother liquor left an oil, which when flash chromatographed on silica gel (75 g) using hexane/EtOAc 3:1 as eluent afforded the chiral auxiliary (393 mg of **5b**,[24] 94% and 402 mg of **5a**,[25] 96%). Mp 179–180 °C. $[\alpha]_D^{23}$ +51 (*c* 1, $CHCl_3$). IR (KBr): ν=2992, 2910, 1426, 1332, 1255, 1094, 966, 788 cm^{-1}. ^1H NMR ($CDCl_3$): δ=0.97 (d, *J*=9.8 Hz, 1H, 7-H), 1.22–1.33 (m, 1H), 1.38–1.61 (m, 2H), 1.94 (d, *J*=9.8 Hz, 1H, 7-H), 1.98–2.07 (m, 1H), 2.22 (s, 1H), 2.98 (d, *J*=13.0 Hz, 1H, NC*H*HPh), 3.11 (s, 1H), 3.25 (s, 1H), 3.32 (d, *J*=13.0 Hz, 1H, NCH*H*Ph), 5.17 (br s, 1H, D_2O exch.), 7.08–7.36 (m, 11H, arom.), 7.60 [dd, *J*=7.3, 1.2 Hz, 2H, H_{ortho}-2 (Ph′)], 7.74 [dd, *J*=7.5, 1.2 Hz, 2H, H_{ortho}-2 (Ph″)]. ^{13}C NMR ($CDCl_3$): δ= 22.14 (C-5), 30.73 (C-6), 36.06 (C-7), 41.21 (C-4), 53.86 (C-1), 58.00 (NCH_2Ph), 75.49 (C-3), 77.34 [C(OH)Ph_2], 126.12 [aromatic, C_{para} (Ph′ and Ph″)], 126.67 and 126.84 [aromatic, 2×C_{ortho} (Ph′ and Ph″)], 127.30 [aromatic C_{para} (Bn)], 128.52 [aromatic C_{meta} (Bn)], 128.56 [aromatic C_{ortho} (Bn)], 128.66 and 129.22 [aromatic, 2×C_{meta} (Ph′ and Ph″)], 139.78 [aromatic C-1 (Bn)], 146.63 and 148.89 [aromatic, 2×C-1 (Ph′ and Ph″)]. MS (CI, *m/z*): 370 (MH^+). Anal. Calcd for $C_{26}H_{27}NO$: C 84.51, H 7.36, N 3.79; found: C 84.28, H 7.51, N 3.84.

4.1.7. (+)-(1*R*)-2-Benzyl-3-(diphenylmethylidene)-2-azabicyclo[2.2.1]heptane, 12. A solution of **11** (500 mg, 1.35 mmol) in HMPA (4.9 mL, 27.9 mmol) was heated at 215–220 °C with stirring for 2 h. Then the mixture was cooled to room temperature and chromatographed on silica gel (170 g) using hexane/EtOAc 4:1 as eluent affording in the early fractions compound **12** as a white solid, which was crystallized from hexane. Yield 452 mg (95%). Mp 139–140 °C. $[\alpha]_D^{23}$ +938 (*c* 1, $CHCl_3$). IR (KBr): ν=3021, 2961, 1609, 1593, 1492, 1350, 1219, 1148, 938, 731 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.26 (d, *J*=9.0 Hz, 1H, 7-H), 1.48 (tdd, J_t=11.7 Hz, J_d=4.5 Hz, J_d=2.4 Hz, 1H), 1.74–2.03 (m, 4H), 3.11 (d, *J*=1.9 Hz, 1H), 3.35 (s, 1H), 3.50 (d, *J*=15.2 Hz, 1H, NC*H*HPh), 4.03 (d, *J*=15.2 Hz, 1H, NCH*H*Ph), 6.98 (tt, *J*=7.3, 1.3 Hz, 1H), 7.07–7.27 (m, 14H, arom.). ^{13}C NMR ($CDCl_3$): δ=24.86 (C-5), 28.75 (C-6), 39.54 (C-7), 44.57 (C-4), 49.74 (C-1), 59.91 (NCH_2Ph), 108.69 (CPh$_2$), 124.98 and 125.53 [aromatic, 2×C_{ortho} (Ph′ and Ph″)], 126.82 [aromatic C_{para} (Bn)], 127.96 [aromatic, 2×C_{para} (Ph′ and Ph″)], 128.00 [aromatic C_{ortho} (Bn)], 128.20 [aromatic C_{meta} (Bn)], 130.34 and 131.02 [aromatic, 2×C_{meta} (Ph′ and Ph″)], 139.45 [aromatic C-1 (Bn)], 143.04 and 145.20 [aromatic, 2×C-1 (Ph′ and Ph″)], 154.02 (C-3). MS (CI, *m/z*): 352 (MH^+). Anal. Calcd for $C_{26}H_{25}N$: C 88.85, H 7.17, N 3.98; found: C 88.73, H 7.28, N 4.14.

4.1.8. (+)-(1*R*)-2-Benzyl-2-azabicyclo[2.2.1]heptan-3-one, 13. To a vigorously stirred solution of **12** (400 mg, 1.14 mmol) in $CHCl_3$ (18 mL) was added Cu_2Cl_2 (ca. 14 mg) at 0 °C and the resulting cooled suspension was bubbled for 6 h with O_2 (air stream). The reaction mixture was filtered. Removal of the solvent from the filtrate in a rotary evaporator left an oil (438 mg) that upon chromatography on silica gel (15 g) with hexane/AcOEt 2:1 as eluent afforded benzophenone (206 mg) in the early fractions and **13**, as an oil, in the later fractions. Yield 208 mg (91%). $[\alpha]_D^{22}$ +41 (*c* 0.56, $CHCl_3$). IR (neat): ν=2954, 2930, 1693, 1409, 1227, 993, 751 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.33 (d, *J*=9.4 Hz, 1H, 7_{anti}-H), 1.47–1.72 (m, 3H), 1.82 (dd, *J*= 9.4, 1.5 Hz, 1H, 7_{syn}-H), 1.82–1.90 (m, 1H), 2.85 (dd, *J*=3.8, 1.5 Hz, 1H, 4-H), 3.68 (s, 1H), 3.93 (d, *J*=15.1 Hz, 1H, NC*H*HPh), 4.68 (d, *J*=15.1 Hz, 1H, NCH*H*Ph), 7.24–7.35 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$): δ=24.94 (C-5), 27.30 (C-6), 40.30 (C-7), 44.35 (C-4), 45.90 (C-1), 59.00 (NCH_2Ph), 127.66 [aromatic C-4 (Bn)], 128.17 [aromatic C-2+C-6 (Bn)], 128.85 [aromatic C-3+C-5 (Bn)], 137.56 [aromatic C-1 (Bn)], 178.21 (C-3). MS (EI, *m/z*): 201 (M^+). Anal. Calcd for $C_{13}H_{15}NO$: C 77.58, H 7.51, N 6.96; found: C 77.33, H 7.72, N 6.84.

4.1.9. (+)-(1*R*)-2-Benzoyl-2-azabicyclo[2.2.1]heptan-3-one, 9. To a solution of **13** (150 mg, 0.75 mmol) and 18-crown-6 (ca. 1 mg) in 10 mL of Me_2CO/AcOH (85:15, v/v) was added water (0.5 mL). The mixture was heated to 60 °C, finely powdered $KMnO_4$ (476 mg, 3 mmol) was added in portions during 5 h, and heating was continued for 10 h more. The reaction mixture was then cooled to

room temperature, 1 M $Na_2S_2O_5$ (8 mL) was added, and the mixture was extracted with CH_2Cl_2 (4×20 mL). The pooled organic layers were washed with 1 M $Na_2S_2O_5$ solution (8 mL) and brine (20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated, affording a solid residue. Purification of the resulting solid through a short column of silica gel (6 g) using $CHCl_3$ as eluent afforded **9** as a white solid. Yield 154 mg (96%). The purity of the compound obtained was verified by GLC [99.9%; semi-capillary column (5 m×0.53 mm i.d., film thickness 2.65 μm); oven temperature 150 °C isothermal, helium as carrier gas]. Mp 180–181 °C (hexane/CCl_4). $[\alpha]_D^{22}$ +286 (*c* 1, $CHCl_3$). IR (KBr): ν=2979, 2954, 2876, 1746, 1660, 1600, 1452, 1337, 1310, 1216, 1178, 1159, 1099, 1056, 1027, 952, 907, 804, 781, 732, 698, 675, 611 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.59 (dt, J_d=10.0 Hz, J_t=1.1 Hz, 1H, 7_{anti}-H), 1.73–1.80 (m, 1H), 1.95–2.03 (m, 3H), 2.06 (dt, J_d=10.0 Hz, J_t=1.8 Hz, 1H, 7_{syn}-H), 2.94 (t, *J*=1.6 Hz, 1H, 4-H), 4.81 (s, 1H, 1-H), 7.37–7.42 [m, 2H, (3′-H, 5′-H)], 7.49–7.54 (m, 1H, 4′-H), 7.61–7.65 [m, 2H, (2′-H, 6′-H)]. ^{13}C NMR ($CDCl_3$): δ=24.99 (C-5), 28.24 (C-6), 37.64 (C-7), 47.36 (C-4), 59.24 (C-1), 127.90 [aromatic C-3+C-5 (Bz)], 129.57 [aromatic C-2+C-6 (Bz)], 132.38 [aromatic C-4 (Bz)], 134.22 [aromatic C-1 (Bz)], 169.56 [N*C*(O)Ph], 175.73 (C-3). MS (EI, *m*/z): 215 (M^+). Anal. Calcd for $C_{13}H_{13}NO_2$: C 72.54, H 6.09, N 6.51; found: C 72.48, H 6.12, N 6.47.

4.1.10. (−)-(1*S*)-2-Azabicyclo[2.2.1]heptan-3-one, 14. To a solution of **3**[23] [(160 mg, 1.47 mmol), $[\alpha]_D$ −563.4 (*c* 1, $CHCl_3$)] in AcOEt (50 mL) was added 10% Pd/C (300 mg). The vigorously stirred black suspension was hydrogenated under a hydrogen pressure of 40 psi at room temperature. After the reaction was complete (1.5 h), the reaction mixture was filtered and the filtrate was concentrated to give a white solid (161 mg, 98%). The purity of the compound obtained was verified by GLC [99.5%, semi-capillary column (5 m×0.53 mm i.d., film thickness 2.65 μm), oven temperature 85 °C isothermal, helium as carrier gas]. An analytical sample was obtained through crystallization from cyclohexane and subsequent sublimation at 90–95 °C (0.05–0.1 mmHg). Mp 96–98 °C. $[\alpha]_D^{22}$ −160 (*c* 1, $CHCl_3$).[26] IR (KBr): ν=3219, 2946, 1684, 1507, 1398, 1239, 1109, 954, 814, 754 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.31 (dq, *J*=9.3, 1.3 Hz, 1H), 1.47–1.57 (m, 2H), 1.72–1.80 (m, 2H), 1.83 (dquint, *J*=9.3, 2.0 Hz, 1H), 2.73 (d, *J*=1.0 Hz, 1H), 3.88 (d, *J*=0.8 Hz, 1H), 6.74 (br s, D_2O exch., 1H). ^{13}C NMR ($CDCl_3$): δ=23.93, 30.43, 41.73, 45.37, 55.70, 181.97. MS (EI, *m*/z): 111 (M^+). Anal. Calcd for C_6H_9NO: C 64.84, H 8.16, N 12.60; found: C 64.63, H 8.33, N 12.54.

4.1.11. (−)-(1*S*)-2-Benzoyl-2-azabicyclo[2.2.1]heptan-3-one, *ent*-9. A solution of **14** (85 mg, 0.765 mmol) in dry Et_2O (3 mL) was added under argon to a stirred suspension of 60% NaH (46 mg, 1.15 mmol) in dry Et_2O (5 mL) at 0 °C. The mixture was stirred for 20 min and then a solution of benzoyl chloride (163 mg, 1.16 mmol) in dry Et_2O (3 mL) was added under argon. The reaction mixture was stirred at room temperature overnight and then filtered through a short column of silica gel using Et_2O as eluent. The solvent was removed in a rotary evaporator affording (−)-**9** as a white solid. Yield 140 mg (85%). The purity of the compound obtained was verified by GLC [99.9%, semi-capillary column (5 m×0.53 mm i.d., film thickness 2.65 μm), oven temperature 150 °C isothermal, helium as carrier gas]. Mp 179–181 °C (CCl_4). $[\alpha]_D^{22}$ −287 (*c* 1, $CHCl_3$). Spectroscopic data (IR, ^1H NMR, ^{13}C NMR) were identical to those of compound (+)-**9**.

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