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Highly diastereoselective synthesis of 2-azabicyclo[2.2.1]hept-5-ene derivatives: Bronsted acid catalyzed aza-Diels–Alder reaction between cyclopentadiene and imino-acetates with two chiral auxiliaries

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ABSTRACT

The cycloaddition between protonated glyoxylate imines possessing two chiral auxiliaries, *N*-(*S*)- or *N*-(*R*)-1-phenylethyl and (−)-8-phenylmenthyl or (+)-8-phenylneomenthyl, and cyclopentadiene is described. The absolute configuration of all adducts formed was unequivocally assigned through NMR, specific optical rotation, and X-ray data of appropriated derivatives. Experimental results confirm the highly *exo*-selectivity for these aza-Diels–Alder reactions, single adducts being obtained from combinations of (8PM)-(*R*-PEA) and (8PNM)-(*S*-PEA).

1. Introduction

The great versatility of cycloadditions, their high stereochemical control, and the fair predictability of their regiochemistry allied to the rapid accumulation of polyfunctionality in a relatively small molecular framework, have contributed to the popularity of these reactions.[1] Within the diverse transformations comprising cycloadditions, aza-Diels–Alder reactions of imine derivatives and dienes leading to six-membered aza-heterocycles, monocyclic and bicyclic molecules, have attracted much interest, especially those employing cyclopentadiene as starting material.[2,3] The imines, used as aza-dienophiles, generally require activation by an electron-withdrawing group and a Lewis acid (LA) and/or Bronsted acid (BA) to participate in these [4+2] cycloaddition reactions.[3] It has been shown that the electronic nature of the substituents at the diene/dienophile pair may strongly influence the reaction pathways and determine either a concerted mechanism (synchronous or asynchronous) or a stepwise one.[4] In addition, experimentalists have always employed catalysts to change the kinetics of this class of reactions. In particular, a wide range of homogeneous and heterogeneous Lewis acids have been used to improve the rate and *exo*/*endo* selectivities of these cycloadditions.[2,3]

The products obtained, 2-azabicyclo[2.2.1]hept-5-enes,[3] can be used as precursors of a large variety of compounds of chemical, biological, and pharmaceutical interest.[5,6] The products obtained in these reactions contain a highly functionalized bridged [2.2.1] ring system that may undergo further transformations (Scheme 1). Oxidation of the double bond, ring opening of the vicinal-diol, reduction or hydrolysis of the ester functionality would lead to a great number of chiral nonnatural amino alcohols and α-amino acids (pyrrolidine derivatives). Many of these 'glycomimetics', also called azasugars, may show useful activity as glycosidase inhibitors[7] with application as antiviral,[8] included potential nonnucleosidic inhibitors of HIV replication,[9] antineoplastic,[10] and antidiabetic agents.[8a,11] On the other hand, the sequence based on Barbier–Wieland degradation and the cleavage of the N–C_3 bond, would lead to chiral bicyclic lactams, useful as precursors of GABA analogs,[12] and chiral amino alcohols, derived from cyclopentene and cyclopentane, useful for the synthesis of carbocyclic nucleosides with antiviral and antineoplastic properties.[13]

Bailey and co-workers[14] investigated cycloadditions of (−)-8-phenylmenthyl (*R*)- and (*S*)-*N*-1-phenylethylimino glyoxylates with cyclopentadiene. The reaction showed high diastereoselectivity when the *R*-1-phenylethyl group was incorporated in the imine (>95%), and poor selectivity when the *S*-1-phenylethyl group was incorporated in the imine (<49%). The absolute configuration of the stereoisomers obtained was not determined, but the

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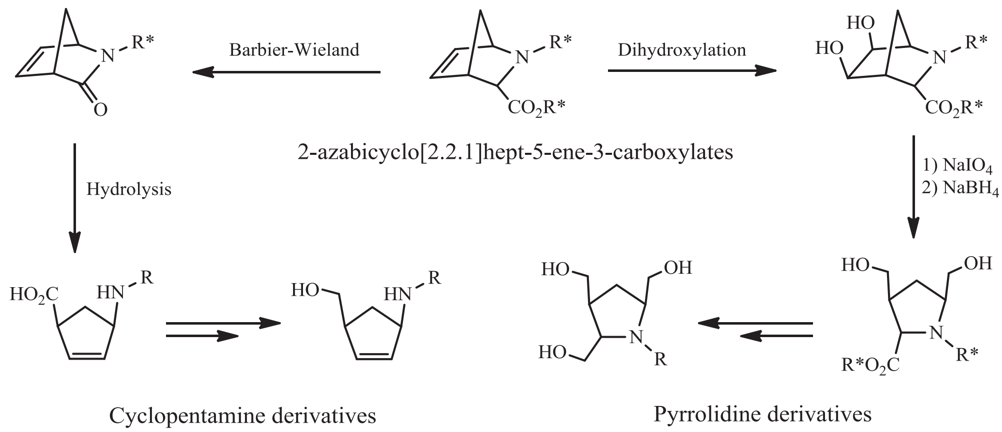


Scheme 1. 2-Azabicyclo[2.2.1]hept-5-enes as precursors of a large variety of compounds.

stereochemistry of the single product (bicycle) obtained in the case of the imine with the *R*-1-phenylethyl group was assumed to be (3*S*,*exo*), according to results obtained before by Stella and co-workers[3e] with racemic methyl 1-phenylethylimine glyoxylate. Obviously, the reaction outcomes cannot be compared, as in one case (Bailey) 8-phenylmenthyl glyoxylate and in the other case (Stella) methyl glyoxylate was used. In fact, and as can be confirmed further in this paper, using 8-phenylneomenthyl glyoxylate and (*R*)-1-phenylethylamine (*R*-PEA) three diastereoisomers were obtained.

Our reasons to re-visit these reactions were first, to confirm the stereochemistry of these reactions for which no conclusive evidences had been apported before; and second, to enlarge the scope of these cycloadditions incorporating another menthyl chiral auxiliary, (+)-8-phenylneomenthyl, instead of the virtually inaccessible (+)-8-phenylmenthol (~500 euro/g), providing an alternative route to the obtention of the reverse adducts.

In a previous work on cycloadditions between chiral iminodienophiles of glyoxylates of 8-phenylmenthols and cyclopentadiene, we showed these reactions to be highly accelerated by the addition of an LA, due to the formation of an iminium cation complex that rapidly undergoes cycloaddition under mild conditions to give products with high stereo *exo*-selectivity.[3c,d,6b] Herein we describe the most efficient synthesis of all the adducts formed in the cycloaddition of *N*-(*S*)- or *N*-(*R*)-1-phenylethylimines of (−)-8-phenylmenthyl or (+)-8-phenylneomenthyl glyoxylates, and cyclopentadiene. The assignment of the absolute configuration of all the adducts formed was achieved through NMR, specific optical rotation, and X-ray data of the appropriated derivatives.

2. Results and discussion

(−)-8-Phenylmenthol (**1a**),[15a] and (+)-8-phenylneomenthol (**1b**),[15b,c] were obtained before in our laboratory in good yields, from inexpensive (+)-(*R*)-pulegone, and are therefore non-expensive chiral auxiliaries. Conversion of the alcohols into the corresponding glyoxylates (**3a** and **3b**) was achieved by reaction with acryloyl chloride in the presence of Et_3N and DMAP, followed by treatment of the resulting acrylates (**2a** and **2b**) with either ozone (with Me_2S quenching) or OsO_4 and $NaIO_4$.[3c,15d,e] Treatment of the glyoxylate (**3a** or **3b**) with equimolar amounts of 1-phenylethylamine (*R*-PEA or *S*-PEA), trifluoroacetic acid (TFA), and $BF_3 \cdot OEt_2$ in DCM generated the corresponding iminium salt (protonated imine) (**4**), which reacted in situ with excess cyclopentadiene at −78 °C to give the corresponding adducts (**5**/**6**) (Scheme 2). The reaction was monitored by TLC (aliquots treated with $NaHCO_3$), and the total consumption of the imine was observed after 5 h.

Treatment of the *exo*-cycloadducts **5a**, **5b** and the *endo*-cycloadduct **6a** with $LiAlH_4$[3i–k] afforded the corresponding amino alcohols **7**, while allowing quantitative recovery of the chiral auxiliaries (**1a** and **1b**, respectively)[16] with retention of configuration in all cases. Attempts to reduce *endo*-cycloadduct **6b** with $LiAlH_4$ were not successful.

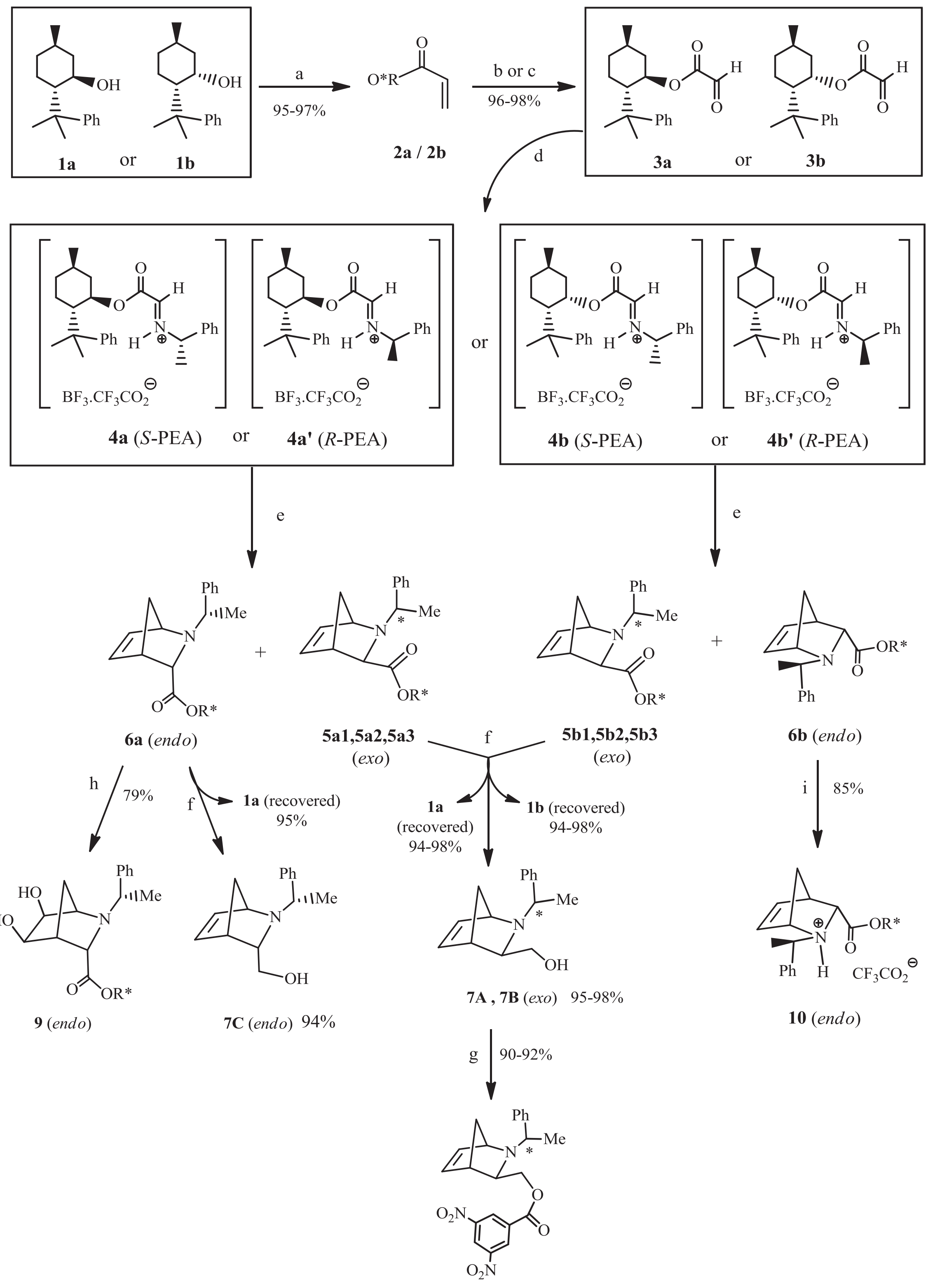
The results of the aza-Diels–Alder reactions are presented in Table 1.

As can be seen, on reaction with cyclopentadiene (−)-8-phenylmenthyl (*R*)-*N*-phenylethylimino glyoxylate (entry 1) gave the single product **5a1** (1*S*,3*exo*) in 79% yield; (−)-8-phenylmenthyl (*S*)-*N*-phenylethylimino glyoxylate (entry 2) gave a mixture of products: **5a2** (1*S*,3*exo*), 25% yield; **5a3** (1*R*,3*exo*), 35% yield; **6a** (1*R*,3*endo*), 15% yield; (+)-8-phenylneomenthyl (*S*)-*N*-phenylethylimino glyoxylate (entry 3) gave the single product **5b1** (1*R*,3*exo*) in 76% yield; (+)-8-phenylneomenthyl (*R*)-*N*-phenylethylimino glyoxylate derivative (entry 4) gave a mixture of cycloadducts: **5b2** (1*R*,3*exo*), 26% yield; **5b3** (1*S*,3*exo*) in 37% yield; **6b** (1*R*,3*endo*) in 10% yield. Resuming, reactions of cyclopentadiene with **3a** and (*R*)-PEA and with **3b** and (*S*)-PEA yielded only one optically pure adduct (reverse adduct families (1*S*,3*exo*)- and (1*R*,3*exo*)-2-azabicyclo[2.2.1]hept-5-enes, respectively). The other combinations of these two reagents (**3a**/(*S*)-PEA and **3b**/(*R*)-PEA) led to a mixture of three diastereomeric adducts.

In an attempt to explain this outcome we present in Scheme 3 a model for the approach of diene and dienophile. Taking into account, simultaneously, polar effects (hydrogen bonding) and repulsive interactions in the different conformations, the geometry corresponding to a *syn*–*syn*–*syn* alignment[3d] is the one which best explains the obtention of the single adduct (1*S*,3*exo*) with the chiral auxiliaries 8-phenylmenthol/*R*-phenylethyl (attack on the *si*-face) and the obtention of other single adduct (1*R*,3*exo*) with the chiral auxiliaries 8-phenylneomenthol/*S*-phenylethyl (attack on the *re*-face). The high *exo*-selectivity observed in these cases may be explained considering that:

* the iminium ion, which acts as dienophile in the reaction, should have an *E* configuration, more stable for stereochemical (bulky groups far apart) and polar (hydrogen bonding C=O/N±H) reasons.
* in the close vicinity of the C=N bond, the 1-phenylethyl group exerts a larger steric hindrance than the ester group.

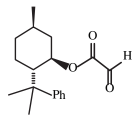
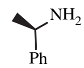
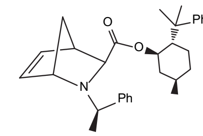
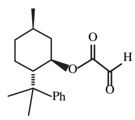
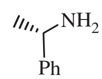
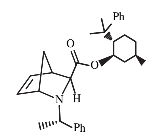
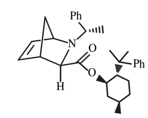
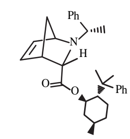
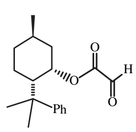
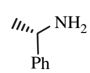
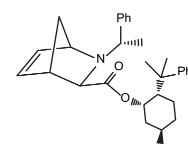
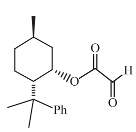
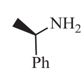
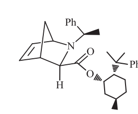
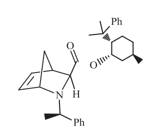
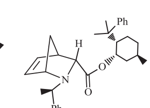
Consequently, in order to minimize stereochemical interactions (in the transition state) between the methylene group of the diene and the bulky substituents of the dienophile, the



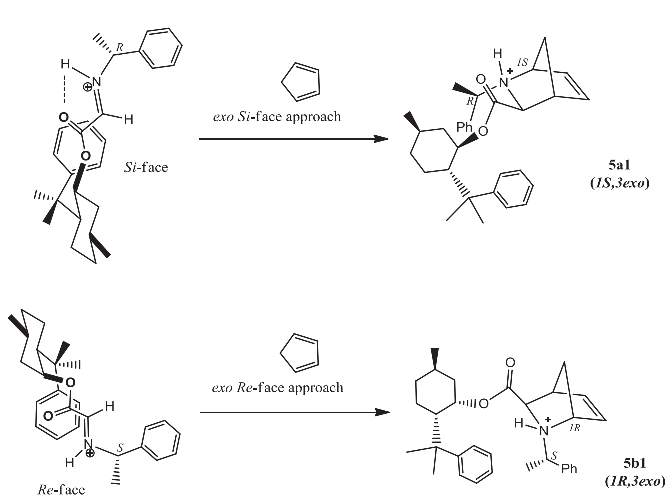
Scheme 2. Synthesis of 2-azabicyclo[2.2.1]hept-5-ene derivatives via cycloadducts **5** and **6**. Reagents and conditions: (a) acryloyl chloride, DCM, Et_3N, DMAP, 0 °C; (b) (1) O_3, DCM, −78 °C; (2) SMe_2; (c) OsO_4, $NaIO_4$, dioxane/H_2O; (d) (1) *R*-PEA or *S*-PEA, DCM, 0 °C, 1 h; (2) TFA, $BF_3\cdot OEt_2$, −78 °C; (e) (1) cyclopentadiene, −78 °C, 5 h; (2) $NaHCO_3/H_2O$; (f) (1) $LiAlH_4$, Et_2O, 12 h; (2) H_2O; (g) 3,5-dinitrobenzoyl chloride, DMAP, DCM; (h) OsO_4, NMO, *tert*-butanol/THF/H_2O; (i) TFA, Et_2O.

approach diene–dienophile must occur in an *exo* manner. 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, after work up (HCO_3^-), capable of undergoing inversion of the lone pair of electrons to achieve the most stable conformation.

Table 1
The results for the aza-Diels–Alder reaction between cyclopentadiene and in situ generated *N*-phenylethyliminoacetates of (−)-8-phenylmenthol and (+)-8-phenylneomenthol (−78 °C, 5 h)

Entry	Glyoxylate	Phenylethylamine	Products-yield[a] (%)
1	 **3a**	 **(*R*)-PEA**	 **5a1** (*1S,3exo*) 79%
2	 **3a**	 **(*S*)-PEA**	 **5a2** 25%  **5a3** 35%  **6a** 15%
3	 **3b**	 **(*S*)-PEA**	 **5b1** (*1R,3exo*) 76%
4	 **3b**	 **(*R*)-PEA**	 **5b2** 26%  **5b3** 37%  **6b** 10%

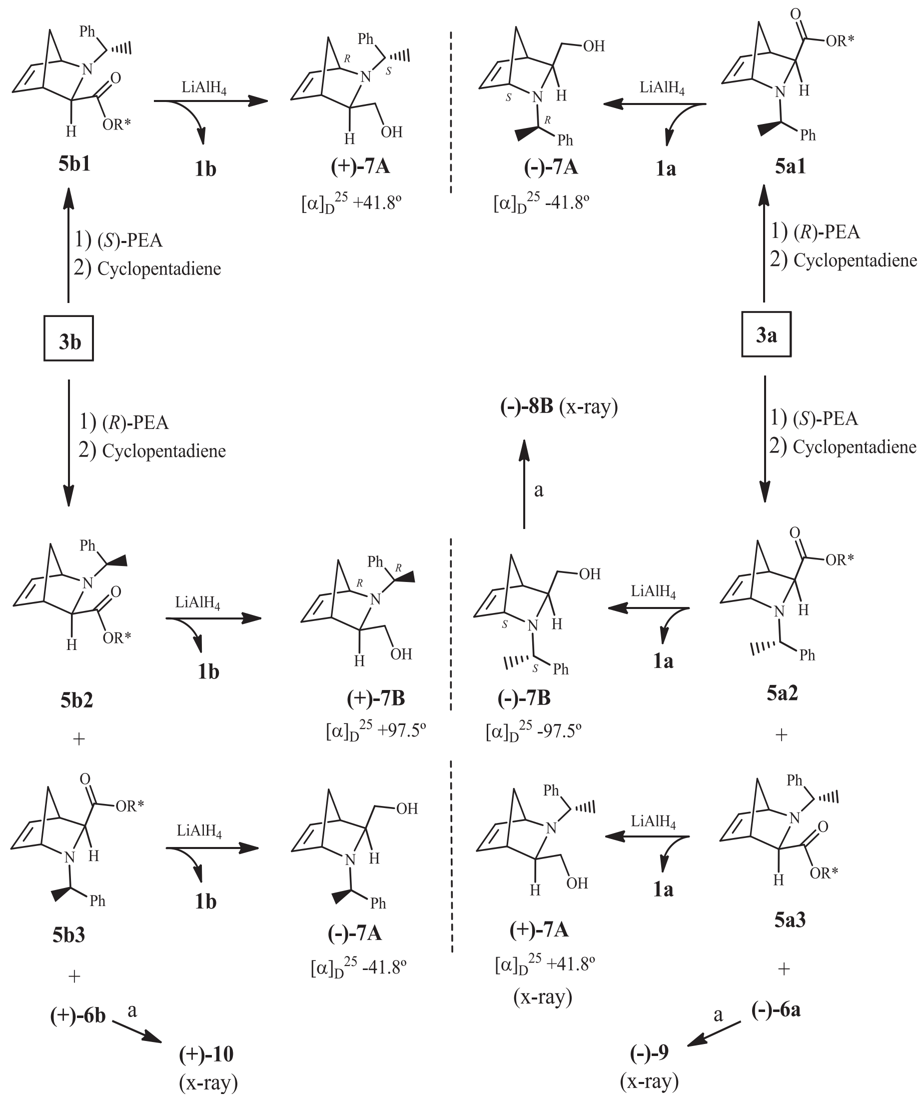
[a] After chromatographic purification.



Scheme 3. Model for the approach of diene (cyclopentadiene) and iminium cations of corresponding imino-acetates to afford single adducts **5a1** and **5b1**.

In what concerns the preference observed in the approach of the diene to the diastereotopic faces of the dienophile, it is more difficult to suggest a hypothesis. The presence of two chiral auxiliaries and in particular the stereochemistry of the phenylethyl group must play an important role in the obtention of the single adducts, since the need for coplanarity of the benzene rings and for maximum distance of bulky substituents turns one of the diastereotopic faces much less hindered than the other. In the case of *R*-phenylethylamine, coplanarity of the benzene ring and maximum distance of this substituent from the phenylmenthyl group places the methyl group of the phenylethylamine backwards to the *re*-face and favors therefore highly attack from the less hindered *si*-face. In the case of *S*-phenylethylamine a similar rationalizing explains the preference for the *re*-face.

For the determination of the absolute configurations of adducts **5** and **6**, the transformations outlined in Scheme 4 were performed. Reduction with $LiAlH_4$ of the *exo*-cycloadducts **5a**,**b** gave the four alcohols (+)-**7A**, (−)-**7A**, (+)-**7B**, (−)-**7B**, whose optical rotations were determined. The absolute configuration of adduct **5a3** (1*R*,3*exo*) was unequivocally determined from

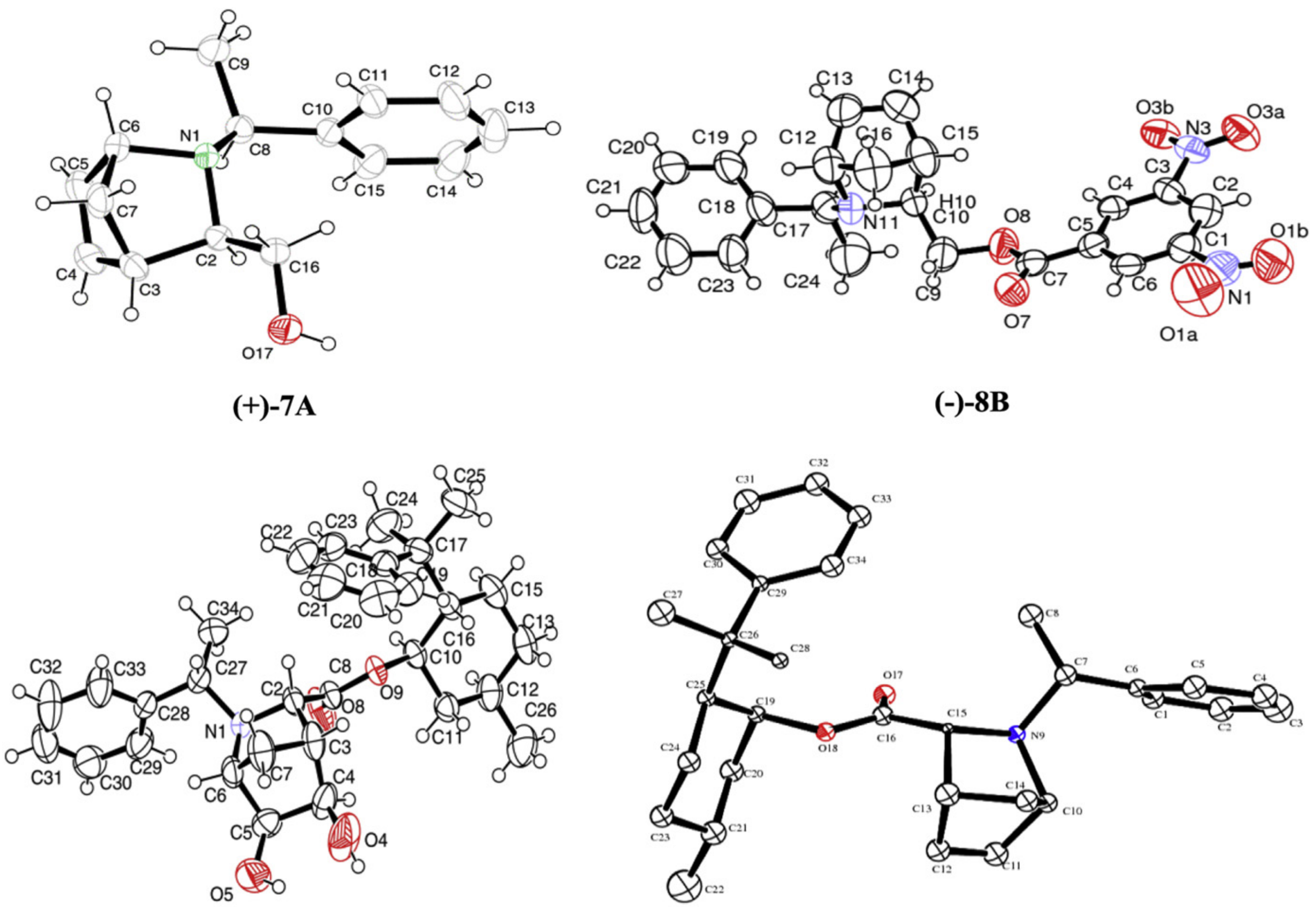


Scheme 4. Determination of the absolute configuration of adducts **5** and **6**: transformations performed. [a]See Scheme 2.

crystallographic data of X-ray diffraction of the corresponding aminoalcohol (+)-**7A** (1*R*,3*exo*) (Fig. 1).[17] Amino alcohols **7A** and 7**B** were transformed into the corresponding 3,5-dinitrobenzoates (**8**) by reaction with 3,5-dinitrobenzoyl chloride. The absolute configuration of adduct **5a2** (1*S*,3*exo*) was unequivocally determined from crystallographic data of X-ray diffraction of the corresponding 3,5-dinitrobenzoyl derivative (−)-**8B** (Fig. 1)[18] prepared from the corresponding aminoalcohol (−)-**7B** (1*S*,3*exo*). The absolute configurations of the remaining adducts, **5b1** (1*R*,3*exo*), **5b2** (1*R*,3*exo*), and **5b3** (1*S*,3*exo*), were determined by comparison of NMR spectroscopic data (^{1}H and ^{13}C) and specific rotation data of the corresponding aminoalcohol derivatives, (+)-**7A**, (+)-**7B**, and (−)-**7A**, respectively, with the values obtained for their enantiomers (configuration determined by X-ray). Dihydroxylation of *endo*-cycloadduct **6a** with OsO_4 in the presence of *N*-methylmorpholine-*N*-oxide yielded diol **9** as crystals suitable for X-ray analysis (Fig. 1).[19] In the case of *endo*-adduct **6b** (1*S*,3*endo*), the absolute configuration was unequivocally determined from crystallographic data of X-ray diffraction of the corresponding ammonium trifluoroacetate **10** (1*S*,3*endo*) (Fig. 1).[20]

3. Conclusions

The results obtained illustrate the utility of (−)-8-phenylmenthol and (+)-8-phenylneomenthol (used instead of virtually inaccessible (+)-8-phenylmenthol) as easily recoverable stereo controlling auxiliaries, affording optically pure 3-functionalized 2-azabicyclo[2.2.1]hept-5-enes from aza-Diels–Alder reaction between cyclopentadiene and chiral protonated phenylethylimines, formed from the corresponding (*R*)- or (*S*)-phenylethylamine and the glyoxylates of these alcohols. For the combination of the auxiliaries *N*-(*S*)-phenylethyl/8-phenylmenthyl and *N*-(*R*)-phenylethyl/8-phenylneomenthyl, the reaction yielded three diastereomers, (1*R*,3*exo*)-**5a3**, (1*S*,3*exo*)-**5a2**, (1*R*,3*endo*)-**6a** (2.3:1.7:1) and (1*S*,3*exo*)-**5b3**, (1*S*,3*exo*)-**5b2**, (1*S*,3*endo*)-**6b** (3.7:2.6:1), respectively. However, when *N*-(*R*)-phenylethyl/8-phenylmenthyl and *N*-(*S*)-phenylethyl/8-phenylneomenthyl were used in combination, only a single diastereomeric adduct was obtained, (1*S*,3*exo*)-**5a1** (79%) and (1*R*,3*exo*)-**5b1** (76%), respectively. We have unambiguously the absolute configuration of all the adducts assigned, using NMR, specific optical rotation and X-ray data of the appropriated derivatives (amino alcohols **7**, 3,5-dinitrobenzoates **8**, diol **9**, and ammonium trifluoroacetate **10**).



(+)-7A **(-)-8B**

(-)-9 **(+)-10**

Fig. 1. X-ray single crystal structures of compounds (+)-**7A**,[17] (−)-**8B**,[18] (−)-**9**,[19] and (+)-10.[20]

4. Experimental

4.1. General methods

All reactions were carried out under anhydrous conditions. Solvents were dried according to standard procedures and distilled prior to use. All reagents were commercially available and used without further purification, unless otherwise stated. Flash column chromatography was performed on silica gel (60 Å, 230–240 mesh) and analytical thin-layer chromatography (TLC) on pre-coated silica gel 60 F_{254} plates using iodine vapor and/or UV light (254 nm) for visualization. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on FT/IR spectrophotometers and main bands are given in cm^{-1}. The ^{1}H NMR (300 MHz or 400 MHz) and ^{13}C NMR (75.47 MHz) spectra were recorded using $CDCl_3$ as solvent and are reported in parts per million downfield from TMS. Optical rotations were measured on a conventional thermostated polarimeter using a sodium lamp and are reported as follows: $[\alpha]_D^t$ (*c* in g per 100 mL, solvent). Elementary analyses were obtained on a microanalyser apparatus.

4.2. General procedure for the synthesis of acrylates (2a,b)[3c,15d,e]

A solution of acryloyl chloride (2.10 mL, 25.8 mmol) in dry DCM (40 mL) was added dropwise under argon to a solution of 8-phenylmenthol (**1a** or **1b**) (3.00 g, 12.9 mmol), Et_3N (3.6 mL; 26 mmol), and DMAP (227 mg, 1.81 mmol) in dry DCM (60 mL) at 0 °C. The mixture was stirred for 2 h at rt and was then treated with saturated $NaHCO_3$ solution (125 mL) and extracted with DCM (3×100 mL). The pooled organic layers were washed with saturated $NaHCO_3$ 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 the corresponding acrylate as a yellow oil.

*4.2.1. (−)-(1R,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl acrylate (**2a**)*[15e]. Yield: 97%. $[\alpha]_D^{25}$ −9.5 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.89 (d, 3H, *J* 6.6 Hz, 5′-CH_3), 0.80–1.2 (m, 3H, menthyl), 1.25 (s, 3H, 8′-CH_3), 1.34 (s, 3H, 8′-CH_3), 1.38–1.59 (m, 1H, menthyl), 1.60–1.74 (m, 2H, menthyl), 1.76–1.96 (m, 2H, menthyl), 1.97–2.35 (m, 2H, menthyl), 4.90 (dt, 1H, J_t 10.7 Hz, J_d 4.3 Hz, H1′), 5.55–5.65 (m, 2H, H2+$H3_a$), 6.02–6.11 (dd, 1H, *J* 13.9, 5.0 Hz, $H3_b$), 7.10–7.14 (m, 1H, Ph), 7.23–7.30 (m, 4H, Ph). ^{13}C NMR ($CDCl_3$): δ=22.2 (5′-CH_3), 25.8 (8′-CH_3), 27.0 (C4′), 28.0 (8′-CH_3), 31.7 (C5′), 35.0 (C3′), 40.1 ($C8_q$′), 42.0 (C6′), 50.9 (C2′), 75.0 (C1′), 125.4 ($C4_{Ph}$), 126.4 ($C3_{Ph}$+$C5_{Ph}$), 128.4 ($C2_{Ph}$+$C6_{Ph}$), 129.3 (C2), 130.3 (C3), 152.0 ($C1_{Ph}$), 165.8 (C(O)O). IR (NaCl): ν=2954, 2924, 1740, 1719, 1634, 1457, 1405, 1371, 1270, 1181, 1131, 1048, 984, 809, 700 cm^{-1}. Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.67; H, 9.15; found: C, 79.53; H, 9.41.

*4.2.2. (+)-(1S,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl acrylate (**2b**)*. Yield: 95%. $[\alpha]_D^{25}$ +53.1 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.82 (d, 3H, *J* 6.6 Hz, 5′-CH_3), 0.85–1.10 (m, 2H, neomenthyl), 1.33 [s, 6H, 8′-$(CH_3)_2$], 1.46–1.67 (m, 4H, neomenthyl), 1.67–1.80 (m, 1H, neomenthyl), 1.86–1.99 (m, 1H, neomenthyl), 5.15 (br s, 1H, H1′), 5.80 (dd, 1H, J_{cis} 10.4 Hz, J_{gem} 1.6 Hz, $H3_E$), 6.07 (dd, 1H, J_{trans} 17.3 Hz, J_{cis} 10.4 Hz, H2), 6.34 (dd, 1H, J_{trans} 17.3 Hz, J_{gem} 1.6 Hz, $H3_Z$), 7.10–7.22 (m, 1H, Ph), 7.25–7.30 (m, 4H, Ph). ^{13}C NMR ($CDCl_3$): δ=22.4 (5′-CH_3), 22.8 (C4′), 26.5, 27.0 and 27.3 (8′-CH_3, C5′), 35.7 (C3′), 40.2 (C6′), 40.4 ($C8_q$′), 51.7 (C2′), 71.9 (C1′), 126.0 ($C4_{Ph}$), 126.4 ($C2_{Ph}$+$C6_{Ph}$), 128.4 ($C3_{Ph}$+$C5_{Ph}$), 129.8 (C2), 130.5 (C3), 149.9 ($C1_{Ph}$), 165.6 (C(O)O). IR (NaCl): ν=2948, 1718, 1636, 1496, 1456, 1404, 1369, 1270, 1197, 1147, 1047, 984, 810, 760, 700 cm^{-1}. Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.67; H, 9.15; found: C, 79.85; H, 9.23.

4.3. General procedure for the synthesis of glyoxylates (3a,b)[3c,15d,e]

Method A. A vigorously stirred solution of acrylate (**2a** or **2b**) (3.20 g, 11.1 mmol) in 140 mL of MeOH/DCM 4:1 at −78 °C was bubbled for 20 min with ozone at a rate of 6 g/h in a 60 L/h current of O_2 (as specified by manufactures of the Fischer Mod. 503 ozone apparatus). Me_2S (2 mL), was added and stirring was continued under argon for a further 12 h, time after which the solvent was evaporated and the residue extracted with DCM (3×100 mL). The pooled organic layers were washed with water (100 mL) and brine (100 mL) and dried over Na_2SO_4. Removal of the solvent in a rotary evaporator afforded a yellow oil, which was purified on a short column of silica gel using hexane/EtOAc 3:1 as eluent yielding the corresponding glyoxylate as a mixture of the glyoxylate and its hydrate, which was used without further purification.

Method B. A mixture of acrylate (**2a** or **2b**) (2.35 g, 8.205 mmol), OsO_4 (20.8 mg, 10 mequiv), water (9 mL), and dioxane (30 mL) was stirred at rt for 5 min, time during which 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 rt 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 corresponding glyoxylate as a mixture of the glyoxylate and its hydrate, which was used without further purification. After heating a small sample for 2 h at 50 °C under reduced pressure (10^{-3} mmHg), the ^{1}H and ^{13}C NMR spectra showed it to be essentially (>85%) the anhydrous form of the corresponding glyoxylate.

*4.3.1. (−)-(1R,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl glyoxylate (**3a**).* Yield: 97% (method A). Yield: 98% (method B).

An analytical sample of the mono-hydrate was obtained by recrystallization from hexane.

4.3.1.1. (−)-(1R,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl glyoxylate hydrate. Mp 146–148 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.85 (d, 3H, J 6.4 Hz, 5′-CH_3), 0.97–1.18 (m, 2H, phenylmenthyl), 1.30 (s, 3H, 8′-CH_3), 1.38 (s, 3H, 8′-CH_3), 1.40–1.70 (m, 5H, phenylmenthyl), 1.81–2.21 (m, 3H, phenylmenthyl+$C(OH)_2$), 4.87 (dt, 1H, J_t 10.7 Hz, J_d 4.4 Hz, H1′), 7.10–7.15 (m, 1H, Ph), 7.23–7.29 (m, 4H, Ph). ^{13}C NMR ($CDCl_3$): δ=22.1, 25.4, 28.1, 29.2, 31.7, 34.8, 40.6, 41.6 (C8′), 50.9 (C2′), 77.5 ($C1_{PM}$), 125.8 ($C4_{Ph}$), 126.1 ($C2_{Ph}$+$C6_{Ph}$), 128.4 ($C3_{Ph}$+$C5_{Ph}$), 150.6 ($C1_{Ph}$), 159.9 ($CH(OH)_2$), 162.9 [C(O)O]. IR (NaCl): ν=3464, 2955, 2924, 2870, 1732, 1497, 1389, 1370, 1289, 1227, 1094, 980, 766, 702 cm^{-1}. Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55; found: C, 70.79; H, 8.33.

*4.3.2. (+)-(1S,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl glyoxylate (**3b**) (mixture of glyoxylate/hydrate).* Yield: 96% (method A). Yield: 98% (method B). $[\alpha]_D^{25}$ +36 (c 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.82 (d, 3H, J 6.4 Hz, 5′-CH_3), 0.88–1.27 (m, 2H, phenylneomenthyl), 1.34 (s, 3H, 8′-CH_3), 1.35 (s, 3H, 8′-CH_3), 1.50–1.93 (m, 6H, phenylneomenthyl), 4.85–5.15 (m, 1H, H1′), 7.14–7.19 (m, 1H, Ph), 7.24–7.28 (m, 4H, Ph), 9.17 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$): δ=22.4 (5′-CH_3), 22.7 (C4′), 26.3 (C5′), 27.1 (8′-CH_3), 27.7 (8′-CH_3), 35.6 (C3′), 40.3 (C6′), 40.4 (C8′), 51.6 (C2′), 74.6 (C1′), 126.2($C4_{Ph}$), 126.37 ($C2_{Ph}$+$C6_{Ph}$), 128.61 ($C3_{Ph}$+$C5_{Ph}$), 148.78 ($C1_{Ph}$), 159.19 (C(O)O), 184.53 (HC=O). IR (NaCl): ν=3445, 2948, 1733, 1601, 1496, 1456, 1404, 1371, 1219, 1096, 918, 836, 760, 700 cm^{-1}. Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39; found: C, 75.15; H, 8.21.

Compound (**3a** or **3b**) was converted into the corresponding 2,4-dinitrophenylhydrazone derivative, by the usual procedure.[21]

A solution of 2,4-dinitrophenylhydrazine (82 mg, 0.42 mmol) and H_2SO_4 (0.2 mL) in absolute MeOH was added to a solution of the glyoxylate and its hydrate (100 mg, approx. 0.3467 mmol) in the minimum quantity of MeOH, at rt. The solid obtained was isolated by filtration and recrystallized from absolute MeOH, yielding a yellow solid (0.145 g), which was identified as the corresponding 2,4-dinitrophenylhydrazone.

*4.3.3. 2,4-Dinitrophenylhydrazone of (−)-8-phenylmenthyl glyoxylate (**3a**-2,4-DNP)[21].* Yield 89%. Mp 159–162 °C (MeOH). $[\alpha]_D^{25}$ −17.5 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.91 (d, 3H, J 6.5 Hz, 5′-CH_3), 0.95–1.17 (m, 2H, phenylmenthyl), 1.12 (s, 3H, 8′-CH_3), 1.32 (s, 3H, 8′-CH_3), 1.49–1.60 (m, 2H, phenylmenthyl), 1.70–1.78 (m, 1H, phenylmenthyl), 1.91–1.97 (m, 2H, phenylmenthyl), 2.18 (td, 1H, J_t 11.4 Hz, J_d 3.4 Hz, phenylmenthyl), 5.03 (td, 1H, J_t 10.7 Hz, J_d 4.4 Hz, H1′), 6.07 (s, 1H, CH=N), 7.06–7.11 (m, 1H, Ph), 7.19–7.29 (m, 4H, Ph), 8.04 (d, 1H, J 9.5 Hz, $H6_{DNP}$), 8.38 (dd, 1H, J 9.5, 2.6 Hz, $H5_{DNP}$), 9.15 (d, 1H, J 2.6 Hz, $H3_{DNP}$), 14.08 (s, 1H, NH). IR (KBr): ν=3272, 2965, 1687, 1618, 1596, 1570, 1423, 1336, 1310, 1215, 1139, 1085, 1052, 920, 871, 834, 763, 742, 700 cm^{-1}. Anal. Calcd for $C_{24}H_{28}N_4O_6$: C, 61.53; H, 6.02; N, 11.96; found: C, 61.46; H, 6.18; N, 12.02.

*4.3.4. 2,4-Dinitrophenylhydrazone of (+)-8-phenylneomenthyl glyoxylate (**3b**-2,4-DNP)[3c].* Yield 90%. Mp 105–108 °C (MeOH). $[\alpha]_D^{25}$ +35 (c 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.84 (d, 3H, J 6.5 Hz, 5-CH_3), 0.90–1.28 (m, 2H, phenylneomenthyl), 1.39 (s, 6H, 8′-$(CH_3)_2$), 1.55–1.85 (m, 5H, phenylneomenthyl), 1.90–2.05 (m, 1H, phenylneomenthyl), 5.10 (br s, 1H, H1′), 6.87 (s, 1H, CH=N), 7.10–7.23 (m, 1H, Ph), 7.26–7.30 (m, 4H, Ph), 8.12 (d, 1H, J 9.5 Hz, $H6_{DNP}$), 8.44 (dd, 1H, J 9.5, 2.6 Hz, $H5_{DNP}$), 9.15 (d, 1H, J 2.6 Hz, $H3_{DNP}$), 14.40 (s, 1H, NH). ^{13}C NMR (300 MHz, $CDCl_3$): δ=22.3 (5′-CH_3), 22.7 (C4′), 26.5 (C5′), 27.3 (8′-CH_3), 27.7 (8′-CH_3), 35.6 (C3′), 40.0 (C6′), 40.4 (C8′), 51.6 (C2′), 74.0 (C1′), 118.1 ($C6_{DNP}$), 123.4 ($C3_{DNP}$), 126.0 ($C4_{Ph}$), 126.3 ($C2_{Ph}$+$C6_{Ph}$), 126.4 ($C5_{DNP}$), 128.5 ($C3_{Ph}$+$C5_{Ph}$), 131.6 ($C2_{DNP}$), 137.3 ($C4_{DNP}$), 140.6 ($C1_{DNP}$), 144.4 (CH=N), 149.3 ($C1_{Ph}$), 161.8 (C(O)O). IR (KBr): ν=3292, 3106, 2949, 1718, 1654, 1619, 1583, 1506, 1424, 1324, 1269, 1212, 1138, 1097, 918, 834, 758, 742, 701 cm^{-1}. Anal. Calcd for $C_{24}H_{28}N_4O_6$: C, 61.53; H, 6.02; N, 11.96; found: C, 61.37; H, 6.18; N, 12.17.

4.4. General procedure for aza-Diels–Alder reaction

*4.4.1. (−)-(1R,2S,5R)-8-Phenylmenthyl (1S,3S,4R)-2-[(1R)-1-phenylethyl]-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (**5a1**)[6].* A solution of (R)-1-phenylethylamine (1.86 mL, 1.70 g, 14.0 mmol) in dry DCM (10 mL) was added dropwise under argon to a stirred suspension of (−)-8-phenylmenthyl glyoxylate (**3a**) (4.04 g, ca. 14.0 mmol) and 3 Å molecular sieves (10 g) in dry DCM (50 mL) at 0 °C. The reaction mixture was stirred for 1 h and then cooled to −78 °C and treated successively with TFA (1.08 mL, 1.60 g, 14.0 mmol), $BF_3 \cdot OEt_2$ (1.77 mL, 1.99 g, 14.0 mmol), and freshly distilled cyclopentadiene (2.3 mL, ca. 28 mmol). After 5 h a mixture of saturated aqueous $NaHCO_3$ solution (28 mL) and then solid $NaHCO_3$ (3.3 g) were added. The reaction mixture was allowed to reach rt and filtered through a pad of Celite. The two layers were separated and the aqueous layer was extracted with DCM

(3×100 mL). The aqueous layer was extracted with DCM (3×100 mL). The pooled organic layers were washed with saturated $NaHCO_3$ solution (3×100 mL) and brine (100 mL) and dried (Na_2SO_4). Removal of the solvent on a rotavap yielded an orange oil, which was purified by column chromatography (silica gel) using hexane/AcOEt 3:1 as eluent. Fractions 7–10 (R_f 0.6.) afforded a colorless oil (5.09 g) identified as the pure single adduct (1*R*,3*exo*) (**5a1**). Yield 79%. $[\alpha]_D^{25}$ −66.5 (*c* 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=0.67 (s, 3H, 8′-CH_3), 0.65–0.90 (m, 3H, H3$_a$′+H6$_a$′+H4$_a$′), 0.81 (d, 3H, *J* 6.3 Hz, 5′-CH_3), 0.89 (s, 3H, 8′-CH_3), 1.11–1.27 (m, 1H, H3$_b$′), 1.37 (d, 3H, *J* 6.5 Hz, CHC*H*$_3$Ph), 1.28–1.37 (m, 2H, H7$_{anti}$+H5′), 1.38–1.51 (m, 1H, H4′$_b$), 1.70–1.79 (m, 1H, H2′), 1.80–1.93 (m, 2H, H7$_{syn}$+H6$_b$′), 1.99 (s, 1H, H3$_{endo}$), 2.80 (br s, 1H, H4), 3.03 (q, 1H, *J* 6.5 Hz, C*H*CH$_3$Ph), 4.29 (br s, 1H, H1), 4.50 (dt, 1H, *J* 10.6, 4.2 Hz, H1′), 6.28 (dd, 1H, *J* 5.6, 1.4 Hz, H6), 6.35 (dd, 1H, *J* 5.6, 2.9 Hz, H5), 7.00 (d, 2H, *J* 7.4 Hz, H2$_{Ph}$+H6$_{Ph}$), 7.01–7.38 (m, 6H, Ph), 7.37 (d, 2H, *J* 7.2 Hz, H2$_{PhCH}$+H6$_{PhCH}$). ^{13}C NMR ($CDCl_3$): δ=22.2 (5′-*C*H$_3$), 23.8 (*C*H$_3$CHPh), 24.8 (8′-*C*H$_3$), 27.3 (C3′), 28.4 (8′-*C*H$_3$), 31.5 (C5′), 35.0 (C4′), 40.1 (C8′), 41.6 (C6′), 45.7 (C7), 49.9 (C4), 50.9 (C2′), 63.6 (*C*HPh), 64.4 (C1), 65.6 (C3), 75.1 (C1′), 125.2, 125.8, 127.5, 128.1, 128.3 and 128.7 (*C*H$_{Ph}$), 133.9 (C6), 136.4 (C5), 145.4 (C1$_{Ph-C8'}$), 151.9 (C1$_{Ph-CH}$), 172.9 [C(O)O]. IR (NaCl): 3086, 3059, 2954, 2870, 1741 (CO), 1600, 1564, 1494, 1454, 1371, 1347, 1325, 1289, 1244, 1219, 1191, 1169, 1108, 1078, 1059, 1032, 1009, 982 cm^{-1}. Anal. Calcd for $C_{31}H_{39}NO_2$: C, 81.36; H, 8.59; N, 3.06; found: C, 81.15; H, 8.62; N, 2.99.

*4.4.2. (+)-(1S,2S,5R)-8-Phenylmenthyl (1R,3R,4S)-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (**5b1**).* Following the same procedure as above, using (*S*)-1-phenylethylamine (1.88 g, 15.5 mmol) and (+)-8-phenylneomenthyl glyoxylate (**3b**) (4.47 g, ca. 15.5 mmol). Flash chromatography of the crude product (hexane/EtOAc 1:1) afforded a colorless oil (5.39 g) identified as pure single adduct (1*S*,3*exo*) (**5b1**). Yield 76%; R_f 0.7. $[\alpha]_D^{23}$ +53.2 (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ=0.77 (s, 3H, 8′-CH_3), 0.80 (d, 3H, *J* 6.5 Hz, 5′-CH_3), 0.90 (s, 3H, 8′-CH_3), 0.70–0.98 (m, 2H, H4$_a$′+H6$_a$′), 1.13–1.19 (m, 1H, H5′), 1.42 (d, 3H, *J* 6.5 Hz, CHC*H*$_3$Ph), 1.25–1.49 (m, 3H, H7$_{anti}$+H2′+H4$_b$′), 1.50–1.71 (m, 2H, H3′), 1.75–1.86 (m, 1H, H6$_b$′), 2.0 (d, 1H, *J* 8.4 Hz, H7$_{syn}$), 2.34 (br s, 1H, H3$_{endo}$), 2.93 (br s, 1H, H4), 3.10 (q, *J* 6.5 Hz, 1H, C*H*CH$_3$Ph), 4.36 (br s, 1H, H1), 4.98 (br s, 1H, H1′), 6.35 (dd, 1H, *J* 5.6, 1.7 Hz, H5), 6.47–6.51 (m, 1H, H6), 7.12–7.41 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$): δ=22.0 (C4′), 22.1 (5′-*C*H$_3$), 23.2 (C5′), 23.9 (*C*H$_3$CHPh), 27.0 (8′-*C*H$_3$), 27.1 (8′-*C*H$_3$), 35.3 (C3′), 39.6 (two, C8′+C6′), 45.4 (C7), 49.6 (C4), 50.9 (C2′), 63.1 (C1), 64.1 (*C*HPh), 65.5 (C3), 70.7 (C1′), 125.3, 126.0, 127.2, 127.8 (double) and 128.4 (*C*H$_{Ph}$), 133.6 (C6), 135.9 (C5), 145.0 (C1$_{Ph-C8'}$), 150.5 (C1$_{Ph-CH}$), 172.5 [C(O)O]. IR (NaCl): 2949, 1737 (CO), 1493, 1450, 1379, 1323, 1245, 1219, 1191, 1168, 1148, 1109, 1079, 1061, 1033, 1009, 918, 833 cm^{-1}. Anal. Calcd for $C_{31}H_{39}NO_2$: C, 81.36; H, 8.59; N, 3.06; found: C, 81.18; H, 8.61; N, 3.04.

*4.4.3. (−)-(1R,2S,5R)-8-Phenylmenthyl (1S,3S,4R)-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (**5a2**), (+)-(1R,2S,5R)-8-phenylmenthyl (1R,3R,4S)-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (**5a3**), and (−)-(1R,2S,-5R)-8-phenylmenthyl (1R,3S,4S)-2-[(1S)-1-phenylethyl]-2-azabicyclo [2.2.1]hept-5-ene-3-carboxylate (**6a**).* Following the same procedure as above, using (*S*)-1-phenylethylamine (3.65 g, 30.1 mmol) and (−)-8-phenylmenthyl glyoxylate (**3a**) (8.69 g, ca. 30.1 mmol). Flash chromatography of the crude product (hexane/EtOAc 10:1) afforded three pure compounds (75% global).

(1*S*,3*exo*) (**5a2**): R_f 0.6; 3.44 g (25%). $[\alpha]_D^{25}$ −100.7 (*c* 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=0.88 (d, 3H, *J* 6.4 Hz, 5′-CH_3), 0.83–0.93 (m, 1H, H3$_a$′), 0.94–1.12 (m, 2H, H6$_a$′+H4$_a$′), 1.13 (d, 1H, *J* 8.4 Hz, H7$_{anti}$), 1.23 (d, 3H, *J* 6.5 Hz, CHC*H*$_3$Ph), 1.26 (s, 3H, 8′-CH_3), 1.38 (s, 3H, 8′-CH_3), 1.45–1.70 (m, 3H, H3$_b$′+H4$_b$′+H5′), 1.61 (d, 1H, *J* 8.4 Hz, H7$_{syn}$), 2.01 (s, 1H, H3$_{endo}$), 1.90–2.15 (m, 2H, H2′+H6$_b$′), 2.86 (s, 1H, H4), 2.95 (q, 1H, *J* 6.5 Hz, C*H*CH$_3$Ph), 3.48 (d, 1H, *J* 1.3 Hz, H1), 4.85 (dt, 1H, *J* 10.6, 4.3 Hz, H1′), 5.98 (dd, 1H, *J* 5.54, 1.82 Hz, H6), 6.28 (dd, 1H, *J* 5.54, 2.31 Hz, H5), 7.17–7.41 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$): δ=22.3 (5′-CH_3), 24.6 (*C*H$_3$CHPh), 26.9 (8′-CH_3), 27.29 (C4′), 27.31 (8′-*C*H$_3$), 31.7 (C5′), 35.1 (C3′), 40.4 (C8′), 41.95 (C6′), 46.2 (C7), 49.7 (C4), 50.7 (C2′), 63.7 (*C*HPh), 64.0 (C1), 64.9 (C3), 75.4 (C1′), 125.6, 125.9, 127.4, 128.1, 128.4 and 128.7 (*C*H$_{Ph}$), 134.1 (C6), 136.2 (C5), 145.6 (C1$_{Ph-C8'}$), 152.0 (C1$_{Ph-CH}$), 173.7 [C(O)O]. IR (NaCl): ν=3059, 2954, 1742, 1600, 1495, 1454, 1371, 1323, 1285, 1243, 1171, 1109, 1094, 1052, 1007, 918, 839, 765, 730, 700 cm^{-1}. Anal. Calcd for $C_{31}H_{39}NO_2$: C, 81.36; H, 8.59; N, 3.06; found: C, 81.27; H, 8.65; N, 3.09.

(1*R*,3*exo*) (**5a3**): R_f 0.25; 4.82 g (35%). $[\alpha]_D^{25}$+85.3 (*c* 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=0.55–0.75 (m, 1H, H3$_a$′), 0.78 (d, 3H, *J* 6.2 Hz, 5′-CH_3), 0.81–0.99 (m, 2H, H4$_a$′+H6$_a$′), 1.14 (s, 3H, 8′-CH_3), 1.25 (s, 3H, 8′-CH_3), 1.35 (d, 3H, *J* 6.5 Hz, CHC*H*$_3$Ph), 1.20–1.44 (m, 4H, H4$_b$′+H7$_{syn}$+H5′+H3$_b$′), 1.45–1.55 (m, 1H, H2′), 1.65–1.80 (m, 1H, H6$_b$′), 1.82 (s, 1H, H3$_{endo}$), 2.12 (d, 1H, *J* 8.3 Hz, H7$_{syn}$), 2.69 (s, 1H, H4), 2.91 (q, 1H, *J* 6.5 Hz, C*H*(CH_3)Ph), 4.25 (br s, 1H, H1), 4.47 (dt, 1H, *J* 10.6, 4.1 Hz, H1′), 6.23 (dd, 1H, *J* 5.5, 1.5 Hz, H6), 6.32 (dd, 1H, *J* 5.6, 2.9 Hz, H5), 7.12–7.29 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$): δ=22.1 (5′-*C*H$_3$), 23.0 (*C*H$_3$CHPh), 26.6 (8′-*C*H$_3$), 27.2 (C4′), 27.9 (8′-*C*H$_3$), 31.4 (C3′), 34.9 (C5′), 40.3 (C8′), 41.40 (C6′), 45.53 (C7), 48.7 (C4), 50.0 (C2′), 63.0 (CH_3*C*HPh), 64.3 (C1), 65.2 (C3), 75.3 (C1′), 125.4, 125.9, 127.5, 128.3, 128.4 and 128.7 (*C*H$_{Ph}$), 133.6 (C6), 136.6 (C5), 145.6 (C1$_{Ph-C8'}$), 151.8 (C1$_{Ph-CH}$), 173.8 [C(O)O]. IR (NaCl): ν=3058, 2955, 1739, 1600, 1493, 1453, 1371, 1323, 1290, 1247, 1167, 1107, 1055, 1031, 1009, 917, 838, 763, 699 cm^{-1}. Anal. Calcd for $C_{31}H_{39}NO_2$: C, 81.36; H, 8.59; N, 3.06; found: C, 81.29; H, 8.64; N, 3.10.

(1*R*,3*endo*) (**6a**): R_f 0.4; 2.07 g (15%). $[\alpha]_D^{25}$ −50.5 (*c* 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=0.87 (d, 3H, *J* 6.5 Hz, 5′-CH_3), 0.75–0.99 (m, 3H, H3$_a$′+H3$_a$′+H4$_a$′), 1.00–1.26 (m, 1H, H6$_a$′), 1.23 (s, 3H, 8′-CH_3), 1,28 (d, 1H, *J* 8.3 Hz, H7$_{anti}$), 1.34 (d, 3H, *J* 6.5 Hz, CHC*H*$_3$Ph), 1.35 (s, 3H, 8′-CH_3), 1.54 (d, 1H, *J* 8.3 Hz, H7$_{syn}$), 1.51–1.52 (m, 2H, H4$_b$′+H5′), 1.88–1.99 (m, 1H, H2′), 2.05–2.13 (m, 1H, H6$_b$′), 2.90 (br s, 1H, H4), 3.36–3.52 (m, 3H, H3$_{exo}$+H1+C*H*CH$_3$Ph), 4.70 (dt, 1H, J_t 10.54 Hz, J_d 4.2 Hz, H1′), 5.96 (dd, 1H, *J* 5.52, 2.58 Hz, H5), 6.28 (dd, 1H, *J* 5.52, 2.91 Hz, H6), 7.17–7.42 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$): δ=22.3 (5′-*C*H$_3$), 24.9 (CH*C*H$_3$Ph), 25.7 (8′-*C*H$_3$), 27.0 (C4′), 28.3 (8′-*C*H$_3$), 31.6 (C5′), 35.1 (C3′), 40.1 (C8′), 41.9 (C6′), 44.70 (C7), 48.4 (C4), 50.8 (C2′), 64.1 (*C*HPh), 64.8 (C1), 65.2 (C3), 75.0 (C1′), 125.3, 125.8, 127.3, 127.9, 128.4 and 128.8 (*C*H$_{Ph}$), 134.9 (C5), 139.2 (C6), 146.7 (C1$_{Ph-C8'}$), 152.60 (C1$_{Ph-CH}$), 172.78 [C(O)O]. IR (NaCl): ν=3059, 2953, 1734, 1600, 1495, 1455, 1370, 1323, 1244, 1172, 1094, 1052, 1007, 910, 839, 765, 730, 700 cm^{-1}. Anal. Calcd for $C_{31}H_{39}NO_2$: C, 81.36; H, 8.59; N, 3.06; found: C, 81.40; H, 8.63; N, 3.11.

*4.4.4. (+)-(1S,2S,5R)-8-Phenylneomenthyl (1R,3R,4S)-2-[(1R)-1-phenylethyl]-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (**5b2**), (−)-(1S,2S,5R)-8-phenylneomenthyl (1S,3S,4R)-2-[(1R)-1-phenylethyl]-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (**5b3**), and (+)-(1S,2S,5R)-8-phenylneomenthyl (1S,3R,4R)-2-[(1R)-1-phenylethyl]-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (**6b**).* Following the same procedure as above, using (*R*)-1-phenylethylamine (3.67 g, 30.3 mmol) and (−)-8-phenylneomenthyl glyoxylate (**3b**) (8.74 g, ca. 30.3 mmol). Flash chromatography of the crude product (hexane/EtOAc 8:1) afforded three pure compounds (73% global).

(1*R*,3*exo*) (**5b2**): R_f 0.5; 3.60 g (26%). $[\alpha]_D^{23}$ +35.2 (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ=0.89 (d, 3H, *J* 6.4 Hz, 5′-CH_3), 0.85–0.99 (m, 1H, H3$_a$′), 1.00–1.15 (m, 1H, H6$_a$′), 1.25 (d, 1H, *J* 8.0 Hz, H7$_{anti}$), 1.29 (d, 3H, 6.4 Hz, CHC*H*$_3$Ph), 1.38 (s, 3H, 8′-CH_3), 1.39 (s, 3H, 8′-CH_3), 1.27–1.43 (m, 1H, H5′), 1.48–1.58 (m, 1H, H4$_a$′), 1.59–1.87 (m, 3H, H2′+H4$_b$′+H3$_b$′), 1.90 (d, 1H, *J* 8.0 Hz, H7$_{syn}$), 1.92–2.05 (m, 1H, H6$_b$′), 2.48 (br s, 1H, H3$_{endo}$), 3.10 (q, 1H, *J* 6.4 Hz, C*H*(CH$_3$)Ph), 3.13 (br s, 1H, H4), 3.57 (br s, 1H, H1), 5.13 (br s, 1H, H1′), 6.07 (dd, 1H, *J* 5.6, 2.0 Hz, H5), 6.46 (dd, 1H, *J* 4.4, 3.2 Hz, H6), 7.18–7.40 (m, 10H, Ph). ^{13}C NMR (CDCl$_3$): δ=22.1 (5′-*C*H$_3$), 22.5 (C4′), 24.3 (*C*H$_3$CHPh), 26.2 (8′-*C*H$_3$), 26.3 (8′-*C*H$_3$), 27.0 (C5′), 35.4 (C3′), 39.9 (C6′), 40.0 (C8′), 45.9 (C7), 49.3 (C4), 51.2 (C2′), 63.4 (C1), 63.5 (*C*HPh), 65.0 (C3), 71.7 (C1′), 125.6, 125.9, 127.0, 127.5, 128.0 and 128.3 (*C*H$_{Ph}$), 133.8 (C6), 135.9 (C5), 145.3 (C1$_{Ph-C8'}$), 149.8 (C1$_{Ph-CH}$), 173.6 [C(O)O]. IR (NaCl): 2924, 2869, 1738, 1716, 1662, 1600, 1449, 1370, 1276, 1245, 1218, 1169, 1147, 1109, 1080, 1032, 1005, 973, 919, 809 cm^{-1}. Anal. Calcd for $C_{31}H_{39}NO_2$: C, 81.36; H, 8.59; N, 3.06; found: C, 81.42; H, 8.66; N, 3.10.

(1*S*,3*exo*) (**5b3**): R_f 0.3; 5.13 g (37%). $[\alpha]_D^{23}$ −15.6 (*c* 1, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ=0.66 (d, 3H, *J* 5.6 Hz, 5′-CH$_3$), 0.67–0.71 (m, 1H, H3$_a$′), 0.71–0.77 (m, 1H, H6$_a$′), 1.27 (s, 6H, 8′-CH$_3$), 1.29 (s, 6H, 8′-CH$_3$), 1.22–1.35 (m, 3H, H4$_a$′+H5′+H6$_b$′), 1.41 (d, 3H, *J* 6.4 Hz, CHC*H*$_3$Ph), 1.36–1.48 (m, 3H, H7$_{anti}$+H2′+H4$_b$′), 1.49–1.57 (m, 1H, H3$_b$′), 2.12 (d, 1H, *J* 8.4 Hz, H7$_{syn}$), 2.28 (br s, 1H, H3$_{endo}$), 3.06 (q, 1H, *J* 6.4 Hz, C*H*CH$_3$Ph), 3.09 (br s, 1H, H4), 4.35 (br s, 1H, H1), 4.86 (br s, 1H, H1′), 6.35 (dd, 1H, *J* 5.6, 1.6 Hz, H6), 6.45–6.51 (m, 1H, H5), 7.14–7.35 (m, 10H, Ph). ^{13}C NMR (CDCl$_3$): δ=22.0 (C4′), 22.3 (5′-*C*H$_3$), 22.9 (*C*H$_3$CHPh), 25.7 (8′-*C*H$_3$), 26.0 (C5′), 26.5 (8′-*C*H$_3$), 35.2 (C3′), 39.4 (C6′), 39.9 (C8′), 45.0 (C7), 48.6 (C4), 51.0 (C2′), 62.7 (C1), 64.0 (*C*HPh), 65.0 (C3), 71.3 (C1′), 125.5, 125.8, 127.1, 127.8, 127.93 and 127.94 (*C*H$_{Ph}$), 133.6 (C6), 135.8 (C5), 144.9 (C1$_{Ph-C8'}$), 149.9 (C1$_{Ph-CH}$), 172.9 [C(O)O]. IR (NaCl): 2948, 1737, 1601, 1494, 1453, 1368, 1324, 1246, 1222, 1190, 1166, 1146, 1108, 1078, 1057, 1032, 1006, 964, 922, 853, 830, 810, 757cm^{-1}. Anal. Calcd for $C_{31}H_{39}NO_2$: C, 81.36; H, 8.59; N, 3.06; found: C, 81.32; H, 8.51; N, 3.12.

(1*S*,3*endo*) (**6b**): R_f 0.4; 1.39 g (10%). $[\alpha]_D^{23}$ +45.1 (*c* 1, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ=0.85 (d, 3H, *J* 6.6 Hz, 5′-CH$_3$), 0.88–0.94 (m, 1H, H3$_a$′), 0.95–1.05 (m, 1H, H6$_a$′), 1.39 (s, 3H, 8′-CH$_3$), 1.40 (s, 3H, 8′-CH$_3$), 1.42 (d, 3H, *J* 6.7 Hz, CHC*H*$_3$Ph), 1.43–1.47 (m, 1H, H7$_{anti}$), 1.53–1.65 (m, 3H, H4$_a$′+H2′+H5′), 1.67–1.77 (m, 1H, H4$_b$′), 1.73–1.81 (m, 2H, H3$_b$′+H7$_{syn}$), 1.92–2.01 (m, 1H, H6$_b$′), 3.46 (br s, 2H, H4+H3$_{exo}$), 3.56 (br s, 1H, H1), 3.60 (q, 1H, *J* 6.7 Hz, C*H*CH$_3$Ph), 4.93 (br s, 1H, H1′), 6.08 (d, 1H, *J* 5.3 Hz, H5), 6.42 (dd, 1H, *J* 5.6, 3.0 Hz, H6), 7.17–7.45 (m, 10H, Ph). ^{13}C NMR (CDCl$_3$): δ=22.1 (5′-*C*H$_3$), 22.6 (C4′), 24.7 (*C*H$_3$CHPh), 26.2 (8′-*C*H$_3$), 26.6 (8′-*C*H$_3$), 27.1 (C5′), 35.3 (C3′), 39.6 (C6′), 40.0 (C8′), 44.6 (C7), 48.4 (C4), 51.1 (C2′), 64.2 (C3), 64.5 (C1), 64.8 (*C*HPh), 71.7 (C1′), 125.5, 125.6, 126.0, 126.2, 126.9, 127.4, 127.9, 128.0, 128.2 and 128.4 (*C*H$_{Ph}$), 134.5 (C5), 139.2 (C6), 146.2 (C1$_{Ph-C8'}$), 149.7 (C1$_{Ph-CH}$), 172.4 [C(O)O]. IR (NaCl): 2926, 1738, 1658, 1599, 1578, 1494, 1447, 1370, 1317, 1276, 1175, 1148, 1115, 1073, 1029, 1000, 941, 919, 810, 762 cm^{-1}. Anal. Calcd for $C_{31}H_{39}NO_2$: C, 81.36; H, 8.59; N, 3.06; found: C, 81.42; H, 8.64; N, 3.13.

*4.4.5. (+)-(1S,3R,4R)-2-[(1R)-1-Phenylethyl]-3-[(1S,2S,5R)-8-phenylneomenthyl-oxycarbonyl]-2-azabicyclo[2.2.1]hept-5-ene-2-ammonium trifluoroacetate (**10**).* Compound **6b** was converted into the corresponding ammonium trifluoroacetate derivative (**10**), by the usual procedure: A 1 M solution of TFA in dry Et$_2$O (200 μL, 0.20 mmol) was added to a solution of amine **6b** (100 mg, 0.19 mmol) in dry Et$_2$O (10 mL), at ambient temperature. Upon slow evaporation of the solvent a white crystalline solid precipitated. The solid was isolated by filtration (931 mg, 85%) and identified as the corresponding *ammonium trifluoroacetate* (**10**). Suitable crystals of (+)-**10** were obtained and the structure was confirmed by X-ray crystallographic analysis.[20] Mp 91–93 °C. $[\alpha]_D^{23}$ +10.2 (*c* 1, DMSO). ^{1}H NMR (400 MHz, DMSO-d_6): δ=0.84 (d, 3H, *J* 6.5 Hz, 5′-CH$_3$), 0.83–0.89 (m, 1H, H4$_a$′), 0.90–1.01 (m, 1H, H3$_a$′), 1.02–1.10 (m, 1H, H6$_a$′), 1.28 (s, 3H, 8′-CH$_3$), 1.30 (s, 3H, 8′-CH$_3$), 1.50–1.70 (m, 6H, H4$_b$′+H6$_b$′+H5′+C*H*$_3$CHPh), 1.71–1.83 (m, 3H, H7$_{anti}$+H3$_b$′+H2′), 2.29 (br s, 1H, H7$_{syn}$), 3.75 (br s, 1H, H4), 4.09 (br s, 1H, H1), 4.61 (br s, 1H, H1′), 4.75 (br s, 1H, CH$_3$C*H*Ph), 5.08 (br s, 1H, H3$_{exo}$), 6.40 (br s, 1H, H5), 6.43 (br s, 1H, H6), 7.15–7.70 (m, 10H, Ph), 9.36 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ=18.3 (*C*H$_3$CHPh), 21.7 (C4′), 21.8 (5′-*C*H$_3$), 24.7 (8′-CH$_3$), 26.7 (C5′), 27.8 (8′-*C*H$_3$), 34.4 (C3′), 38.7 (C6′), 38.79–40.15 (DMSO, C8′), 45.0 (C7), 47.2 (C4), 49.4 (C2′), 65.7 (*C*HPh), 66.2 (C3), 69.9 (C1), 74.5 (C1′), 125.4 (*C*F$_3$COO), 125.66, 125.73, 125.80, 126.54, 126.68, 128.06, 128.42, 128.46, 128.74 and 129.07 (*C*H$_{Ph}$), 135.5 (C1$_{Ph-C8'}$), 136.2 (C6), 139.7 (C5), 136.2 (C6), 149.6 (C1$_{Ph-CH}$), 169.6 [C(O)O], 184.4 [CF$_3$*C*(O)O].

4.5. General procedure for reduction of cycloadducts

*4.5.1. (−)-(1S,3S,4R)-2-[(1R)-1-Phenylethyl]-2-azabicyclo[2.2.1]hept-5-en-3-yl]methanol [(−)-**7A**] from **5a1**[6].* A solution of **5a1** (1.70 g; 3.71 mmol) in dry Et$_2$O (10 mL) was added dropwise under argon to a suspension of LiAlH$_4$ (ca. 6 equiv; 0.85 g; 22.3 mmol) in dry Et$_2$O (10 mL) at 0 °C. The reaction mixture was stirred for 12 h at rt, and then MeOH (20 mL) and H$_2$O (100 mL) were added dropwise at 0 °C. The resulting mixture was extracted with AcOEt (4×100 mL) and the pooled organic layers were washed with brine (100 mL) and dried with Na$_2$SO$_4$. Removal of the solvent in a rotary evaporator left a yellow oil that when chromatographed on silica gel with hexane/EtOAc 3:1 as eluent afforded the chiral auxiliary, (−)-8-phenylmenthol (R_f 0.4; 0.84 g; 97%),[16] in the early fractions and compound **7A** (R_f 0.1; 0.82 g; 96%), as white solid, in the latter ones. Mp 110–113 °C (hexane/Et$_2$O). $[\alpha]_D^{25}$ −41.81 (*c* 1, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$): 1.35 (d, 1H, *J* 8.5 Hz, H7$_{anti}$), 1.39 (d, 3H, *J* 6.5 Hz, C*H*$_3$CH), 1.80 (d, 1H, *J* 8.5 Hz, H7$_{syn}$), 1.74–1.82 (br s, 1H, H3$_{endo}$), 2.70–2.77 (m, 2H, C*H*HOH+H4), 3.05 (q, 1H, *J* 6.5 Hz, C*H*Me), 2.99–3.08 (m, 1H, CH*H*OH), 4.15 (d, 1H, *J* 1.4 Hz, H1), 4.73 (br s, 1H, D$_2$O exch, OH), 6.20 (dd, *J* 5.6, 1.7 Hz, 1H, H6), 6.46 (m, 1H, H5), 7.19–7.31 (m, 5H, Ph). ^{13}C NMR (CDCl$_3$): 22.5 (CH*Me*), 45.3 (C7), 47.5 (C4), 63.3 (C1), 63.9 (*C*HMe), 64.3 (C3), 65.3 (*C*H$_2$OH), 127.8, 128.2 and 128.8 (*C*H$_{Ph}$), 132.1 (C6), 138.1 (C5), 146.2 (C1$_{Ph-CH}$). IR (KBr): 3272, 3214 (OH), 2988, 2863, 1454, 1375, 1323, 1181, 1034, 1011, 806 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11; found: C, 78.49; H, 8.41; N, 6.02.

*4.5.2. (+)-(1R,3R,4S)-2-[(1S)-1-Phenylethyl]-2-azabicyclo[2.2.1]hept-5-en-3-yl]methanol [(+)-**7A**] from **5a3**.* Following the same procedure as above, using adduct **5a3** (2.05 g, 4.48 mmol). Flash chromatography of the crude product (hexane/EtOAc 3:1) afforded the auxiliary, (−)-8-phenylmenthol (R_f 0.4; 1.02 g; 98%),[16] in the early fractions and compound (+)-**7A** (R_f 0.1; 0.98 g; 95%), as white solid, in the latter ones. Mp 110–113 °C (hexane/Et$_2$O). $[\alpha]_D^{25}$ +41.80 (*c* 1, CHCl$_3$). The NMR (^{1}H, ^{13}C) spectra are identical to those of compound (−)-**7A**. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11; found: C, 78.51; H, 8.39; N, 6.05. Suitable crystals of (+)-(1*R*,3*exo*)-**7A** were obtained from hexane/Et$_2$O and the structure was confirmed by the X-ray crystallographic analysis.[6b,17]

*4.5.3. (+)-(1R,3R,4S)-2-[(1S)-1-Phenylethyl]-2-azabicyclo[2.2.1]hept-5-en-3-yl]methanol [(+)-**7A**] from **5b1**.* Following the same procedure as above, using adduct **5b1** (2.00 g, 4.37 mmol). Flash chromatography of the crude product (hexane/EtOAc 3:1) afforded the auxiliary, (+)-8-phenylneomenthol (R_f 0.6; 0.99 g; 98%),[16] in the early fractions and compound (+)-**7A** (R_f 0.1; 0.96 g; 96%), as white solid, in the latter ones. Mp 110–113 °C (hexane/Et$_2$O). $[\alpha]_D^{25}$ +41.82 (*c* 1, CHCl$_3$). The NMR (^{1}H, ^{13}C) spectra are identical to those of compound (−)-**7A**. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11; found: C, 78.50; H, 8.38; N, 6.07.

*4.5.4. (−)-(1S,3S,4R)-2-[(1R)-1-Phenylethyl]-2-azabicyclo[2.2.1]hept-5-en-3-yl]methanol [(−)-**7A**] from **5b3**.* Following the same procedure as above, using adduct **5b3** (1.02 g, 2.23 mmol). Flash chromatography of the crude product (hexane/EtOAc 3:1) afforded the auxiliary, (+)-8-phenylneomenthol (R_f 0.6; 0.49 g; 95%),[16] in the early fractions and compound (−)-**7A** (R_f 0.1; 0.49 g; 96%), as white solid, in the later fractions. Mp 110–113 °C (hexane/Et_2O). $[\alpha]_D^{25}$ −41.81 (*c* 1, $CHCl_3$). The NMR (^1H, ^{13}C) spectra are identical to those of compound (−)-**7A**. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11; found: C, 78.52; H, 8.37; N, 6.09.

*4.5.5. (−)-(1S,3S,4R)-2-[(1S)-1-Phenylethyl]-2-azabicyclo[2.2.1]hept-5-en-3-yl]methanol [(−)-**7B**] from **5a2**.* Following the same procedure as above, using adduct **5a2** (2.40 g, 5.24 mmol). Flash chromatography of the crude product (hexane/EtOAc 3:1) afforded the auxiliary, (−)-8-phenylmenthol (R_f 0.4; 1.16 g; 95%),[16] in the early fractions and compound (−)-**7B** (R_f 0.1; 1.13 g; 94%), as yellow oil, in the latter ones. $[\alpha]_D^{25}$ −97.50 (*c* 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=1.22 (d, 1H, *J* 8.5 Hz, $H7_{anti}$), 1.28 (d, 3H, *J* 6.5 Hz, CH_3), 1.76 (d, 1H, *J* 8.5 Hz, $H7_{syn}$), 2.04–2.07 (m, 1H, $H3_{endo}$), 2.88 (br s, 1H, H4), 2.80–2.90 (br s, 1H, D_2O exch, OH), 3.14 (q, 1H, *J* 6.5 Hz, C*H*CH_3), 3.44 (d, 1H, *J* 1.2 Hz, H1), 3.69 (dd, 1H, *J* 10.6, 7.2 Hz, C*H*HOH), 3.78 (dd, 1H, *J* 10.6, 3.2 Hz, CH*H*OH), 6.04 (dd, 1H, *J* 5.6, 1.9 Hz, H6), 6.42 (m, 1H, H5), 7.22–7.36 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ=24.6 (CH_3), 45.6 (C7), 48.8 (C4), 62.7 (C1), 63.7 ($CHCH_3$), 64.0 (C3), 66.2 (CH_2OH), 127.5, 127.7 and 128.9 (CH_{Ph}), 133.5 (C6), 138.1 (C5), 145.1 ($C1_{Ph-CH}$). IR (NaCl): ν=3382, 3060, 2971, 2873, 1659, 1601, 1493, 1453, 1371, 1324, 1283, 1246, 1210, 1187, 1080, 1020, 912, 893, 831, 762, 702 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11; found: C, 78.51; H, 8.39; N, 6.13.

*4.5.6. (+)-(1R,3R,4S)-2-[(1R)-1-Phenylethyl]-2-azabicyclo[2.2.1]hept-5-en-3-yl]methanol [(+)-**7B**] from **5b2**.* Following the same procedure as above, using adduct **5b2** (1.07 g, 2.34 mmol). Flash chromatography of the crude product (hexane/EtOAc 3:1) afforded the auxiliary, (+)-8-phenylneomenthol (R_f 0.6; 0.52 g; 95%),[16] in the early fractions and compound (+)-**7B** (R_f 0.1; 0.52 g; 96%), as yellow oil, in the latter ones. $[\alpha]_D^{25}$ −97.51 (*c* 1, $CHCl_3$). The NMR (^1H, ^{13}C) spectra are identical to those of compound (−)-**7B**. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11; found: C, 78.52; H, 8.38; N, 6.12.

*4.5.7. (−)-(1R,3S,4S)-2-[(1S)-1-Phenylethyl]-2-azabicyclo[2.2.1]hept-5-en-3-yl]methanol [(−)-**7C**] from endo-**6a**.* Following the same procedure as above, using adduct **6a** (2.02 g, 4.41 mmol). Flash chromatography of the crude product (hexane/EtOAc 3:1) afforded the auxiliary, (−)-8-phenylmenthol (R_f 0.4; 0.97 g; 95%),[16] in the early fractions and compound (−)-**7C** (R_f 0.1; 0.93 g; 92%), as yellow oil, in the later fractions. $[\alpha]_D^{25}$ −46.16 (*c* 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=1.34 (d, 3H, *J* 6.5 Hz, CH_3), 2.12–2.21 (m, 1H, $7H_{anti}$), 2.56–2.71 (m, 2H, $H7_{syn}$+$H3_{exo}$), 3.22 (q, 1H, *J* 6.5 Hz, C*H*CH_3), 3.15–3.25 (m, 1H, H4), 3.72–3.82 (m, 2H, C*H*$_2$OH), 4.72 (br s, 1H, D_2O exch, OH), 5.05 (d, 1H, *J* 7.1 Hz, H1), 5.65 (dd, 1H, *J* 5.6, 2.2 Hz, H5), 5.96 (m, 1H, H6), 7.22–7.33 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ=24.6 (CH_3), 33.0 (C7), 42.0 (C4), 57.4 (C1), 58.7 ($CHCH_3$), 69.4 (CH_2OH), 89.2 (C3), 127.1, 127.5 and 128.8 (CH_{Ph}), 130.2 (C5), 136.3 (C6), 146.1 ($C1_{Ph-CH}$). IR (NaCl): ν=3310, 3059, 2962, 2851, 1676, 1492, 1450, 1357, 1208, 1134, 1041, 990, 929, 861, 762, 701 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11; found: C, 78.55; H, 8.34; N, 6.10.

4.6. General procedure for preparation of 3,5-dinitrobenzoates[15a]

*4.6.1. (−)-(1S,3S,4R)-2-[(1S)-1-Phenylethyl]-2-azabicyclo[2.2.1]hept-5-en-3-yl]methyl 3,5-dinitrobenzoate [(−)-**8B**] from (−)-**7B**.* A mixture of alcohol (−)-**7B** (71 mg, 0.31 mmol), 3,5-dinitrobenzoyl chloride (144 mg, 0.62 mmol; freshly crystallized from CCl_4), and DMAP (76.3 mg, 0.62 mmol) in dry DCM (10 mL) was stirred under argon for 48 h at rt. The mixture was washed with 0.5 M NaOH solution (3×60 mL), 0.5 M HCl solution (3×80 mL), and brine (80 mL). The organic layer was dried (Na_2SO_4), and removal of the solvent left a yellow oil. Flash chromatography of the crude product (hexane/EtOAc 9:1) afforded a white solid (R_f 0.7; 1.21 g, 92%) identified as the pure 3,5-dinitrobenzoate (−)-**8B**. Mp 127–130 °C. $[\alpha]_D^{25}$ −43.47 (*c* 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=1.32 (d, 1H, *J* 8.6 Hz, $H7_{anti}$), 1.36 (d, 3H, *J* 6.5 Hz, CH_3), 1.72 (d, 1H, *J* 8.5 Hz, $H7_{syn}$), 2.25 (dd, 1H, *J* 10.0, 3.8 Hz, $H3_{endo}$), 2.99 (s, 1H, H4), 3.16 (q, 1H, *J* 6.5 Hz, C*H*CH_3), 3.44–3.51 (m, 1H, H1), 4.24–4.31 (t, 1H, *J* 11.1 Hz, C*H*HO), 4.86 (dd, 1H, *J* 11.1, 3.8 Hz, CH*H*O), 6.07 (dd, 1H, *J* 5.6, 1.8 Hz, H6), 6.38 (dd, 1H, *J* 5.0, 3.4 Hz, H5), 7.23–7.36 (m, 5H, Ph), 9.20 (d, 2H, *J* 2.1 Hz, $H2_{ortho}$+$H6_{ortho}$), 9.24 (t, 1H, *J* 2.1 Hz, $H4_{para}$). ^{13}C NMR ($CDCl_3$): δ=25.0 (CH_3), 45.0 (C7), 46.6 (C4), 60.1 (C3), 63.4 (C1), 63.8 ($CHCH_3$), 71.2 (CH_2O), 122.8 ($C4_{Ph}$), 127.4, 127.7 and 128.9 (CH_{Ph}), 129.9 (double) ($C2_{DNP}$+$C6_{DNP}$), 134.2 (C5), 134.4 ($C1_{Ph}$), 136.0 (C6), 145.7 ($C1_{DNP}$), 149.1 ($C3_{DNP}$+$C5_{DNP}$), 162.9 [C(O)O]. IR (KBr): ν=2974, 1723, 1684, 1653, 1629, 1541, 1457, 1343, 1280, 1169, 1136, 1074, 964, 913, 770, 729, 702 cm^{-1}. Anal. Calcd for $C_{22}H_{21}N_3O_6$: C, 62.41; H, 5.00; N, 9.92; found: C, 62.39; H, 4.95; N, 9.89. Suitable crystals of (−)-(1*S*,3*exo*)-**8B** were obtained from hexane/Et_2O and the structure was confirmed by the X-ray crystallographic analysis.[18]

*4.6.2. (+)-(1R,3R,4S)-2-[(1S)-1-Phenylethyl]-2-azabicyclo[2.2.1]hept-5-en-3-yl]methyl 3,5-dinitrobenzoate [(+)-**8A**] from (+)-**7A**.* Following the same procedure as above, using the alcohol (+)-**7A** (80 mg, 0.35 mmol). Flash chromatography of the crude product (hexane/EtOAc 9:1) afforded compound (+)-**8A** (R_f 0.7; 135 mg; 91%), as white solid. Mp 95–98 °C (pentane). $[\alpha]_D^{25}$ +3.02 (*c* 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=1.40 (d, 3H, *J* 6.5 Hz, CH_3), 1.48 (d, 1H, *J* 8.4 Hz, $7H_{anti}$), 1.76 (d, 1H, *J* 8.4 Hz, $7H_{syn}$), 2.08 (dd, 1H, *J* 9.6, 4.1 Hz, $H3_{endo}$), 2.84 (d, 1H, *J* 1.2 Hz, H4), 3.11 (q, 1H, *J* 6.5 Hz, C*H*CH_3), 3.72 (dd, 1H, *J* 11.0, 4.2 Hz, C*H*HO), 3.92 (dd, 1H, *J* 11.0, 9.9 Hz, CH*H*O), 4.24 (d, 1H, *J* 1.2 Hz, H1), 6.27 (dd, 1H, *J* 5.7, 1.7 Hz, H6), 6.45 (dd, 1H, *J* 4.8, 3.3 Hz, H5), 7.18–7.35 (m, 5H, Ph), 9.00 (d, 2H, *J* 2.0 Hz, $H2_{ortho}$+$H6_{ortho}$), 9.18 (t, 1H, *J* 4.2 Hz, J_d 2.0 Hz, $H4_{para}$). ^{13}C NMR ($CDCl_3$): δ=22.7 (CH_3), 45.0 (C7), 45.9 (C4), 61.8 (C3), 63.5 (C1), 63.8 ($CHCH_3$), 70.0 (CH_2O), 122.6 ($C4_{Ph}$), 127.8, 128.3 and 128.9 (CH_{Ph}), 129.8 (double) ($C2_{DNP}$+$C6_{DNP}$), 133.0 (C6), 134.4 ($C1_{Ph}$), 136.6 (C5), 146.1 ($C1_{DNP}$), 149.0 (double) ($C3_{DNP}$+$C5_{DNP}$), 162.4 [C(O)O]. IR (KBr): ν=2968, 1726, 1653, 1629, 1547, 1457, 1344, 1284, 1172, 1072, 968, 919, 756, 720, 704 cm^{-1}. Anal. Calcd for $C_{22}H_{21}N_3O_6$: C, 62.41; H, 5.00; N, 9.92; found: C, 62.37; H, 4.93; N, 9.87.

*4.6.3. (−)-(1S,3S,4R)-2-[(1R)-1-Phenylethyl]-2-azabicyclo[2.2.1]hept-5-en-3-yl]methyl 3,5-dinitrobenzoate [(−)-**8A**] from (−)-**7A**.* Following the same procedure as above, using the alcohol (−)-**7A** (90 mg, 0.39 mmol). Flash chromatography of the crude product (hexane/EtOAc 9:1) afforded compound (−)-**8A** (R_f 0.7; 149 mg; 90%), as white solid. Mp 95–98 °C (pentane). $[\alpha]_D^{25}$ −3.01 (*c* 1, $CHCl_3$). The NMR (^1H, ^{13}C) spectra are identical to those of compound (+)-**8A**. Anal. Calcd for $C_{22}H_{21}N_3O_6$: C, 62.41; H, 5.00; N, 9.92; found: C, 62.39; H, 4.96; N, 9.90.

*4.6.4. (−)-(1R,2S,5R)-8-Phenylmenthyl (1R,3S,4S,5R,6S)-5,6-dihydroxy-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (−)-**9** from (−)-**6a**.* A solution of adduct (−)-**6a** (0.60 g, 1.3 mmol), NMO (0.21 g, 1.01 equiv), and OsO_4 (1,5 mL, 0.0039 M sol in water, 0.45 mol %) in *tert*-butanol/THF/water 9:15:1 (7 mL) was stirred at ambient temperature under argon for 1 h. The reaction mixture was then filtered through a Celite pad and washed with THF. Removal of the solvent on a rotavapor yielded a bordeaux residue, which was purified by column chromatography (silica gel) using hexane/EtOAc 3:2 as eluent. Fractions 3–9 (R_f 0.35) afforded a light pink oil (0.50 g), which solidified on standing and which was identified as the dihydroxylated adduct (−)-**9**. Yield 79%. Suitable white crystals of (−)-**9** were obtained from hexane/EtOAc and the structure was confirmed by X-ray crystallographic analysis.[19] Mp

202–204 °C (hexane). $[\alpha]_D^{23}$ −15.1 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.91 (d, 3H, *J* 6.4 Hz, 5′-CH_3), 0.92–1.07 (m, 2H, $H4_a'+H6_a'$), 1.08–1.19 (m, 1H, $H3_a'$), 1.21 (d, 3H, *J* 6.4 Hz, CHC*H*$_3$Ph), 1.23 (s, 3H, 8′-CH_3), 1.27 (d, 1H, *J* 10.8 Hz, $H7_{syn}$), 1.34 (s, 3H, 8′-CH_3), 1.45–1.57 (m, 1H, H5′), 1.58 (d, 1H, *J* 10.8 Hz, $H7_{anti}$), 1.62–1.79 (m, 2H, $H4_b'+H3_b'$), 1.99–2.08 (m, 1H, $H6_b'$), 2.09–2.15 (m, 1H, H2′), 2.16 (d, 1H, *J* 2.0 Hz, H4), 2.45 (br s, 1H, exch D_2O, OH), 2.69 (d, 1H, *J* 4.0 Hz, $H3_{exo}$), 2.76 (br s, 1H, exch D_2O, OH), 2.82 (br s, 1H, H1), 3.46 (q, 1H, *J* 6.4 Hz, C*H*CH$_3$Ph), 3.68 (br s, 1H, H5), 3.84 (br s, 1H, H6), 4.74 (dt, 1H, J_t 10.8 Hz, J_d 6.4 Hz, H1′), 7.15–7.43 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$): δ=21.8 (5′-*C*H$_3$), 22.5 (*C*H$_3$CHPh), 24.9 (8′-*C*H$_3$), 26.5 (C3′), 28.0 (8′-*C*H$_3$), 29.0 (C7), 31.3 (C5′), 34.6 (C4′), 39.6 (C8′), 41.29 (C6′), 47.6 (C4), 50.1 (C2′), 63.2 (*C*HPh), 64.0 (C1), 65.0 (C3), 69.9 (C5), 73.3 (C6), 75.3 (C1′), 124.9, 125.3, 127.0, 127.2, 127.9 and 128.4 (CH_{Ph}), 145.8 ($C1_{Ph-C8'}$), 152.0 ($C1_{Ph-CH}$), 172.0 [C(O)O]. IR (neat): 3435, 2952, 1725, 1493, 1454, 1373, 1134, 1074, 1026, 980, 910, 842, 781, 764, 729 cm^{-1}. Anal. Calcd for $C_{31}H_{41}NO_4$: C, 75.73; H, 8.41; N, 2.85; found: C, 75.81; H, 8.50; N, 2.78.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.06.097.

References and notes

1. (a) Denis, N. *Org. React. Mech.* **2007**, 427; (b) Battiste, M. A.; Pelphrey, P. M.; Wright, D. L. *Chem.—Eur. J.* **2006**, *12*, 3438; (c) Ess, D. H.; Jones, G. O.; Houk, K. N. *Adv. Synth. Catal.* **2006**, *348*, 2337; (d) Domingo, L. R. *Mini-Rev. Org. Chem.* **2005**, *2*, 47.
2. (a) Kleemann, A.; Engel, J.; Kutscher, B.; Reischert, D. *Pharmaceutical Substances: Synthesis, Patents, Applications*, 3rd ed.; Thieme: Würtsburg, Germany, 1999; (b) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1; (c) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099; (d) Heintzelman, G. R.; Meigh, I. R.; Mahajan, Y. R.; Weinreb, S. M. *Org. React.* **2005**, *65*, 141; (e) Weinreb, S. M. In *Comprehensive Organic Synthesis*; Paquette, L. A., Ed.; Pergamon: Oxford, 1991, Chapter 4.2.
3. (a) Timén, A. S.; Somfai, P. *J. Org. Chem.* **2003**, *68*, 9958; (b) Rodríguez-Borges, J. E.; García-Mera, X.; Fernández, F.; Lopes, V. H. C.; Magalhães, A. L.; Cordeiro, M. N. D. S. *Tetrahedron* **2005**, *61*, 10951; (c) Fernández, F.; García-Mera, X.; Vale, M. L. C.; Rodriguez-Borges, J. E. *Synlett* **2005**, 319; (d) Vale, M. L. C.; Rodriguez-Borges, J. E.; Caamaño, O.; Fernández, F.; García-Mera, X. *Tetrahedron* **2006**, *62*, 9475; (e) Stella, L.; Feneau-Dupont, j.; Tinant, B.; Declercq, J. P. *Tetrahedron Lett.* **1990**, *31*, 2306; (f) Ekegren, J. K.; Modin, S. A.; Alonso, D. A.; Andersson, P. G. *Tetrahedron: Asymmetry* **2002**, *13*, 447; (g) Abraham, H.; Stella, L. *Tetrahedron* **1992**, *48*, 9707; (h) Szymanski, S.; Chapuis, C.; Jurczak, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1939; (i) Alves, C. N.; da Silva, A. B. F.; Marti, S.; Moliner, V.; Oliva, M.; Andrés, J.; Domingo, L. R. *Tetrahedron* **2002**, *58*, 2695; (j) García, J. I.; Martinez-Merino, V.; Mayoral, J. A.; Salvatelha, L. *J. Am. Chem. Soc.* **1998**, *120*, 2415; (k) Fernández, F.; García-Mera, X.; Rodríguez-Borges, J. E.; Vale, M. L. C. *Tetrahedron Lett.* **2003**, *44*, 431; (l) Domingo, L. R.; Oliva, M.; Andrés, J. *J. Org. Chem.* **2001**, *66*, 6151.
4. (a) Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558; (b) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron* **1999**, *55*, 7601.
5. (a) Alonso, D. A.; Guijarro, D.; Pinho, P.; Temme, O.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 2749; (b) Sodergren, M. J.; Bertilsson, S. K.; Andersson, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 6610; (c) Brandt, P.; Andersson, P. G. *Synlett* **2000**, 1092; (d) Murata, K.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1999**, *64*, 2186; (e) O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439; (f) de Sousa, S. E.; O'Brien, P.; Steffens, H. C. *Tetrahedron Lett.* **1999**, *40*, 8423; (g) Pinho, P.; Andersson, P. G. *Tetrahedron* **1998**, *54*, 7897; (h) Guijarro, D.; Pinho, P.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 2530.
6. (a) Alves, M. J.; García-Mera, X.; Vale, M. L. C.; Santos, T. P.; Aguiar, F. R.; Rodriguez-Borges, J. E. *Tetrahedron Lett.* **2006**, *47*, 7595; (b) Rodriguez-Borges, J. E.; Vale, M. L. C.; Aguiar, F. R.; Alves, M. J.; García-Mera, X. *Synthesis* **2008**, 971 and references cited therein; (c) Maison, W. *Eur. J. Org. Chem.* **2007**, 2276 and references cited therein.
7. (a) Johns, B. A.; Pan, Y. T.; Elbein, A. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 4856; (b) Robinson, K. M.; Rhinehart, B. L.; Ducep, J. B.; Danzin, C. *Drugs Future* **1992**, *17*, 705.
8. (a) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645; (b) Dwek, R. A.; Butters, T. D.; Platt, F. M.; Zitzmann, N. *Nat. Rev. Drug Discovery* **2002**, *1*, 65.
9. (a) Greimel, P.; Spreitz, J.; Stutz, A. E.; Wrodniggm, T. M. *Curr. Top. Med. Chem.* **2003**, *3*, 513; (b) Fleet, G. W. J.; Karpas, A.; Dwek, R. A.; Fellows, L. E.; Tyms, A. S.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Smith, P. W.; Son, J. C.; Wilson, F. X.; Witty, D. R.; Jacob, G. S.; Rademacher, T. W. *FEBS Lett.* **1988**, *237*, 128.
10. (a) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 5546; (b) Pearson, W. H.; Guo, L. *Tetrahedron Lett.* **2001**, *42*, 8267; (c) Fleet, G. W. J.; Nash, R. J.; Fellows, L. E.; Parekh, R. J.; Rademacher, T. W. *Chem. Lett.* **1986**, 1051.
11. Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265.
12. Ashby, C. R.; Paul, M.; Gardner, E. L.; Gerasimov, M. R.; Dewey, S. L.; Lennon, I. C.; Taylor, S. J. C. *Synapse* **2002**, *44*, 61.
13. (a) Zhu, X.-F. *Nucleosides, Nucleotides Nucleic Acids* **2000**, *19*, 651; (b) Rodríguez, J. B.; Comin, M. J. *Mini-Rev. Med. Chem.* **2003**, *3*, 95; (c) Mehellou, Y.; De Clercq, E. *J. Med. Chem.* **2010**, *53*, 521; (d) *Nucleoside Analogs in Cancer Therapy*; Cheson, B. D., Keating, M. J., Plunkett, W., Eds.; Marcel Dekker: New York, NY, 1997; (e) Ena, J.; Pasquau, F. *Clin. Infect. Dis.* **2003**, *36*, 1186.
14. (a) Bailey, P. D.; Londesbrough, D. J.; Hancox, T. C.; Heffernan, J. D.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1994**, 2543; (b) Bailey, P. D.; Wilson, R. D.; Brown, G. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1337; (c) Bailey, P. D.; Brown, G. R.; Korber, F.; Reed, A.; Wilson, R. D. *Tetrahedron: Asymmetry* **1991**, *12*, 1263.
15. (a) Fernández, F.; García-Mera, X.; Lopez, C.; Rodríguez, G.; Rodríguez-Borges, J. E. *Tetrahedron: Asymmetry* **2000**, *41*, 4805; (b) Caamaño, O.; Fernández, F.; García-Mera, X.; Rodríguez-Borges, J. E. *Tetrahedron Lett.* **2000**, *41*, 4123; (c) Halterman, R. L.; Vollhard, K. P. C. *Organometallics* **1988**, *7*, 883; (d) Whitesell, J. K.; Liu, C.-L.; Buchanan, C. M.; Chen, H.-H.; Minton, M. A. *J. Org. Chem.* **1986**, *51*, 551; (e) Whitesell, J. K.; Bhattacharya, A.; Buchanan, C. M.; Chen, H.-H.; Deyo, D.; James, D.; Liu, C.-L.; Minton, M. A. *Tetrahedron* **1986**, *42*, 2993.
16. The recovered alcohols were identified as (−)-8-phenylmenthol [$[\alpha]_D^{25}$ −25.2 (*c* 0.5, $CHCl_3$)] and (+)-8-phenylneomenthol [$[\alpha]_D^{23}$ +34.0 (*c* 1.0, $CHCl_3$)] by comparison of its spectroscopic and specific rotation data with those reported in literature.[15a]
17. The crystallographic data for the structure (+)-**7A**[6b] have been deposited at the Cambridge Crystallographic Data Center as supplementary publication number CCDC 240700. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2, 1EZ, UK.
18. The crystallographic data for the structure (−)-**8B** have been deposited at the Cambridge Crystallographic Data Center as supplementary publication number CCDC 240701. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2, 1EZ, UK.
19. The crystallographic data for the structure (−)-**9** have been deposited at the Cambridge Crystallographic Data Center as supplementary publication number CCDC 240702. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2, 1EZ, UK.
20. The crystallographic data for the structure (+)-**10** have been deposited at the Cambridge Crystallographic Data Center as supplementary publication number CCDC 801195. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2, 1EZ, UK.
21. Blanco, J. M.; Caamaño, O.; Fernández, F.; García-Mera, X.; López, C.; Rodríguez-Borges, J. E. *Synthesis* **1998**, 1590.