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Highly stereoselective cycloadditions of Danishefsky's diene to (−)-8-phenylmenthyl and (+)-8-phenylneomenthyl glyoxylate *N*-phenylethylimines

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ABSTRACT

Enantiopure 4-oxo-pipecolic acid derivatives were obtained by double asymmetric induction aza-Diels–Alder reactions between chiral glyoxylate *N*-phenylethylimines and Danishefsky's diene mediated by zinc iodide. The key to success was the use of iminoacetates possessing two chiral auxiliaries, *N*-(*S*)- or *N*-(*R*)-1-phenylethyl and (−)-8-phenylmenthyl or (+)-8-phenylneomenthyl. Adducts were formed in good yields (78–81%), with complete regioselectivity and high diastereoselectivity (87–96%). The absolute configuration of the adducts formed was unequivocally assigned through NMR, specific optical rotation and X-ray data of appropriated derivatives. These cycloadducts can serve as precursors for bioactive piperidinic azasugars and pipecolic acid derivatives.

1. Introduction

The importance of cycloadditions in organic chemistry stems mainly from their great versatility and high stereochemical and regiochemical control in the construction of cyclic frameworks.[1] Within cycloadditions, the aza-Diels–Alder reaction is one of the most efficient methods available for the formation of nitrogen heterocycles, allowing for the synthesis of a wide range of chiral piperidinic derivatives with regio-, diastereo- and enantioselectivities.[2,3] The imines used as aza-dienophiles generally require activation by an electron-withdrawing group and a Lewis acid. The electronic nature of the substituents at the diene/dienophile pair is known to influence the reaction pathways and determine either a concerted mechanism[2,3] (synchronous or asynchronous[2h,s–u]) or a stepwise one.[4]

In the case of the aza-Diels–Alder reaction between Danishefsky's diene and iminoacetates, the products obtained, 4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylates,[3f] can be used as precursors of a large variety of nonproteinogenic α-amino acids and of pipecolic acid and its derivatives, which are components of many pharmacologically active compounds.[5] The significant biological activity of these compounds has resulted in the development of many synthetic approaches for their preparation (Scheme 1).

The cycloadducts obtained in these reactions contain a piperidinic functionalized ring system that may undergo further transformations[6,7] to yield chiral nonnatural amino alcohols and α-amino acids (piperidinic derivatives) as well as pipecolic acid derivatives. The former compounds have shown useful activity as glycosidase inhibitors[8] with application as antiviral,[9] included potential non-nucleosidic inhibitors of HIV replication,[10] antineoplastic[11] and antidiabetic agents.[9a,12] The pipecolic acid derivatives are useful as synthetic intermediates in the preparation of potential therapeutic agents such as *N*-methyl-D-aspartate (NMDA) receptor agonists,[5b–d] anti-HIV agents,[5e–g] antibiotics,[5g,h] antineoplastic agents,[5i–k] protein tyrosine phosphatase modulators,[5l] thrombin inhibitors,[5l,m] anaesthetics[5n] and immunosuppressive agents.[5o,p] Because of this potential, in the last two decades several catalytic asymmetric methods for producing asymmetric induction in the construction of nitrogen heterocycles have been developed, with the use of chiral Lewis acids to promote asymmetric induction being the most commonly used strategy. However, this methodology suffers from low reproducibility and in most cases the chiral Lewis acids are toxic and expensive.

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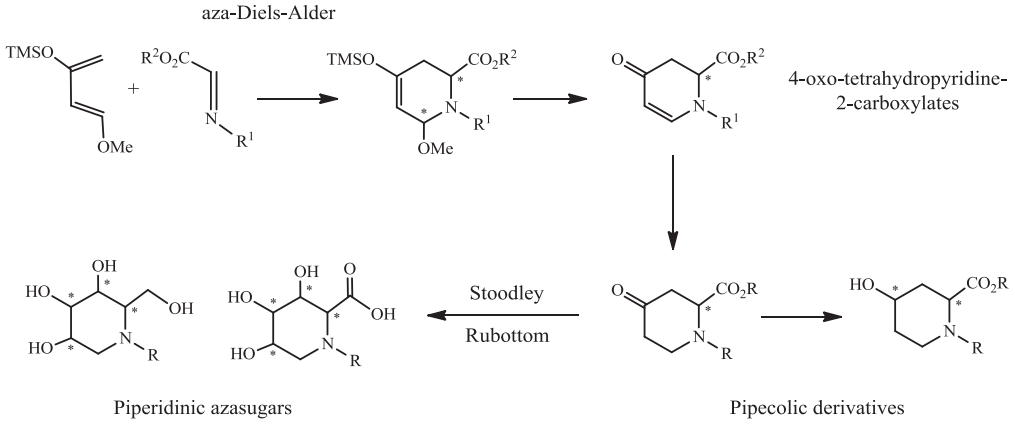


Scheme 1. 4-Oxo-1,2,3,4-tetrahydropyridine-2-carboxylates (aza-Diels–Alder cycloadducts) as precursors of a large variety of compounds.

Concerning the imino-Diels–Alder reaction, L. Stella and co-workers investigated the cycloaddition of methyl (*S*)-*N*-(1-phenylethyl)-α-iminoacetate with Danishefsky's diene.[3f] Cyclic α-amino-esters were formed with complete regioselectivity but with low diastereoselectivity (24% de at rt). The diastereomers were not separated and the absolute configuration of the stereoisomers was not determined. However, the cycloaddition occurred in good yield (85%) when using ZnI_2 as Lewis acid and THF as solvent. The authors postulated the in situ formation of a square-planar zinc–imine complex to explain the cycloaddition mechanism.[3f,g]

More recently, we described the highly diastereoselective cycloaddition between cyclopentadiene and protonated glyoxylate imines possessing two chiral auxiliaries, *N*-(*S*)- or *N*-(*R*)-1-phenylethyl and 8-phenylmenthyl or 8-phenylneomenthyl, to afford optically pure 3-functionalized 2-azabicyclo [2.2.1]hept-5-enes.[2t] These reactions showed to be highly accelerated in the presence of a Lewis acid, due to the formation of an iminium cation complex that rapidly undergoes cycloaddition under mild conditions to give products with high stereoselectivity.[2,3]

Considering the results obtained by Stella and ourselves, we decided to explore the enantioselective synthesis of 4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylates, performing an aza-Diels–Alder reaction between Danishefsky's diene and chiral phenylethylimines, formed from the corresponding (*R*)- or (*S*)-phenylethylamine and the glyoxylates of chiral alcohols. The presence of two chiral auxiliaries in the imine was expected to promote asymmetric induction with no need for chiral Lewis acids, resulting in an effective and inexpensive enantioselective synthesis of piperidinic derivatives, including pipecolic acid derivatives.

Hence we describe herein the most efficient asymmetric synthesis of the adducts formed in the cycloaddition of Danishefsky's diene and *N*-(*S*)- or *N*-(*R*)-1-phenylethylimines of (−)-8-phenylmenthyl or (+)-8-phenylneomenthyl glyoxylates. The assignment of the absolute configuration of all the adducts formed was achieved through NMR, specific optical rotation and X-ray data of the appropriate derivatives.

2. Results and discussion

(−)-8-Phenylmenthol (HOPM, **1a**)[13] and (+)-8-phenylneomenthol (HOPNM, **1b**)[14] were obtained from (+)-(*R*)-pulegone. Conversion of the alcohols into the corresponding glyoxylates (**2a** and **2b**) was achieved by reaction with acryloyl chloride in the presence of Et_3N and DMAP, followed by treatment of the resulting acrylates with OsO_4 and $NaIO_4$.[2i,t,15] Treatment of the glyoxylate (**2a** or **2b**) with equimolar amounts of 1-phenylethylamine (*R*-PEA or *S*-PEA) and ZnI_2 in THF generated the corresponding iminium complex, which reacted in situ with excess Danishefsky's diene (2 equiv) at rt yielding the corresponding adducts (**3a**,**4a**/**3b**,**4b**) (Scheme 2).

The reaction was monitored by TLC (aliquots treated with $NaHCO_3$), and the total consumption of the imine was observed after 3 days. The results of the aza-Diels–Alder reactions are presented in Table 1.

As can be seen (Table 1), reaction of the glyoxylates with Danishefsky's diene gave, in each case, rise to a mixture of the two possible isomers (epimers) in good yields (≈80%). In each case, a high diastereomeric excess was observed and the major adduct was isolated from the mixture either by recrystallization or by column chromatography.

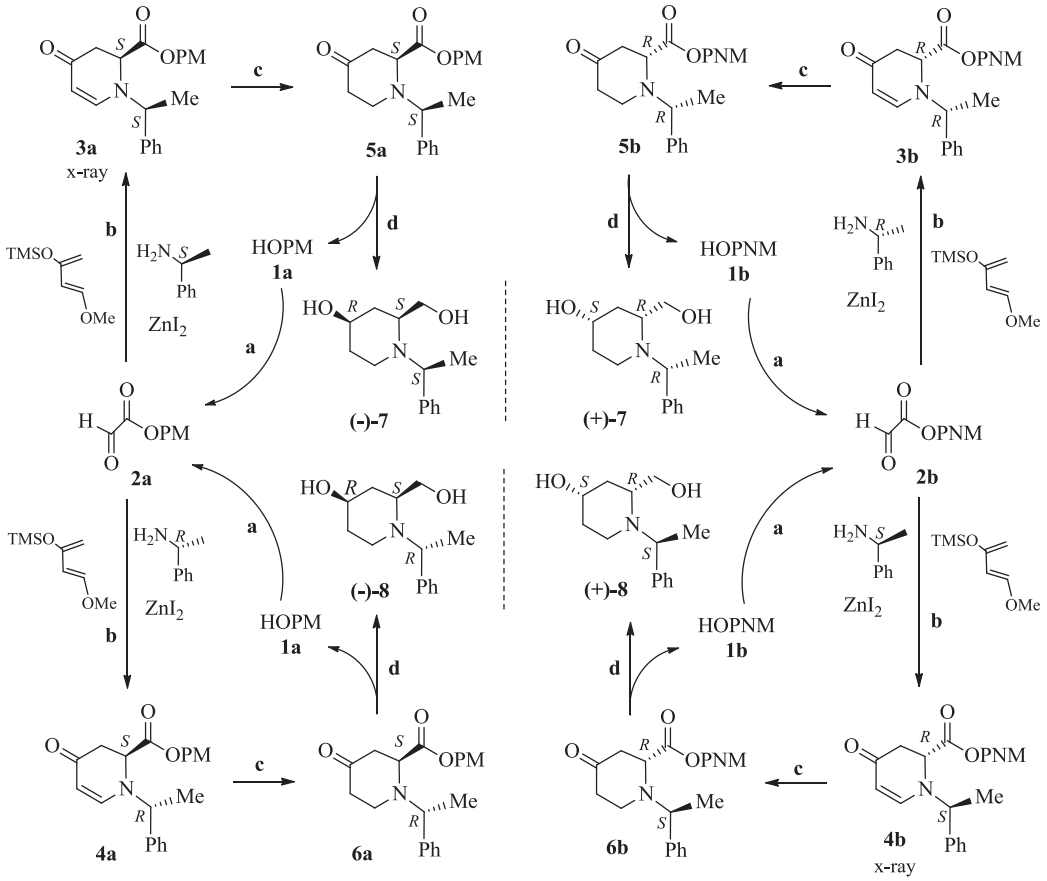
The absolute configurations of adducts **3a** (2*S*) and **4b** (2*R*) were unequivocally determined from crystallographic data of X-ray diffraction (Fig. 1).[16,17]

For the determination of the absolute configuration of the other adducts, the transformations outlined in Scheme 2 were performed. Treatment of the enantiopure cycloadducts (**3a**, **4a**, **3b**, **4b**) with L-Selectride afforded the corresponding enantiopure 4-oxo-2-pipecolates (*4-piperidones*) [(−)-**5a**,(−)-**6a**, (+)-**5b**, (+)-**6b**], which by reaction with $LiAlH_4$[2i–k,t] afforded the enantiopure aminodiols [(−)-**7**, (−)-**8**, (+)-**7**, (+)-**8**, respectively]. The absolute configurations of adducts **4a** (2*S*) and **3b** (2*R*) were determined by comparison of NMR spectroscopic data (^1H and ^{13}C) and specific rotation data of the corresponding aminodiol derivatives, (+)-**7** (from **3b**) and (−)-**8** (from **4a**), respectively, with the values obtained for their enantiomers (configuration confirmed by X-ray), (−)-**7** (from **3a**) and (+)-**8** (from **4b**), respectively.

2.1. Regio and stereoselectivity of reductions

T.J. Donohoe and co-workers[18] have described the regioselective conjugate addition of hydride to dihydropyridones using L-Selectride to obtain the corresponding 4-piperidones. Following this same methodology, translated by a Michael-type attack of the hydride to the olefinic bond of the α,β-unsaturated system, we obtained the enantiopure 4-piperidones [(−)-**5a**, 71%; (−)-**6a**, 70%/(+)-**5b**, 73%; (+)-**6b**, 76%] from the corresponding cycloadducts (**3a**, **4a**, **3b**, **4b**, respectively).

Applying a methodology developed in our research group, the piperidones (**5a**, **6a**, **5b** and **6b**) were then transformed, by treatment with $LiAlH_4$,[2i–k,t] into the corresponding enantiopure aminodiols [(−)-**7**, 70%, (−)-**8**, 72%; (+)-**7**, 71%; (+)-**8**, 73%, respectively], while allowing quantitative recovery of the corresponding chiral auxiliaries (**1a** or **1b**).[13,14] The high diastereoselectivity observed in this reduction step, under thermodynamic and kinetic control, can be explained by assuming that the $LiAlH_4$ prefers the *axial* attack at



Scheme 2. Synthesis of pipecolic acid derivatives. Reagents and conditions: (a) (1) acryloyl chloride, DCM, Et_3N, DMAP, 0 °C; (2) OsO_4, $NaIO_4$, dioxane/H_2O; (b) (1) *R*-PEA or *S*-PEA, ZnI_2, Danishefsky's diene (2 equiv), THF, rt, 3 days; (c) (1) L-Selectride, THF; 0 °C; (2) H_2O_2, NaOH; (d) (1) $LiAlH_4$, rt, THF, 12 h; (2) H_2O.

the ring carbonyl (C4), on the face opposite the bulky ester group at the C2 position (*equatorial*), generating only the corresponding pseudoequatorial alkoxide.[19] The reductive cleavage of the ester group occurs later because it is less reactive (less electrophilic) than the ketone carbonyl group. Reduction of the intermediate aldehyde occurs in situ yielding, after final treatment by oxidative protonation and extraction, the *cis*-aminodiol with recovery of the chiral alcohol R*OH (chiral auxiliary).

2.2. Diastereoselectivity of aza-Diels–Alder reaction

In an attempt to explain the diastereoselectivity observed we present in Schemes 3–5 models for the approach of diene and dienophile. After formation of the phenylethylimine, from the corresponding primary amine and the glyoxylates of PM and PNM, the Lewis acid (ZnI_2) promotes the formation of a plane square imino-cationic-Zn intermediate complex (activated dienophile)[3f–i] with *S-cis* conformation, which allows the concerted attack of the diene to form the intermediate adducts. Attack of Danishefsky's diene results in the formation of a cyclic intermediate, which upon desilylation and elimination of the methoxy group yields mainly one of the two possible diastereoisomers of the final adduct (de 74–92%).

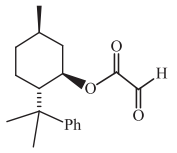
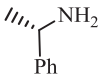
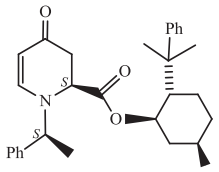
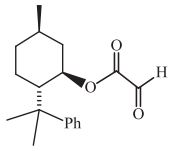
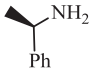
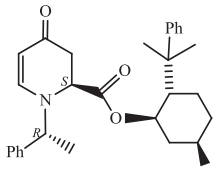
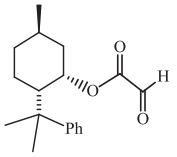
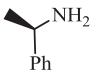
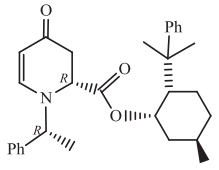
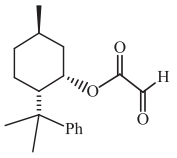
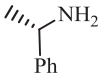
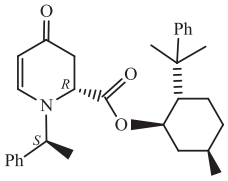
In order to account for the high diastereoselectivity observed, and based on previous DFT studies on cycloadditions of the imines with CPD, performed in our research group,[2h,s,u] an asynchronous concerted mechanism is proposed. In fact, most studies on reactions of Danishefsky's diene with imines refer a concerted [4+2] cyclic transition state, giving rise to the corresponding cyclic adducts with good to high diastereoselectivities, depending on solvent, catalyst, Lewis acid and temperature.[3] Exceptions are observed when using *N*-arylimines as dienophiles, where, depending on the diene used, either a Mannich-like or an inverse-electron-demand aza-Diels–Alder mechanism seems to operate.[3i,4] In the present case, and in analogy to what Stella refers,[3f] the cyclic silylenolether intermediates could not be isolated, and their hydrolysis followed by a retro-Michael elimination of the methoxy group gives rise to the final tetrahydropyridin-4-ones isolated. No products other than these cycloadducts were observed.

In the case of combinations of PM/*S*-PEA (Scheme 3) and PM/*R*-PEA (Scheme 5) the *exo* or *endo* attack of diene would be on the *Si* face of the imino-cationic Zn-complex providing the corresponding cycloadducts with 2*S* configuration (**3a** and **4a**, respectively). Moreover, combinations of PNM/*S*-PEA (Scheme 4) and PNM/*R*-PEA (Scheme 5) favour diene attack on the *Re* face providing the corresponding adducts with 2*R* configuration (**4b** and **3b**, respectively).

Taking into account, simultaneously, polar effects (hydrogen bonding) and repulsive interactions in the different conformations, the geometries **9a**, **9b**, **10a** and **10b** are those which best explain the obtention of the major adducts (**3a**, **4b**, **4a** and **3b**, respectively). The high selectivity observed in these cases may be explained considering that:

* *S-cis* conformation of the imine caused by metal complexation with Zn and establishment of hydrogen bonding interactions between the carboxylate group and the hydrogen atoms of the imine and of carbon C1′ (menthol ring), favour diene approach on the *Si* face in the case of the 8-phenylmenthol group (PM), and on the *Re* face in the case of the 8-phenylneomenthol group (PNM).
* The relative position of the two phenyl groups on each intermediate complex should be such as to minimize non-favourable interactions: (a) for PM/*S*-PEA (**9a**) and PNM/*R*-PEA

Table 1
Results for the aza-Diels–Alder reaction between Danishefsky's diene and in situ generated *N*-phenylethyliminoacetates of (−)-8-phenylmenthol and (+)-8-phenylneomenthol in the presence of ZnI_2 (rt, THF, 3 days)

Entry	Glyoxylate	Phenylethylamine	Adducts (de)[a]/yield[b] (%)	Major adduct—yield (%)
1	 **2a**	 **(*S*)-PEA**	96:4 (92%)/(80)	 **3a** (x-ray) (75%)[c]
2	 **2a**	 **(*R*)-PEA**	88:12 (76%)/(78)	 **4a** (68%)[d]
3	 **2b**	 **(*R*)-PEA**	94:6 (88%)/(81)	 **3b** (75%)[d]
4	 **2b**	 **(*S*)-PEA**	87:13 (74%)/(79)	 **4b** (x-ray) (66%)[c]

[c]After recrystallization.
[d]After preparative chromatographic purification.
[a] Determined by ^{1}H NMR analysis.
[b] After chromatographic purification.

(**10b**) the most stable conformation has the two phenyl groups (8-Ph and PhNMe) on opposite sites as to minimize steric hindrance and repulsion. Consequently, the phenyl group of PEA and the imine function have a coplanar arrangement, and the methyl group of PEA (PhNMe) and 8-Ph are on the same side of the complex, thus accounting for the high diastereoselectivity observed, (96:4) and (94:6), respectively; (b) in the case of the complexes PNM/*S*-PEA (**9b**) and PM/*R*-PEA (**10a**), the two phenyl groups (8-Ph and PhNMe) are closer together, possibly due to more favourable secondary interactions. Although the approach of the diene is mainly from one of the faces, steric hindrance promotes the formation of minor conformational intermediates (**9b′** and **10a′**) in which the methyl group blocks the approach of the diene from that same face and therefore a slight reduction of the diastereoselectivity (87:13 and 88:12, respectively) is observed; (c) for all intermediates the 8-phenyl group causes greater steric hindrance on one of the faces of the dienophile (PM blocks the *Re* face and PNM blocks the *Si* face).

3. Conclusions

The results obtained illustrate the utility of (−)-8-phenylmenthol and (+)-8-phenylneomenthol as easily recoverable stereo controlling auxiliaries, affording optically pure 4-oxo-pipecolic acid

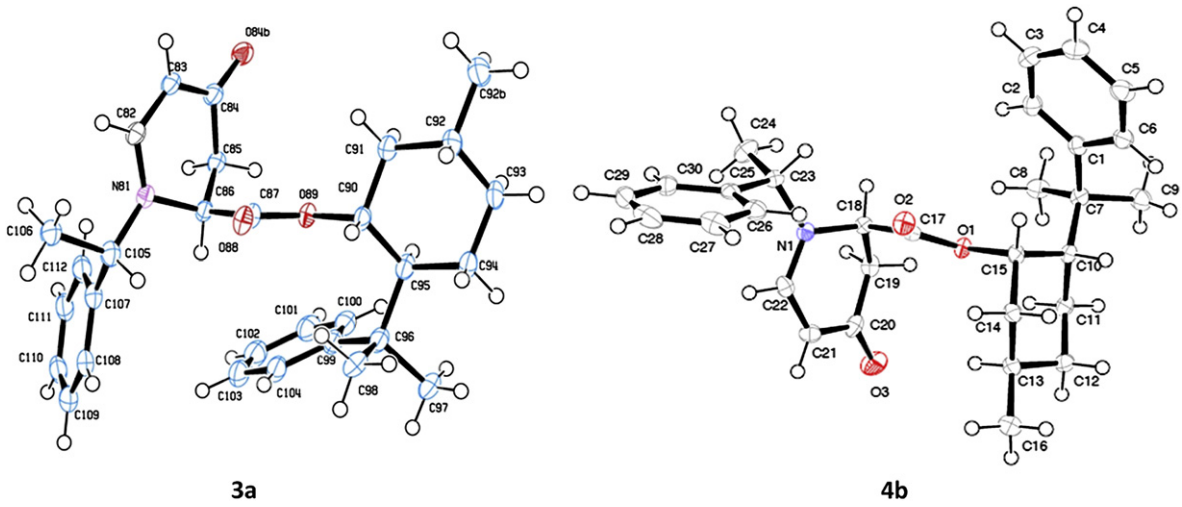
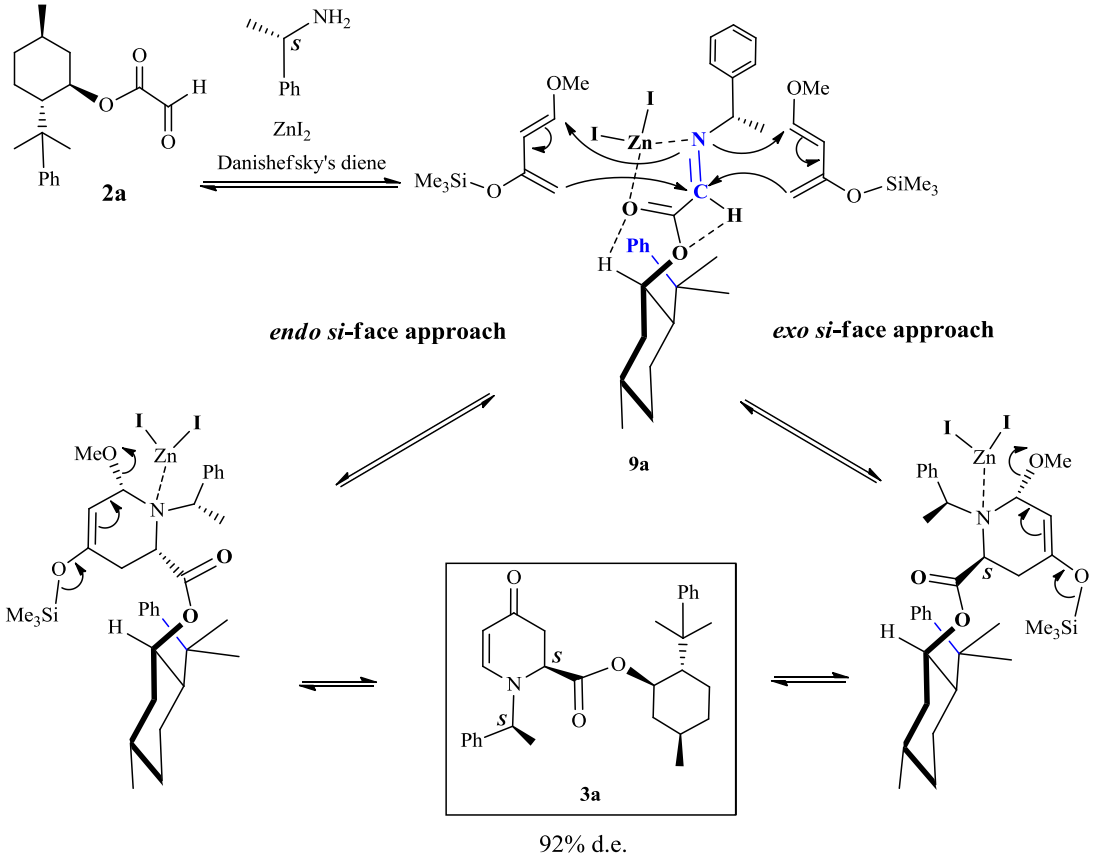
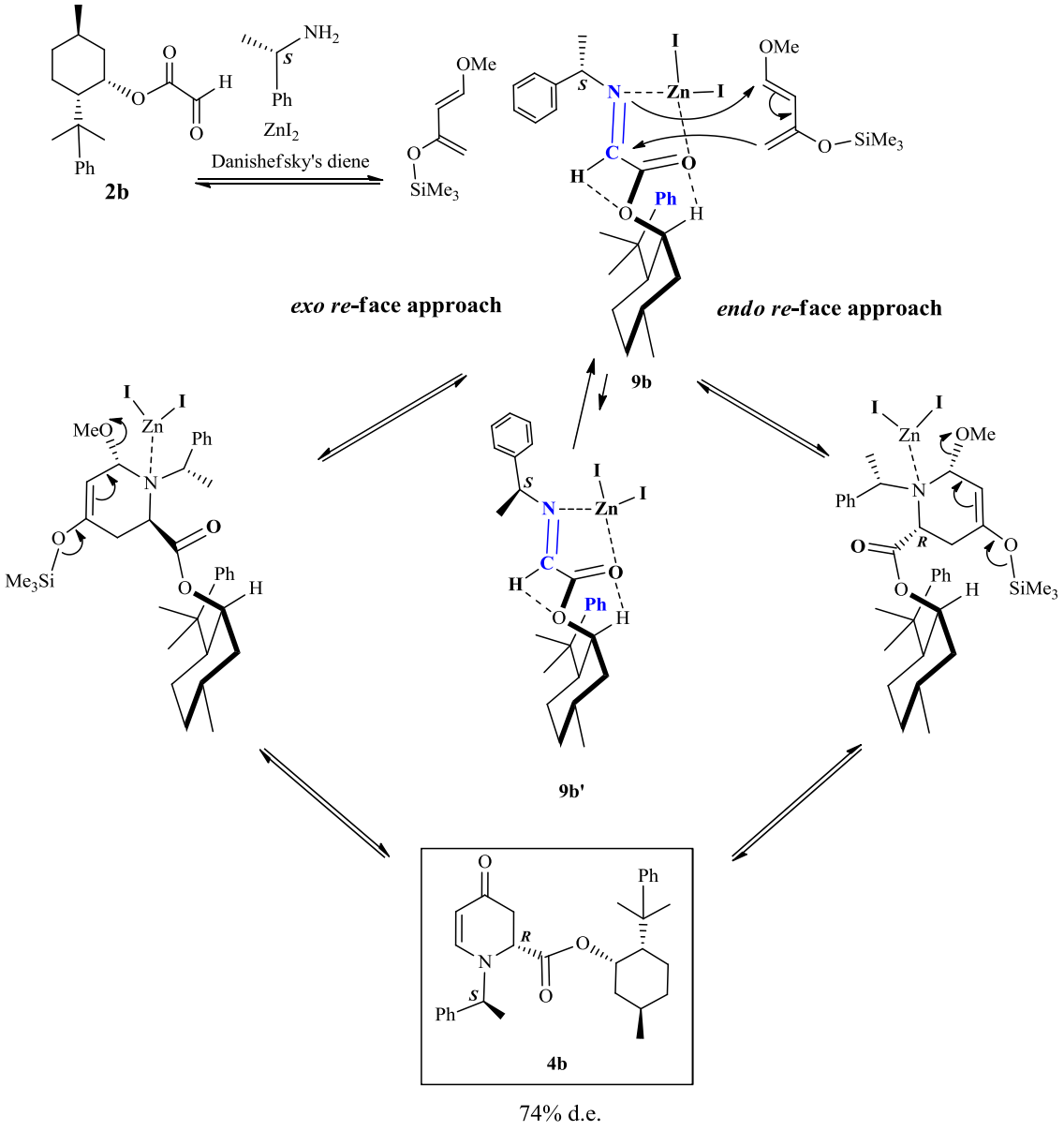


Fig. 1. X-ray single crystal structures of compounds (−)-**3a**[16] and (+)-**4b**.[17]



Scheme 3. Model for the approach of diene and iminium complex of corresponding 8-phenylmenthyl (*S*)-*N*-(1-phenylethyl)-α-iminoacetate to afford the major adduct (−)-**3a** (2*S*).

derivatives from aza-Diels–Alder reaction between Danishefsky's diene and chiral phenylethylimines, formed from the corresponding (*R*)- or (*S*)-phenylethylamine and the glyoxylates of these alcohols. For the combination of the auxiliaries 8-phenylmenthyl/*N*-(*S*)-phenylethyl and 8-phenylmenthyl/*N*-(*R*)-phenylethyl, the major products were diastereomers (−)-(2*S*)-**3a** (75%, 92% de) and (−)-(2*S*)-**4a** (68%, 76% de), respectively. When 8-phenylneomenthyl/*N*-(*R*)-phenylethyl and 8-phenylneomenthyl/*N*-(*S*)-phenylethyl were used in combination, the reaction yielded as major adducts (+)-(2*R*)-**3b** (75%, 88% de) and (+)-(2*R*)-**4b** (66%, 74% de), respectively. The results obtained point to the occurrence of a sole mechanism, involving a cyclic [4+2] transition state, which may be concerted, asynchronous, as the only products observed were the aza-Diels–Alder cycloadducts. We have unambiguously the absolute configuration of all adducts assigned, using NMR, specific optical rotation and X-ray data of the appropriated derivatives, 4-oxo-pipecolates [**5a** (71%), **6a** (70%), **5b** (73%) and **6b** (76%)] and 2-hydromethyl-piperidin-4-ols [(−)-**7** (70%), (−)-**8** (72%), (+)-**7** (71%), (+)-**8** (73%)].



Scheme 4. Model for the approach of diene and iminium complex of corresponding 8-phenylneomenthyl (*S*)-*N*-(1-phenylethyl)-α-iminoacetate to afford the major adduct (+)-**4b** (2*R*).

4. Experimental

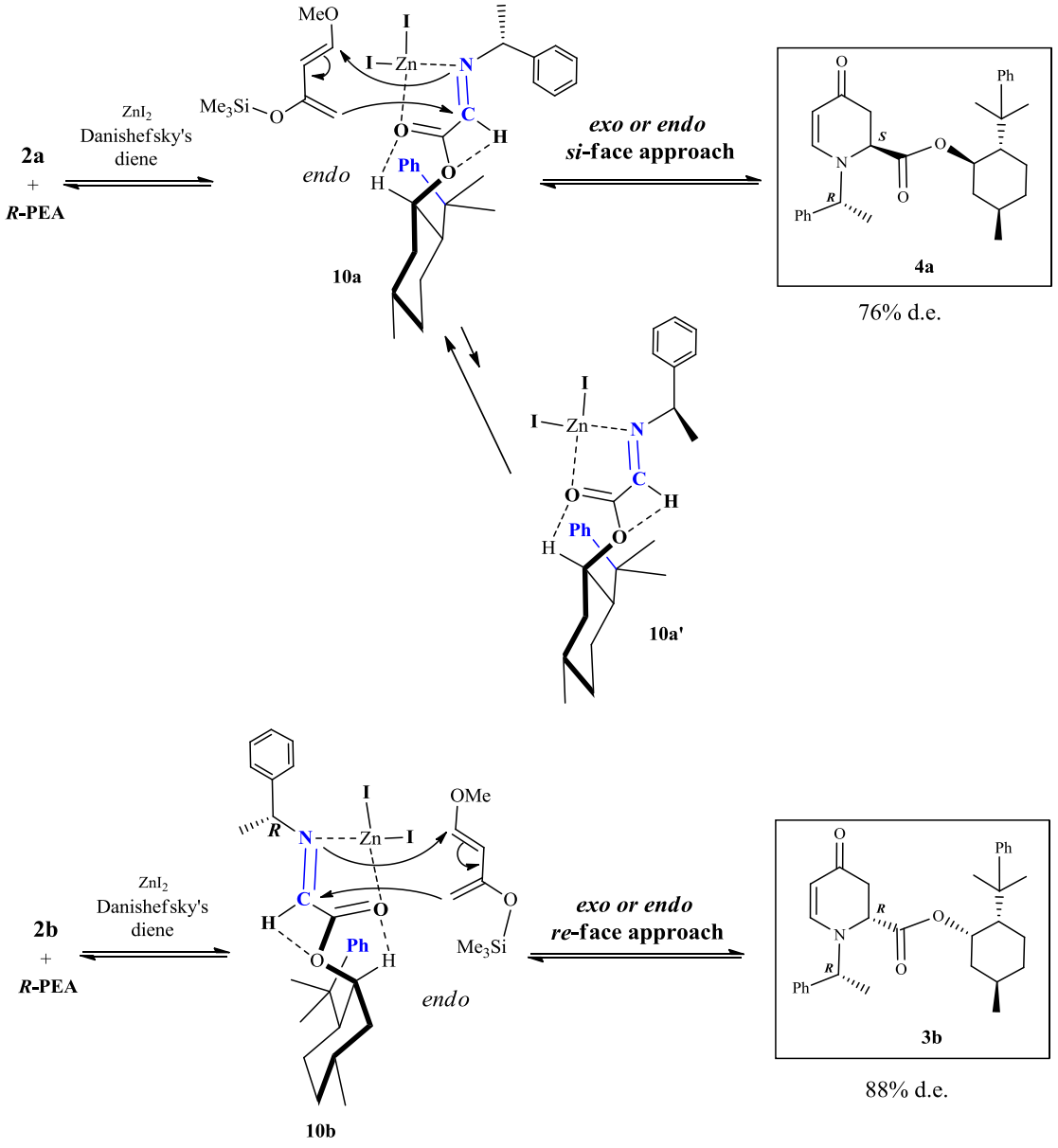
4.1. General methods

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 vapour and/or UV light (254 nm) for visualization. Preparative chromatography was performed on glass plates (20 cm×20 cm) with 200–400 mesh silica gel 60 ACC. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on an FT/IR spectrophotometer and main bands are given in cm^{-1}. The ^1H NMR (400 MHz) and ^{13}C NMR (75.47 MHz) spectra were recorded using $CDCl_3$ as solvent and are reported in parts per million (ppm) downfield from TMS (chemical shifts (δ) in ppm, *J* in Hz). Multiplicities are recorded as broad peaks (br), singlets (s), doublets (d), triplets (t), doublets of doublets (dd), doublets of triplets (dt), quartets (q) and multiplets (m). 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). X-ray diffraction data were collected in a diffractometer apparatus and the structures were designed by Mercury, PLATON and/or ORTEP programs. Elemental analyses were obtained on a microanalyser apparatus. Mass spectra (low and high resolution) were recorded on Hewlett-Packard HP5988A or Autospec spectrometers. ESI-MS analyses were performed on a liquid 35 chromatography Finnigan Surveyor equipment, coupled to a mass detector Finnigan LQC DECA XP MX with an API and an ESI interface.

Chiral alcohols (**1a** and **1b**) and chiral glyoxylates (**2a** and **2b**) were obtained according to the literature procedure.[2i,t,15]

4.2. General procedure for aza-Diels–Alder reaction

*4.2.1. (−)-(1R,2S,5R)-8-Phenylmenthyl (2S)-4-oxo-1-[(1S)-1-phenylethyl]-1,2,3,4-tetrahydropyridine-2-carboxylate (**3a**).* To a solution of



Scheme 5. Model for the approach of diene and iminium complex of corresponding 8-phenylmenthyl (*R*)-*N*-(1-phenylethyl)-α-iminoacetate or 8-phenylneomenthyl (*R*)-*N*-(1-phenylethyl)-α-iminoacetate to afford the major adducts (−)-**4a** (2*S*) and (+)-**3b** (2*R*), respectively.

(−)-8-phenylmenthyl glyoxylate (**2a**) (2.00 g, 6.52 mmol, 1.2 equiv) in dried THF (60 mL) under an argon atmosphere and at 0 °C were added molecular sieves 4 Å (2 g, previously dried under vacuum) and a solution of (*S*)-1-phenylethylamine (0.676 g, 0.72 mL, 5.58 mmol, 1.0 equiv) in dried THF (20 mL). After stirring for 30 min, ZnI_2 (2.08 g, 6.52 mmol, 1.0 equiv) was added and the solution was stirred for 1 h at rt. Then, Danishefsky's diene (1.5 mL, 1.2 g, 6.7 mmol, 1.2 equiv) was added and the reaction mixture was stirred for another 24 h. An additional portion of diene (1.5 mL, 1.2 g, 6.7 mmol) was added and the mixture was allowed to react for another 48 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (40 mL) and solid $NaHCO_3$ (4 g) and EtOAc (50 mL) were added. The two layers were separated and the aqueous layer was extracted with EtOAc (2×50 mL). The pooled organic layers were washed with brine (60 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure yielded an orange oil (3.15 g), which was purified by column chromatography (silica gel) using hexane/EtOAc 1:2 as eluent. Fractions of R_f 0.6 afforded a white cream solid (2.06 g, 80.2%) identified (NMR) as a mixture of two diastereomeric cycloadducts (epimers) (2*S*/2*R*) in a ratio of 96:4. Purification by slow recrystallization of the mixture with hexane/Et_2O afforded pure major adduct (**3a**) (75%).

*4.2.1.1. Compound (**3a**).* White solid. Mp=109–111 °C. R_f=0.63 (hexane/EtOAc 1:2). $[\alpha]_D^{25}$ −18.5 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ=0.88 (d, 3H, *J* 6.4 Hz, 5′-Me), 0.90–1.03 (m, 2H, H4′$_a$+H6′$_a$), 1,15 (s, 3H, 8′-Me), 1.16–1.20 (m, 1H, H3′$_a$), 1.23 (s, 3H, 8′-Me), 1.38–1.55 (m, 1H, H5′), 1,63 (d, 3H, *J* 6.8 Hz, CH_3CHPh), 1.68–1.75 (m, 1H, H4′$_b$), 1.76–1.86 (m, 1H, H6′$_b$), 1.87–1.95 (m, 1H, H3′$_b$), 1.99 (dt, 1H, *J* 16.8, 2.0 Hz, H3$_{anti}$), 2.09 (td, 1H, *J* 11.0, 3.6 Hz, H2′), 2.26 (dd, 1H, *J* 16.8, 7.2 Hz, H3$_{syn}$), 3.02 (dt, 1H, *J* 7.2, 1.6 Hz, H2), 4.49 (q, 1H, *J* 6.8 Hz, CH_3CHPh), 4.77 (td, 1H, *J* 10.8, 4.4 Hz, H1′), 4.97 (dd, 1H, *J* 7.6, 1.1 Hz, H5), 6.77 (t, 1H, *J* 7.4 Hz, H4$_{Ph}$), 6.91 (t, 2H, *J* 7.8 Hz, H3$_{Ph}$+H5$_{Ph}$), 7.14 (dd, 2H, *J* 8.6, 1.0 Hz, H2$_{Ph}$+H6$_{Ph}$), 7.20–7.33 (m, 2H, Ph), 7.39 (dd, 1H, *J* 7.6, 1.2 Hz, H6), 7.41–7.50 (m, 3H, Ph). ^{13}C NMR ($CDCl_3$): 21.6 (CH_3CHPh), 21.7 (5′-Me), 22.0 (8′-Me), 26.1 (C3′), 30.2 (8′-Me), 31.3 (C5′), 34.4 (C4′), 37.5 (C3′), 39.2 (C8′), 41.0 (C6′), 49.9 (C2′), 58.8 (C2), 62.3 (CH_3CHPh), 76.4 (C1′), 98.6 (C5), 124.8 (CH, Ph), 124.9 (CH, Ph),

126.1 (CH, Ph), 127.8 (CH, Ph), 128.2 (CH, Ph), 129.2 (CH, Ph), 142.8 ($C1_{Ph-CH}$), 149.0 (C6), 152.2 ($C1_{Ph\text{-}8'}$), 169.5 (COO), 189.0 (CO). IR (KBr): 1758, 1691 cm^{-1}. Anal. Calcd for $C_{30}H_{37}NO_3$: C 78.40, H 8.11, N 3.05. Found: C 78.38, H 8.15, N 3.03. HRMS (EI) calcd for $C_{30}H_{37}NO_3$ 459.2773, found 459.2769. Suitable crystals of **3a** were obtained from hexane/Et_2O and the structure was confirmed by the X-ray crystallographic analysis.[16]

*4.2.2. (+)-(1S,2S,5R)-8-Phenylneomenthyl (2R)-4-oxo-1-[(1S)-1-phenylethyl]-1,2,3,4-tetrahydropyridine-2-carboxylate (**4b**).* Following the same procedure as above, using (*S*)-1-phenylethylamine (0.749 g, 0.80 mL, 6.18 mmol) and (+)-8-phenylneomenthyl glyoxylate (**2b**) (2.21 g, 7.22 mmol). Flash chromatography of the crude product (hexane/EtOAc 1:2) afforded a white solid (2.24 g, 79.0%) identified (NMR) as a mixture of two diastereomeric cycloadducts (epimers) (2*R*/2*S*) in a ratio of 87:13. Purification by slow recrystallization of the mixture with hexane/Et_2O afforded pure major adduct (**4b**) (66%).

*4.2.2.1. Compound (**4b**).* White solid. Mp=164–165 °C. R_f=0.63 (hexane/EtOAc 1:2). $[\alpha]_D^{25}$ +52.1 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ=0.80 (d, 3H, *J* 6.4 Hz, 5′-Me), 0.82–0.93 (m, 1H, $H4'_a$), 0.94–1.03 (m, 1H, $H6'_a$), 1,30 (s, 3H, 8′-Me), 1.33 (s, 3H, 8′-Me), 1.52–1.61 (m, 4H, H5′+H2′+$H3'_a$+$H3'_b$), 1.63 (d, 3H, *J* 7.2 Hz, CH_3CHPh), 1.68–1.86 (m, 2H, $H4'_b$+$H6'_b$), 2.65 (dd, 1H, *J* 16.8, 2.8 Hz, $H3_{anti}$), 2.70 (dd, 1H, *J* 16.8, 6.8 Hz, $H3_{syn}$), 4.04 (ddd, 1H, *J* 6.8, 2.8, 0.8 Hz, H2), 4.69 (q, 1H, *J* 7.2 Hz, CH_3CHPh), 4.90 (d, 1H, *J* 7.6 Hz, H5), 5.03 (s, 1H, H1′), 6.94 (d, 1H, *J* 7.6 Hz, H6), 7.12–7.14 (m, 1H, Ph), 7.15–7.46 (m, 9H, Ph). ^{13}C NMR ($CDCl_3$): 19.7 (CH_3CHPh), 22.9 (5′-Me), 23.4 (C3′), 27.4 (8′-Me), 27.6 (C5′), 28.3 (8′-Me), 36.1 (C4′), 39.3 (C3), 40.7 (C6′), 40.8 (C8′), 52.2 (C2′), 58.2 (C2), 62.9 (CH_3CHPh), 74.7 (C1′), 100.1 (C5), 126.6 (CH, Ph), 127.0 (CH, Ph), 128.4 (CH, Ph), 128.9 (CH, Ph), 129.4 (CH, Ph), 130.0 (CH, Ph), 140.8 ($C1_{Ph-CH}$), 149.9 ($C1_{Ph\text{-}8'}$), 153.0 (C-6), 170.3 (COO), 189.8 (CO). IR (KBr): 1758, 1691 cm^{-1}. Anal. Calcd for $C_{30}H_{37}NO_3$: C 78.40, H 8.11, N 3.05. Found: C 78.39, H 8.10, N 3.00. HRMS (EI) calcd for $C_{30}H_{37}NO_3$ 459.2773, found 459.2770. Suitable crystals of **4b** were obtained from hexane/Et_2O and the structure was confirmed by the X-ray crystallographic analysis.[17]

*4.2.3. (−)-(1R,2S,5R)-8-Phenylmenthyl (2S)-4-oxo-1-[(1R)-1-phenylethyl]-1,2,3,4-tetrahydropyridine-2-carboxylate (**4a**).* Following the same procedure as above, using (*R*)-1-phenylethylamine (0.722 g, 0.77 mL, 5.96 mmol) and (−)-8-phenylmenthyl glyoxylate (**2a**) (2.13 g, 6.96 mmol). Flash chromatography of the crude product (EtOAc/hexane 2:1) afforded a yellow oil (2.14 g, 78.1%) identified (NMR) as a mixture of two diastereomeric cycloadducts (epimers) (2*S*/2*R*) in a ratio of 88:12. Purification by preparative chromatography using EtOAc/hexane 2:1 as eluent afforded pure major adduct (**4a**) (68%).

*4.2.3.1. Compound (**4a**).* Yellow oil. R_f=0.65 (hexane/EtOAc 1:2). $[\alpha]_D^{25}$ −15.3 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ=0.78 (d, 3H, *J* 6.4 Hz, 5′-Me), 0.80–0.94 (m, 2H, $H4'_a$+$H6'_a$), 1.01–1.10 (m, 1H, $H3'_a$), 1.14 (s, 3H, 8′-Me), 1.25 (s, 3H, 8′-Me), 1.34–1.37 (m, 1H, H5′), 1.36 (d, 3H, *J* 7.2 Hz, CH_3CHPh), 1.55–1.64 (m, 1H, $H4'_b$), 1.67–1.75 (m, 2H, $H3'_b$+$H6'_b$), 1.99–2.08 (m, 1H, H2′), 2.46 (dd, 1H, *J* 16.8, 6.8 Hz, $H3_{anti}$), 2.64 (dd, 1H, *J* 16.8, 2.4 Hz, $H3_{syn}$), 3.35 (ddd, 1H, *J* 6.8, 2.8, 0.8 Hz, H2), 4.05 (q, 1H, *J* 7.2 Hz, CH_3CHPh), 4.73 (dd, 1H, *J* 7.6, 0.8 Hz, H5), 4.88 (td, 1H, *J* 10.8, 4.4 Hz, H1′), 6.59 (dd, 1H, *J* 7.6, 0.8 Hz, H6), 7.03–7.16 (m, 1H, $C1_{Ph}$), 7.09–7.36 (m, 9H, Ph). ^{13}C NMR ($CDCl_3$): 19.9_6 (CH_3CHPh), 22.6 (5′-Me), 23.1 (8′-Me), 27.0 (C3′), 31.2 (8′-Me), 32.2 (C5′), 35.3 (C4′), 39.0 (C3), 40.2 (C8′), 41.9 (C6′), 50.7 (C2′), 57.5 (C2), 62.9 (CH_3CHPh), 77.2 (C1′), 99.8 (C5), 125.8 (CH, Ph), 126.1 (CH, Ph), 128.6 (CH, Ph), 128.9 (CH, Ph), 129.3 (CH, Ph), 129.9 (CH, Ph), 140.7 ($C1_{Ph-CH}$), 152.7 (C6), 153.4 ($C1_{Ph\text{-}8'}$), 170.5 (COO), 189.9_6 (CO). IR (NaCl): 1758, 1690 cm^{-1}. Anal. Calcd for $C_{30}H_{37}NO_3$: C 78.40, H 8.11, N 3.05. Found: C 78.39, H 8.09, N 3.06. HRMS (EI) calcd for $C_{30}H_{37}NO_3$ 459.2773, found 459.2780.

*4.2.4. (+)-(1S,2S,5R)-8-Phenylneomenthyl (2R)-4-oxo-1-[(1R)-1-phenylethyl]-1,2,3,4-tetrahydropyridine-2-carboxylate (**3b**).* Following the same procedure as above, using (*R*)-1-phenylethylamine (0.75 g, 0.80 mL, 6.19 mmol) and (−)-8-phenylneomenthyl glyoxylate (**2b**) (2.22 g, 7.24 mmol). Flash chromatography of the crude product (EtOAc/hexane 2:1) afforded a yellow oil (2.31 g 81.2%) identified (NMR) as a mixture of two diastereomeric cycloadducts (epimers) (2*R*/2*S*) in a ratio of 94:6. Purification by preparative chromatography using EtOAc/hexane 2:1 as eluent afforded pure major adduct (**3b**) (75%).

*4.2.4.1. Compound (**3b**).* Yellow oil. R_f=0.64 (hexane/AcOEt 1:2). $[\alpha]_D^{25}$ +73.0 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): ^1H NMR ($CDCl_3$): δ=0.81 (d, 3H, *J* 6.8 Hz, 5′-Me), 0.86–0.96 (m, 1H, $H4'_a$), 0.97–1.05 (m, 1H, $H6'_a$), 1.25 (s, 3H, 8′-Me), 1.26 (s, 3H, 8′-Me), 1.52–1.62 (m, 4H, $H3'_a$+$H3'_b$+H2′+H5′), 1.65 (d, 3H, *J* 6.8 Hz, CH_3CHPh), 1.73–1.87 (m. 2H, $H4'_b$+$H6'_b$), 2.54 (ddd, 1H, *J* 16.8, 2.8, 1.2 Hz, $H3_{anti}$), 2.64 (dd, 1H, *J* 16.8, 6.8 Hz, $H3_{syn}$), 3.70 (ddd, 1H, *J* 7.2, 2.8, 1.2 Hz, H2), 4.56 (q, 1H, *J* 6.8 Hz, CH_3CHPh), 5.01 (s, 1H, H1′), 5.05 (dd, 1H, *J* 8.0, 0.8 Hz, H5), 7.02–7.13 (m, 1H, $H1_{Ph}$), 7.18–7.65 (m, 11H, Ph+H6). ^{13}C NMR ($CDCl_3$): 22.6 (CH_3CHPh), 23.0 (5′-Me), 23.5 (C3′), 27.7 (8′-Me), 27.8 (8′-Me), 28.3 (C5′), 36.3 (C4′), 38.6 (C3), 40.8 (C8′), 40.9 (C6′), 52.4 (C2′), 60.4 (C2), 63.6 ($CHCH_3$Ph), 74.8 (C1′), 99.6 (C5), 126.7 (CH, Ph), 127.1 (CH, Ph), 127.1 (CH, Ph), 129.0 (CH, Ph), 129.9 (CH, Ph), 130.3 (CH, Ph), 143.4 ($C1_{Ph-CH}$), 149.8 ($C1_{Ph\text{-}8'}$), 150.1 (C6), 170.3 (COO), 190.1 (CO). IR (NaCl): 1758, 1690 cm^{-1}. Anal. Calcd for $C_{30}H_{37}NO_3$: C 78.40, H 8.11, N 3.05. Found: C 78.38, H 8.13, N 307. MS (ESI) calcd for $C_{30}H_{37}NO_3$ (M+1) 460.28, found 460.47; dimmer 919.20; 246.00; 142.04; 96.07.

4.3. General procedure for reduction of cycloadducts with L-Selectride

*4.3.1. (−)-(1R,2S,5R)-8-Phenylmenthyl (2S)-4-oxo-1-[(1S)-1-phenylethyl]-piperidine-2-carboxylate (**5a**).* To a solution of **3a** (1.012 g, 2.20 mmol) in dry THF (11 mL) was added, dropwise and under an argon atmosphere, a solution of L-Selectride 1 M (5.5 mL, 5.5 mmol) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C, and then a solution of NaOH 1 M (5.6 mL, 5.6 mmol) and H_2O_2 30% (2.3 mL, ca. 20 mmol) was added dropwise at 0 °C. Brine (50 mL) was added and the resulting mixture was extracted with EtOAc (3×60 mL). The pooled organic layers were washed with more brine (60 mL) and dried with Na_2SO_4. Removal of the solvent in a rotary evaporator left a yellow oil (1.21 g) that when chromatographed on silica gel with hexane/EtOAc 1:2 as eluent afforded a pale yellow oil (0.725 g, 71.3%) identified (NMR) as the piperidine **5a**.

*4.3.1.1. Compound (**5a**).* R_f=0.62 (hexane/EtOAc 1:2). $[\alpha]_D^{25}$ −54.9 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ=0.79 (d, 3H, *J* 6.4 Hz, 5′-Me), 0.79–0.94 (m, 2H, $H4'_a$+$H6'_a$), 0.95 (s, 3H, 8′-Me), 1.03 (s, 3H, 8′-Me), 1.05–1.15 (m, 1H, $H3'_a$), 1.18–1.24 (m, 1H, H5′), 1.25 (d, 3H, *J* 6.4 Hz, $CHCH_3$Ph), 1.31–1.50 (m, 3H, $H4'_b$+$H3'_b$+$H6'_b$), 1.51–1.65 (m, 2H, $H3_{anti}$+$H5_{anti}$), 1.75–1.90 (m, 3H, $H3_{syn}$+$H5_{syn}$+H2′), 2.83–3.01 (m, 2H, $H6_{anti}$+$H6_{syn}$+H2), 4.16 (q, 1H, *J* 6.4 Hz, $CHCH_3$Ph), 4.56 (td, 1H, *J* 10.8, 4.0, 1.2 Hz, H1′), 6.80–6.90 (m, 4H, Ph), 6.21–6.30 (m, 6H, Ph). ^{13}C NMR ($CDCl_3$): 22.2 (CH_3CHPh), 23.1 (5′-Me), 24.6 (8′-Me), 26.8 (C3′), 28.4 (8′-Me), 31.6 (C5′), 35.0 (C4′), 35.7 (C5), 37.4 (C6′), 39.6 (C8′), 41.8 (C3), 42.2 (C6), 50.8 (C2′), 58.2 (C2), 60.5 (CH_3CHPh), 75.1 (C1′), 125.0 (CH, Ph), 125.3 (CH, Ph), 127.4 (CH, Ph), 127.7 (CH, Ph), 128.1 (CH, Ph), 128.9 (CH, Ph), 146.1 ($C1_{Ph-CH}$), 152.3 ($C1_{Ph\text{-}8'}$), 171.9 (COO), 202.5 (CO). IR (NaCl): 1727, 1693 cm^{-1}. Anal. Calcd for $C_{30}H_{39}NO_3$: C 78.05, H 8.52, N 3.03.

Found: C 78.08, H 8.56, N 3.06. MS (ESI) calcd for $C_{30}H_{39}NO_3$ (M+1) 462.30, found 462.34.

*4.3.2. (+)-(1S,2S,5R)-8-Phenylneomenthyl (2R)-4-oxo-1-[(1S)-1-phenylethyl]-piperidine-2-carboxylate (**6b**).* Following the same procedure as above, using adduct **4b** (1.032 g, 2.24 mmol). Flash chromatography of the crude product (hexane/EtOAc 1:2) afforded a pale yellow oil (0.79 g, 76.1%) identified (NMR) as the piperidine **6b**.

*4.3.2.1. Compound (**6b**).* R_f=0.63 (hexane/AcOEt 1:2). $[\alpha]_D^{25}$ +63.6 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ=0.82 (d, 3H, *J* 6.4 Hz, 5′-Me), 0.83–0.96 (m, 1H, H4′$_a$), 1.01 (ddd, 1H, *J* 14.4 Hz, 12.0, 2.4 Hz, H6′$_a$), 1.09 (s, 3H, 8′-Me), 1.18 (s, 1H, 8′-Me), 1.37 (d, 3H, *J* 6.8 Hz, CH*CH*$_3$Ph), 1.42–1.70 (m, 7H, H3′$_a$+H3′$_b$+H5′+H4′$_b$+H6′$_b$+H2′+H5$_{anti}$), 1.85–1.93 (m, 1H, H3$_{anti}$), 1.94–2.02 (m, 1H, H5$_{syn}$), 2.10–2.18 (m, 1H, H3$_{syn}$), 3.03–3.09 (m, 1H, H6$_{anti}$), 3.15 (td, 1H, *J* 12.0, 2.8 Hz, H6$_{syn}$), 3.46 (t, 1H, *J* 4.4 Hz H2), 4.21 (q, 1H, *J* 6.8 Hz, C*H*CH$_3$Ph), 5.03 (s, 1H, H1′), 7.15–7.39 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$): 22.5 (PhCHCH$_3$), 22.6 (5′-Me), 22.8 (C3′), 26.2 (8′-Me), 26.7 (8′-Me), 27.5 (C5′), 30.0 (C4′), 35.6 (C5), 37.9 (C6′), 40.2 (C8′), 40.3 (C3), 41.9 (C6), 51.3 (C2′), 58.7 (C2), 60.6 (PhCHCH$_3$), 71.5 (C1′), 125.9 (CH, Ph), 126.3 (CH, Ph), 127.4 (CH, Ph), 128.2 (CH, Ph), 128.3 (CH, Ph), 128.9 (CH, Ph), 145.5 (C1$_{Ph}$), 150.0 (C1$_{8′\text{-}Ph}$), 172.1 (COO), 208.6 (CO). IR (NaCl): 1727, 1692 cm^{-1}. Anal. Calcd for $C_{30}H_{39}NO_3$: C 78.05, H 8.52, N 3.03. Found: C 78.07, H 8.55, N 3.05. MS (ESI) calcd for $C_{30}H_{39}NO_3$ (M+1) 462.30, found 462.35.

*4.3.3. (−)-(1R,2S,5R)-8-Phenylmenthyl (2S)-4-oxo-1-[(1R)-1-phenylethyl]-piperidine-2-carboxylate (**6a**).* Following the same procedure as above, using adduct **4a** (1.007 g, 2.19 mmol). Flash chromatography of the crude product (hexane/EtOAc 1:2) afforded a pale yellow oil (0.71 g, 70.3%) identified (NMR) as the piperidine **6a**.

*4.3.3.1. Compound (**6a**).* R_f=0.64 (hexane/AcOEt 1:2). $[\alpha]_D^{25}$ −69.8 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ=0.90 (d, 3H, *J* 6.4 Hz, 5′-Me), 0.92–1.08 (m, 2H, H4′$_a$+H6′$_a$), 1.08–1.22 (m, 1H, H3′$_a$), 1.23 (s, 3H, 8′-Me), 1.34 (s, 3H, 8′-Me), 1.39 (d, 3H, *J* 6.4 Hz, C*H*$_3$CHPh), 1.42–1.58 (m, 1H, H5′), 1.65–1.84 (m, 3H, H4′$_b$+H3′$_b$+H6′$_b$), 2.03–2.19 (m, 3H, H2′+H5$_{anti}$+H3$_{anti}$), 2.25–2.42 (m, 2H, H3$_{syn}$+H5$_{syn}$), 2.77–2.89 (m, 2H, H6$_{anti}$+H6$_{syn}$), 2.36 (dd, 1H, *J* 15.0, 6.7 Hz, H2), 4.16 (q, 1H, *J* 6.4 Hz, C*H*CH$_3$Ph), 4.90 (td, 1H, *J* 10.8, 4.4 Hz, H1′), 7.12–7.47 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$): 21.7 (C*H*$_3$CHPh), 22.1 (5′-Me), 24.1 (8′-Me), 26.8 (C3′), 28.9 (8′-Me), 31.6 (C5′), 34.7 (C4′), 39.9 (C8′), 40.8 (C5), 42.0 (C6′), 43.2 (C3), 45.2 (C6), 50.3 (C2′), 58.4 (C2), 60.9 (CH$_3$*C*HPh), 75.7 (C1′), 125.4 (CH, Ph), 125.6 (CH, Ph), 127.2 (CH, Ph), 127.4 (CH, Ph), 128.3 (CH, Ph), 128.8 (CH, Ph), 146.1 (C1$_{Ph-CH}$), 152.2 (C1$_{Ph\text{-}8′}$), 170.9 (COO), 208.4 (CO). IR (NaCl): 1727, 1690 cm^{-1}. Anal. Calcd for $C_{30}H_{39}NO_3$: C 78.05, H 8.52, N 3.03. Found: C 78.07, H 8.55, N 3.01. MS (ESI) calcd for $C_{30}H_{39}NO_3$ (M+1) 462.30, found 462.36.

*4.3.4. (+)-(1S,2S,5R)-8-Phenylneomenthyl (2R)-4-oxo-1-[(1R)-1-phenylethyl]-piperidine-2-carboxylate (**5b**).* Following the same procedure as above, using adduct **3b** (1.027 g, 2.23 mmol). Flash chromatography of the crude product (hexane/EtOAc 1:2) afforded a pale yellow oil (0.754 g, 73.1%) identified (NMR) as the piperidine **5b**.

*4.3.4.1. Compound (**5b**).* R_f=0.64 (hexane/AcOEt 1:2). $[\alpha]_D^{25}$ +79.8 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ=0.85 (d, 3H, *J* 6.8 Hz, 5′-Me), 0.86–1.09 (m, 2H, H4′$_a$+H6′$_a$), 1.23 (s, 3H, 8′-Me), 1.27 (s, 3H, 8′-Me), 1.46 (d, 3H, *J* 6.4 Hz, C*H*$_3$CHPh), 1.47–1.59 (m, 4H, H3′$_a$+H3′$_b$+H5′+H2′), 1.73–1.81 (m, 1H, H4′$_b$), 1.76 (dt, 1H, *J* 14.4, 2.0 Hz, H6′$_b$), 2.34–2.49 (m, 2H, H5$_{anti}$+H3$_{anti}$), 2.50–2.66 (m, 2H, H5$_{syn}$+H3$_{syn}$), 3.15–3.32 (m, 2H, H6$_{anti}$+H6$_{syn}$), 3.72 (dd, 1H, *J* 6.0, 2.2 Hz, H2), 4.27 (q, 1H, *J* 6.4 Hz, CH$_3$C*H*Ph), 5.14 (s, 1H, H1′), 7.11–7.19 (m, 1H, Ph), 7.22–7.47 (m, 9H, Ph). ^{13}C NMR ($CDCl_3$): 22.2$_6$ (*C*H$_3$CHPh), 22.3 (5′-Me), 22.5 (C3′), 26.6 (8′-Me), 26.8 (8′-Me), 27.1 (C5′), 35.5 (C4′), 40.1 (C8′), 40.5 (C5), 40.9 (C6′), 43.2 (C3), 43.3 (C6), 51.5 (C2′), 60.2 (C2), 60.5 (CH$_3$*C*HPh), 72.5 (C1′), 125.9 (CH, Ph), 126.2 (CH, Ph), 127.5 (CH, Ph), 127.6 (CH, Ph), 128.2 (CH, Ph), 128.9 (C1, Ph), 144.6 (C1, Ph), 149.6 (CH, Ph), 170.8 (COO), 207.7 (CO). IR (NaCl): 1727, 1691 cm^{-1}. Anal. Calcd for $C_{30}H_{39}NO_3$: C 78.05, H 8.52, N 3.03. Found: C 78.03, H 8.50, N 3.01. MS (ESI) calcd for $C_{30}H_{39}NO_3$ (M+1) 462.30, found 462.32.

4.4. General procedure for reduction of piperidin-4-ones with $LiAlH_4$

*4.4.1. (−)-(2S,4R)-2-(Hydroxymethyl)-1-[(1S)-1-phenylethyl]-piperidin-4-ol [(−)-**7**].* A solution of **5a** (0.507 g, 1.10 mmol) in dry THF (25 mL) was added dropwise under argon to a suspension of $LiAlH_4$ (ca. 6 equiv; 0.25 g, 6.59 mmol) in dry THF (10 mL) at 0 °C. The reaction mixture was stirred for 16 h at rt, and then EtOAc (2 mL), H_2O (2 mL) and NaOH 15% (2 mL) were added dropwise at 0 °C. More H_2O (20 mL) was added, the resulting mixture was extracted with AcOEt (3×20 mL) and the pooled organic layers were washed with brine (100 mL) and dried with Na_2SO_4. Removal of the solvent in a rotary evaporator left a yellow oil (0.55 g) that when chromatographed on silica gel with hexane/EtOAc 3:1 as eluent afforded the chiral auxiliary, (−)-8-phenylmenthol (R_f 0.4; 0.23 g, 91%),[20] and compound (−)-**7** (R_f 0.51; 0.181 g, 70.2%), as a pale oil, using MeOH/EtOAc 1:10 as eluent.

*4.4.1.1. Compound [(−)-**7**].* R_f=0.51 (MeOH/AcOEt 1:10). $[\alpha]_D^{25}$ −35.51 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ=1.47 (d, 3H, *J* 6.8 Hz, C*H*$_3$CHPh), 1.58 (br s, 2H, 2×OH), 2.13–2.27 (m, 2H, H3$_{anti}$+H5$_{anti}$), 2.50 (dddd, 1H, *J* 14.8, 6.8, 5.6, 1.2 Hz, H5$_{syn}$), 2.62 (ddd, 1H, *J* 15.6, 6.4, 0.8 Hz, H3$_{syn}$), 3.08 (ddd, 1H, *J* 17.6, 10.0, 4.0 Hz, H6$_{anti}$), 3.23–3.35 (m, 2H, H6$_{syn}$+H2), 3.36–3.52 (m, 3H, *CH*$_2$–OH+H4), 4.17 (q, 1H, *J* 6.8 Hz, C*H*CH$_3$Ph), 7.24–7.40 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ=19.5 (CH$_3$*C*HPh), 39.2 (C5), 40.9 (C3), 42.6 (C6), 58.2 (C2+C4), 58.5 (CH$_3$*C*HPh), 61.8 (CH$_2$O), 127.5 (C3$_{Ph}$+C5$_{Ph}$), 128.0 (C4$_{Ph}$), 129.1 (C2$_{Ph}$+C6$_{Ph}$), 144.1 (C1$_{Ph}$). IR (NaCl): 3479, 3400 cm^{-1}. Anal. Calcd for $C_{14}H_{21}NO_2$: C 71.46, H 8.99, N 5.95. Found: C 71.43, H 8.95, N 5.92. MS (ESI) calcd for ($C_{14}H_{21}NO_2$) (M+1) 236.16, found 236.13.

*4.4.2. (+)-(2R,4S)-2-(Hydroxymethyl)-1-[(1S)-1-phenylethyl]-piperidin-4-ol [(+)-**8**].* Following the same procedure as above, using piperidin-4-one **6b** (0.523 g, 1.13 mmol). Flash chromatography of the crude product (hexane/EtOAc 3:1) afforded the chiral auxiliary, (+)-8-phenylneomenthol (R_f 0.60; 0.26 g, 99%),[20] in the early fractions and compound (+)-**8** (0.195 g, 73.1%, R_f 0.50), as a pale yellow oil, using MeOH/EtOAc 1:10 as eluent.

*4.4.2.1. Compound [(+)-**8**].* R_f=0.50 (MeOH/EtOAc 1:10). $[\alpha]_D^{25}$ +23.62 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ=1.18 (br s, 2H, 2×OH), 1.41 (d, 3H, *J* 6.4 Hz, C*H*$_3$CHPh), 1.99–2.17 (m, 1H, H5$_{anti}$), 2.13 (dt, 1H, *J* 14.8, 2.0 Hz, H3$_{anti}$), 2.41 (dddd, 1H, *J* 14.8, 10.8, 6.0, 0.8 Hz, H5$_{syn}$), 2.55 (ddd, 1H, *J* 14.8, 6.4, 0.8 Hz, H3$_{syn}$), 2.79–2.89 (m, 1H, H6$_{anti}$), 2.96 (ddd, 1H, *J* 14.4, 10.8, 4.0 Hz, H6$_{syn}$), 3.34–3.45 (m, 2H, H2+OC*H*$_a$H$_b$), 3.53 (dd, 1H, *J* 10.8, 5.2 Hz, OCH$_a$*H*$_b$), 3.59–3.62 (m, 1H, H4), 4.09 (q, 1H, *J* 6.4 Hz, C*H*CH$_3$Ph), 7.18–7.30 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ=22.0 (Me), 38.6 (C5), 40.8 (C3), 43.4 (C6), 57.4 (C4), 58.9 (*C*HMe), 61.6 (C2), 61.6 (*C*H$_2$O), 127.5 (C3$_{Ph}$+C5$_{Ph}$), 128.0 (C4$_{Ph}$), 129.1 (C2$_{Ph}$+C6$_{Ph}$). IR (NaCl): 3480, 3401 cm^{-1}. Anal. Calcd for $C_{14}H_{21}NO_2$: C 71.46, H 8.99, N 5.95. Found: C 71.44, H 8.98, N 5.97. MS (ESI) calcd for ($C_{14}H_{19}NO_2$) (M+1) 236.16, found 236.20.

*4.4.3. (−)-(2S,4R)-2-(Hydroxymethyl)-1-[(1R)-1-phenylethyl]-piperidin-4-ol [(−)-**8**].* Following the same procedure as above, using piperidin-4-one **6a** (0.533 g, 1.16 mmol). Flash chromatography of the crude product (hexane/EtOAc 3:1) afforded the chiral auxiliary,

(−)-8-phenylmenthol (R_f 0.4; 0.27 g, 98.6%),[20] in the early fractions and compound (−)-**8** (0.196 g, 72.3%, R_f 0.50), as a pale yellow oil, using MeOH/EtOAc 1:10 as eluent.

*4.4.3.1. Compound [(−)-**8**].* R_f=0.50 (MeOH/EtOAc 1:10). $[\alpha]_D^{25}$ −23.63 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ=1.41 (d, 3H, *J* 6.4 Hz, CH_3CHPh), 1.52 (br s, 2H, 2×OH), 1.99–2.17 (m, 1H, H5$_{anti}$), 2.13 (dt, 1H, *J* 14.8, 2.0 Hz, H3$_{anti}$), 2.41 (dddd, 1H, *J* 14.8, 10.8, 6.0, 0.8 Hz, H5$_{syn}$), 2.55 (ddd, 1H, *J* 14.8, 6.4, 0.8 Hz, H3$_{syn}$), 2.79–2.89 (m, 1H, H6$_{anti}$), 2.96 (ddd, 1H, *J* 14.4, 10.8, 4.0 Hz, H6$_{syn}$), 3.34–3.45 (m, 2H, H2+OCH_aH$_b$), 3.53 (dd, 1H, *J* 10.8, 5.2 Hz, OCH$_a$$H_b$), 3.59–3.62 (m, 1H, H4), 4.09 (q, 1H, *J* 6.4 Hz, C*H*CH$_3$Ph), 7.18–7.30 (m, 5H, Ph). The NMR (^{1}H, ^{13}C) spectra were identical with those of compound (+)-**8** except deviations of hydroxylic protons. MS (ESI) calcd for ($C_{14}H_{19}NO_2$) (M+1) 236.16, found 236.19.

*4.4.4. (+)-(2R,4S)-2-(Hydroxymethyl)-1-[(1R)-1-phenylethyl]-piperidin-4-ol [(+)-**7**].* Following the same procedure as above, using the piperidin-4-one **5b** (0.541 g, 1.17 mmol). Flash chromatography of the crude product (hexane/EtOAc 3:1) afforded the chiral auxiliary, (+)-8-phenylneomenthol (R_f 0.60; 0.27 g, 98%),[20] in the early fractions and compound (+)-**7** (0.196 g, 71.2%, R_f 0.50), as a pale yellow oil, using MeOH/EtOAc 1:10 as eluent.

*4.4.4.1. Compound [(+)-**7**].* R_f=0.50 (MeOH/AcOEt 1:10). $[\alpha]_D^{25}$ +35.50 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ=1.47 (d, 3H, *J* 6.8 Hz, CH_3CHPh), 2.13–2.27 (m, 2H, H3$_{anti}$+H5$_{anti}$), 2.50 (dddd, 1H, *J* 14.8, 6.8, 5.6, 1.2 Hz, H5$_{syn}$), 2.62 (ddd, 1H, *J* 15.6, 6.4, 0.8 Hz, H3$_{syn}$), 3.08 (ddd, 1H, *J* 17.6, 10.0, 4.0 Hz, H6$_{anti}$), 3.23–3.35 (m, 2H, H6$_{syn}$+H2), 3.36–3.52 (m, 3H, CH_2–OH+H4), 4.17 (q, 1H, *J* 6.8 Hz, *C*HCH$_3$Ph), 4.71 (br s, 2H, 2×OH), 7.24–7.40 (m, 5H, Ph). The NMR (^{1}H, ^{13}C) spectra were identical with those of compound (−)-**7** except deviations of hydroxylic protons. MS (ESI) calcd for ($C_{14}H_{19}NO_2$) (M+1) 236.16, found 236.23.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.02.027.

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16. The crystallographic data for the structure (−)-**3a** have been deposited at the Cambridge Crystallographic Data Center as supplementary publication number CCDC 817519. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.
17. The crystallographic data for the structure (+)-**4b** have been deposited at the Cambridge Crystallographic Data Center as supplementary publication number CCDC 815905. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.
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20. 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 the literature.[13,14]