# Enantioselective Synthesis of Highly Functionalized 4-Piperidones by the Asymmetric Imino-Diels–Alder Reaction of Chiral 2-Amino-1,3-butadienes**

**José Barluenga,* Fernando Aznar, Cristina Ribas, Carlos Valdés, Mónica Fernández, María-Paz Cabal, and Jesús Trujillo**

**Abstract:** Chiral 2-amino-1,3-butadienes **1** derived from commercially available (*S*)-2-methoxymethylpyrrolidine react with aromatic *N*-trimethylsilylaldimines and *N*-phenylaldimines in the presence of $ZnCl_2$ to give, after the reaction workup, 4-piperidones **4** and **6**, respectively, with moderate to very high enantiomeric excesses. In addition, the absolute configurations of derivatives of **4a** and **4g** were determined by circular dichroism and NMR spectroscopy on the Mosher ester, respectively.

**Keywords**
asymmetric Diels–Alder reactions · butadienes · Diels–Alder reactions · piperidones

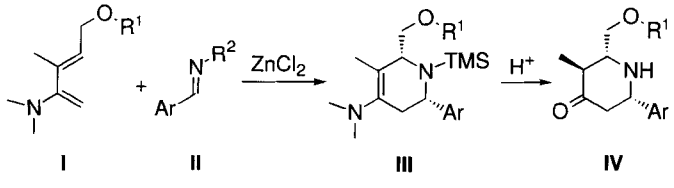
## Introduction

Six-membered azaheterocycles represent a common structure in naturally occurring alkaloids and pharmaceuticals. Among piperidine derivatives, 4-piperidones constitute an important class of synthetic intermediates,[1] which have been extensively used in the preparation of biologically active materials.[2] Manipulation of the ketone group allows substituents to be introduced at the piperidine ring.

Several strategies for the synthesis of chiral 4-piperidones have been developed. They include asymmetric transamination of racemic 4-piperidone methiodides with enantiopure primary amines,[3] Michael addition of chiral 4-enaminopiperidines to activated olefins,[4] and more recently Michael alkylation of chiral imines derived from racemic 4-piperidones[5] and intramolecular Michael addition to chiral $\alpha,\beta$-unsaturated aminoketones.[6] However, problems associated with some of these methods are the lack of generality or low diastereoselectivities.

By analogy with the formation of six-membered carbocycles, a very versatile route to piperidine derivatives is the imino-Diels–Alder reaction.[7] The majority of examples described rely on the use of imines with a chiral auxiliary attached at the nitrogen or at the carbon positions to induce facial diastereoselectivity.[8] However, this strategy has scarcely been used in the preparation of enantiomerically enriched 4-piperidones owing to the difficulties encountered in the removal or destructive cleavage of the chiral auxiliary. In certain cases, Lewis acid catalysts bearing chiral ligands have been used in catalyzed imino-Diels–Alder reactions.[9]

In the context of our study of the synthetic applications of 2-aminodienes **I**, we found that they undergo [4+2] cycloaddition reactions with nonactivated imines **II** in the presence of Lewis acids.[10] The process takes place with a high degree of stereoselectivity and, after hydrolysis of the intermediate 4-aminotetrahydropyridine **III**, gives rise to functionalized 4-piperidones **IV** (Scheme 1). Furthermore, the relative stereochemistry of the process depends on the substituent at the nitrogen atom of the imine.




I II III IV

Scheme 1. [4+2] Cycloaddition reaction of 2-aminodienes with nonactivated imines.

Recently, it has been demonstrated that chiral 2-amino-1,3-butadienes serve as excellent starting materials for the enantioselective synthesis of highly functionalized six- and seven-membered carbo- and heterocycles.[11] In particular, initial reactions with *N*-trimethylsilylaldimines have resulted in the formation of 4-piperidones with very high enantiomeric excesses (86–95%).[11a] Encouraged by these preliminary results, we embarked on a detailed study of this process, as an extension of our earlier work. This present paper explores the effect of the substituents at both the diene and dienophile ($R^1$ and $R^2$, Scheme 2) on the enantiomeric excesses. In addition, the absolute configuration of the major enantiomer of 4-piperidones **4** is determined by two separate methods.

[*] Dr. J. Barluenga, Dr. F. Aznar, C. Ribas, Dr. C. Valdés, M. Fernández, Dr. M. P. Cabal
Instituto Universitario de Química Organometálica "Enrique Moles", Unidad asociada al C. S. I. C.
Julián Clavería s/n, 33071, Oviedo, Asturias (Spain)
Telefax: Int. code +(8)510-3446
Dr. J. Trujillo
Centro de Productos Naturales Orgánicos "Antonio González"
Instituto Universitario de Bio-Orgánica, Universidad de La Laguna
Carretera de La Esperanza 2, 38206, La Laguna, Tenerife (Spain)

[**] Abbreviations used in this article: NaHMDS: sodium bis(trimethylsilyl)-amide; TMS: trimethylsilyl; MOM: methoxymethyl; TBDMS: *tert*-butyldimethylsilyl; 3-Fu: 3-furyl; *p*-MeOPh: 4-methoxyphenyl; *o*-BrPh: 2-bromophenyl; *p*-$BrC_6H_4CO$: 4-bromobenzoyl; (*R*)-MPTA: (*R*)-α-methoxy-α-phenyl-α-trifluoromethylacetyl.

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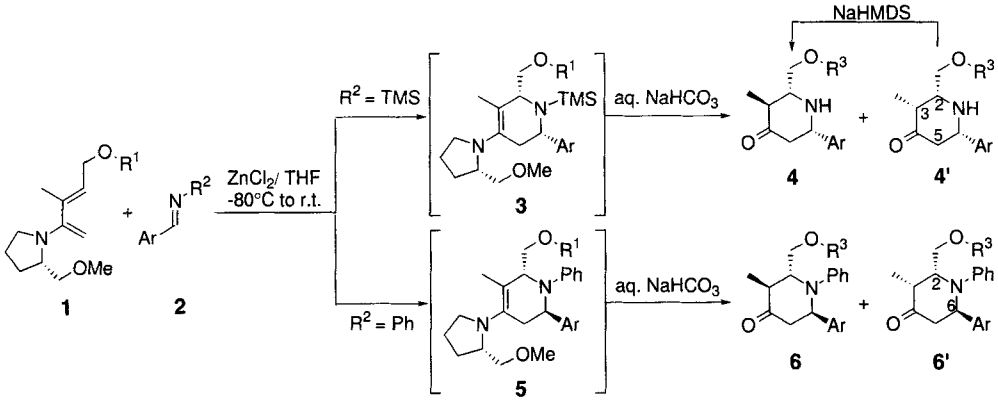
## Results and Discussion

Chiral 2-amino-1,3-butadienes **1** (Scheme 2) were synthesized with different protecting groups $R^1$ by catalytic aminomercuriation reactions of readily available 3-alken-1-ynes with the commercially available (*S*)-2-methoxymethylpyrrolidine.[12]

The cycloaddition reactions take place from −80 °C to room temperature, typically over a period of 16 h in the presence of 2 molar equivalents of $ZnCl_2$ in dry THF. The intermediate tetrahydropyridine derivatives **3** and **5** could not be isolated, as they underwent hydrolysis during the aqueous workup required to eliminate the Lewis acid catalyst. By quenching the reaction




Scheme 2. Asymmetric imino-Diels–Alder reaction of chiral 2-amino-1,3-butadienes **1** with nonactivated aromatic imines.

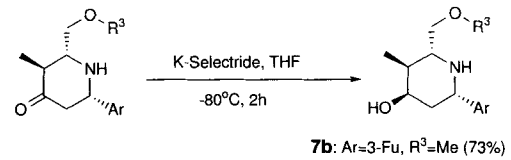
mixture with aqueous $NaHCO_3$ solution, both the N–Si bond and the enamine function were hydrolyzed; the 4-piperidones **4** and **6** were thus obtained directly as a mixture of two epimers at C3. The less stable epimer **4'**[13] could be converted into the thermodynamic isomer **4** (with all the substituents in an equatorial position)[10] by addition of 2 equivalents of sodium bis(trimethylsilyl)amide in THF to the mixture of epimers.[13] When $R^1$ is TMS, the crude product was treated with anhydrous $Na_2CO_3$ in MeOH to complete the O–Si bond cleavage; epimerization occurred at the same time. The results are summarized in Table 1.

The enantiomeric excesses (except for entries 7 and 12) were determined by HPLC (Chiralcel OD-H, 0.8 mL min$^{-1}$, hexane/ethanol or hexane/isopropanol as eluent mixtures) directly on the 4-piperidones (**4a**, **4e**, **4h**, **4k**) or on simple derivatives (desilylated **4d**, **4f**, **4i**, and 4-hydroxyderivatives **7b**, **7c** and **7j**, Scheme 3). In order to use this procedure, the same compounds were synthesized as racemic mixtures by employing the achiral 2-morpholino-1,3-butadienes.

Table 1. Synthesis of chiral 4-piperidones **4** and **6**.

| Entry | $R^1$ | Ar | $R^2$ | $R^3$ | Prod. | % Yield [a] | % *ee* |
|---|---|---|---|---|---|---|---|
| 1 | TMS | 3-Fu | TMS | H | **4a** | 51 | >98 [b] |
| 2 | Me | 3-Fu | TMS | Me | **4b** | 23 | 86 [b] |
| 3 | MOM | 3-Fu | TMS | MOM | **4c** | 33 | 82 [b] |
| 4 | TBDMS | 3-Fu | TMS | TBDMS | **4d** | 30 | 77 [b] |
| 5 | TMS | *p*-MeOPh | TMS | H | **4e** | 43 | 90 [b] |
| 6 | TBDMS | *p*-MeOPh | TMS | TBDMS | **4f** | 29 | 86 [b] |
| 7 | TMS | Ph | TMS | H | **4g** | 65 | 95 [c] |
| 8 | MOM | Ph | TMS | MOM | **4h** | 35 | 87 [b] |
| 9 | TBDMS | Ph | TMS | TBDMS | **4i** | 28 | 84 [b] |
| 10 | Me | *o*-BrPh | TMS | Me | **4j** | 63 | 86 [b] |
| 11 | TBDMS | *o*-BrPh | TMS | TBDMS | **4k** | 32 | 53 [b] |
| 12 | Me | Ph | Ph | Me | **6** | 45 | 35 [d] |

[a] Isolated yields after column chromatography as a mixture of epimers at C3. [b] Determined by HPLC. [c] Determined by $^1H$ and $^{19}F$ NMR from Mosher's ester. [d] Determined by $^1H$ NMR with $Eu(hfc)_3$ as shift reagent.




Scheme 3. Stereoselective reduction of the carbonyl group of **4b**, **4c**, and **4j**.

$R^1$ seems to have more influence on the enantiomeric excesses of 4-piperidones **4** than expected, given that it is relatively far removed from the reacting atoms and that rotation can occur about the C–O bond. The general sequence of the effect of $R^1$ according to the *ee* found for compounds **4** is as follows: TMS > Me > MOM > TBDMS. The chemical yields range from moderate to good. We conclude that 4-piperidones **4** can be synthesized with a high degree of asymmetric induction by employing **1a** ($R^1$ = TMS) as starting material.

In contrast, the Ar substituents on the aldimines **2** cannot be arranged according to the *ee* of the 4-piperidones **4** obtained, as can be seen, for example, by comparing entries 4 and 6 (3-furyl < *p*-methoxyphenyl , $R^1$ = TBDMS) with entries 1 and 5 (3-furyl > *p*-methoxyphenyl , $R^1$ = TMS).

In agreement with results reported for imino-Diels–Alder reactions of 2-morpholinodienes, the nature of the substitutent at the nitrogen of the imine ($R^2$) plays a crucial role in the stereochemical course of the reaction. Thus, the substituents at C2 and C6 in the 4-piperidone products are in a *cis* relationship when $R^2$ is TMS, and in a *trans* arrangement when $R^2$ is Ph (entry 12). Moreover, for *N*-benzylideneaniline ($R^2$ = Ph) there is a dramatic decrease in the asymmetric induction of the cycloaddition. The likely explanation is the different approach of the imine to the dienophile in the cycloaddition process. Based on the stereochemistry of the products, the first step of the reaction with *N*-silylimines must take place with an *endo* approach of the aromatic ring. However, when the dienophile is *N*-benzylideneaniline there is an *endo* preference of the phenyl group attached to the imine. In this case the chiral auxiliary is far removed from the imine compared with the *N*-silylimines in the initial step of the reaction; this decreases the facial differentiation of the diene, and therefore the asymmetric induction.

**Determination of the absolute configuration**: In order to determine the absolute configuration by the CD dibenzoate chirality method,[14, 15] it was necessary to synthesize the di-*p*-bromobenzoylated derivative **10** (Scheme 4). Thus, treatment of compound **4a** with an excess of *p*-bromobenzoyl chloride in pyridine led to the ester **8**; stereoselective reduction of the ketone group by slow addition of K-Selectride at −80 °C afforded the hydroxyl derivative **9**. Deprotonation of the hydroxyl function was best accomplished with sodium bis(trimethylsilyl)amide in THF, and subsequent addition of *p*-bromobenzoyl chloride furnished the di-*p*-bromobenzoylated derivative **10**.



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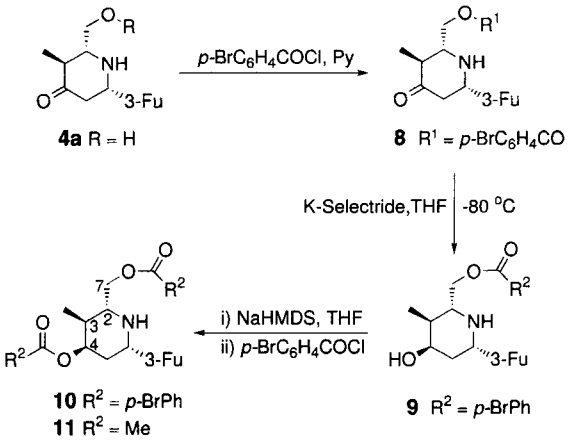



Scheme 4. Synthesis of the derivatives of **4a** required for the determination of the absolute configuration by CD.

In order to deduce the absolute configuration of compound **10** by the CD dibenzoate chirality method, it was necessary to first perform a conformational analysis of the rotamers around the C2–C7 bond to assign the most stable rotamer (Fig. 1). The corresponding analysis was performed by NMR spectroscopy and molecular mechanics (MM) calculations.

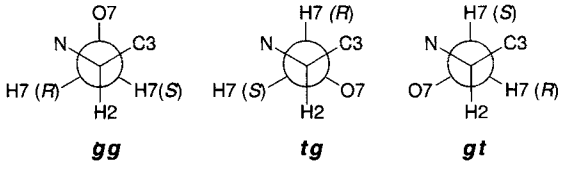



Fig. 1. Rotamers of **10** and **11**.

The $^1$H NMR spectrum ($CDCl_3$, 400 MHz) of the dibenzoate derivative **10** showed for the prochiral protons at C7 ($\delta$ = 4.65 and 4.24) two clearly differentiated doublets of doublets, which allowed their coupling constants with the proton at C2 to be determined, namely, $J$(H2,H7) = 2.8 and 7.7 Hz, respectively. These values and the fact that the corresponding ROESY spectrum exhibited a clear crosspeak between the proton located at $\delta$ = 4.65 and the proton at C2, but not for that at $\delta$ = 4.24, are only consistent with *tg* and *gt* rotamers.

Analysis of molecular models clearly points to the *gt* rotamer as being the most stable. The *gauche* effect stabilizes the *gt* rotamer, and steric interactions between the methyl group at C3 and the C7 *p*-bromobenzoyloxy group destabilizes the *tg* rotamer. Furthermore, the chemical shift of the methyl protons in compound **10** indicated the absence of any anisotropic effect on the methyl group and, therefore, excluded the *tg* rotamer. Moreover, MM calculations[16] on compound **11** (Scheme 4, Table 2) confirmed that the *gt* rotamer was lowest in energy.[17] On the basis of this analysis, the signals in the $^1$H NMR spectrum at $\delta$ = 4.65 and 4.24, corresponding to the prochiral protons at C7, could be assigned as the H7(*R*) and H7(*S*) signals, respectively, since the former is expected to be further downfield.

Table 2. Molecular mechanics data for compound **11**.

| Rotamer | Strain energy, kcal mol$^{-1}$ | Distribution | Dihedral angle O4-C4-C7-O7 |
|---|---|---|---|
| *gt* | 0.00 | 73 | + 61 |
| *gg* | 0.73 | 22 | − 173 |
| *tg* | 1.57 | 5 | − 51 |

The dibenzoate derivative **10** ($\lambda_{max}$ = 245 nm, $\varepsilon$ = 38 200, $CH_3CN$)[18] exhibited only one Cotton effect at the long wavelength of $\lambda_{ext}$ = 249 nm ($\Delta\varepsilon$ = + 9.6) (Fig. 2). On the basis of the bathochromic position of this first Cotton effect, we believe that the second Cotton effect is buried in a strong positive background ellipticity and that the CD spectrum is of the exciton-split type; therefore, application of the dibenzoate chirality rule to the observed positive Cotton effect of compound **10**, in its most stable conformation (*gt*), leads to the absolute configuration shown in Scheme 4.

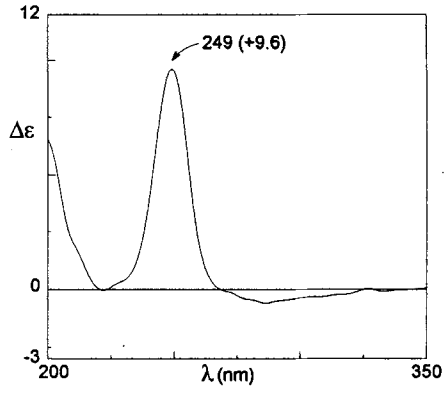
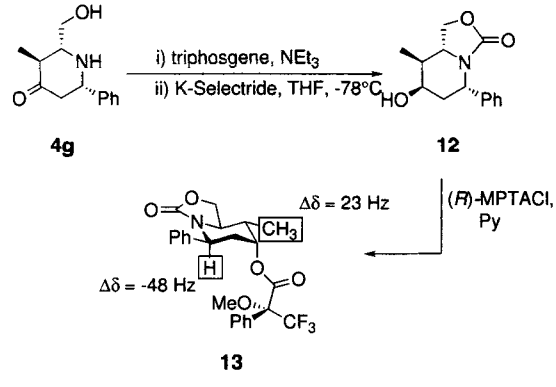



Fig. 2. CD spectrum of compound **10**.

The same absolute configuration was inferred for **4g** by transforming it into the MPTA ester **13** and then using Mosher's method for the determination of absolute configurations of secondary alcohols.[19, 20] Ester **13** was prepared in three steps from piperidone **4g**. The synthetic sequence was carried out with both the racemic and the enantiomerically enriched piperidones (Scheme 5). Treatment of **4g** with triphosgene and $NEt_3$, and




Scheme 5. Synthesis of compound **13**, employed for the determination of the absolute configuration by Mosher's method (the signals of the framed groups are clearly distinguishable in the diastereomeric esters; $\Delta\delta = \delta_{major} - \delta_{minor}$).

diastereoselective reduction of the ketone with K-Selectride at −78 °C gave rise to alcohol **12** as a single diastereoisomer. As expected for Selectride reductions of cyclohexanone derivatives, the stereoisomer bearing the hydroxyl group in the axial position was obtained as shown by $^1$H NMR studies. The resonance for the proton at C4 appears as a multiplet at $\delta$ = 3.88 coupled with H3 and with the two protons at C5. The coupling constants are 2.3, 2.6, and 3.4 Hz, respectively, typical for ax–eq

and eq–eq couplings. Finally, esterification of **12** with (*R*)-MPTACl led to ester **13**.

Comparison of the $^1$H NMR spectra ($CDCl_3$, 300 MHz) of esters **13** obtained from both racemic and enantiomerically enriched **4g** allowed us to determine the differences in chemical shift for certain proton signals between the two diastereoisomers. Clearly separated signals were found for the methyl group and the proton at C6. According to the model proposed by Mosher, the major isomer should be that in which the phenyl ring of the MPTA moiety falls on the same side of the plane defined by the ester as C6, because the resonance for the C6 proton in the major isomer is shifted upfield relative to the corresponding signal in the minor isomer, owing to the shielding effect of the aromatic ring. Moreover, a downfield shift is observed for the resonance of the methyl group in the major isomer; this indicates that it and the phenyl ring of the MPTA moiety must be situated on opposite sides of the plane defined by the ester. These observations point to the same absolute configuration as that deduced by the CD.

## Conclusion

We have described the enantioselective preparation of 4-piperidones by [4+2] cycloaddition reaction of nonactivated imines with chiral 2-amino-1,3-butadienes in the presence of a Lewis acid as catalyst. The chiral auxiliary is readily cleaved during the workup of the reaction, and 4-piperidones **4** are directly obtained with very high enantiomeric excesses. Furthermore, the commercial availability of both enantiomers of the chiral auxiliary would allow the piperidones to be obtained in either enantiomeric form. Investigations aimed at elucidating the mechanism and the origin of the high diastereoselectivity of the reaction are currently in progress; we are also exploring some synthetic applications of these cycloadducts.

## Experimental Section

**General:** Melting points are uncorrected. $^1$H NMR spectra were recorded at 200, 300, or 400 MHz, and $^{13}$C NMR spectra at 50.3, 75, or 100.6 MHz, in $CDCl_3$ at room temperature (RT); chemical shift values are given in ppm relative to the residual solvent peak ($\delta$), and coupling constants in Hz. Specific optical rotation values were measured on a Perkin–Elmer 241 polarimeter. To determine enantiomeric excesses by HPLC, a CHIRALCEL OD-H column was used (25 cm × 0.46 cm i.d., Daicel Chemical Industries), at RT with hexane/ethanol or hexane/isopropanol as the mobile phases (0.8 mL min$^{-1}$) and a Shimadzu photodiode array UV–VIS detector; the racemic compounds were used to choose the operating conditions for the resolution of the enantiomer peaks. Electron impact (EI) mass spectra were determined on a Finnigan Mat-95 Mass Spectrometer. Elemental analysis were carried out with a Perkin–Elmer 240 B microanalyzer.

**Materials:** All catalytic aminomercuriation, cycloaddition, carbonyl group reduction and esterification reactions were run under $N_2$ atmosphere. Commercial (*S*)-(+)-2-methoxymethylpyrrolidine, $ZnCl_2$ 1 M ethereal solution, and K-Selectride 1 M THF solution were purchased from Aldrich. *n*-Hexane, THF, and $Et_2O$ were dried and distilled from sodium benzophenone before use. Pyridine was refluxed over NaOH, distilled, and stored under $N_2$. $Hg(OAc)_2$ was heated at 100 °C at 0.1 mm Hg for 6 h and kept under $N_2$. 4-Bromobenzoyl chloride was distilled at reduced pressure (0.1 mm Hg) prior to use. (*S*)-(+)-2-methoxymethylpyrrolidine was heated at 80 °C with sodium for 10 h, condensed from trap to trap at 0.1 mm Hg, and kept under $N_2$. 3-Alken-1-ynes employed to synthesize chiral 2-amino-1,3-butadienes **1** were obtained by protecting the hydroxyl function of the commercially available 3-methyl-2-penten-4-yn-1-ol, following the general procedures described in the literature [21]. *N*-Trimethylsilylaldimines were obtained following the synthetic procedure developed by Colvin et al. [22]; *N*-benzylideneaniline was prepared by refluxing in toluene a mixture of benzaldehyde and aniline in presence of a catalytic amount of *p*-toluenesulfonic acid in a system equipped with a Dean–Stark trap. All other reagents were of the best commercial grade available and used without further purification. The organic layers were dried with anhydrous $Na_2SO_4$. Column chromatography was carried out on silica gel 60 (40–60 μm).

**General preparative procedure for chiral 2-amino-1,3-butadienes 1:** To a suspension of dry $Hg(OAc)_2$ (26.3 mmol, 8.4 g) in dry $Et_2O$ (150 mL) at room temperature was added the freshly distilled 3-alken-1-yne (35 mmol) under $N_2$. To the clear solution, dry (*S*)-(+)-2-methoxymethylpyrrolidine (105 mmol, 13.0 mL) was added. The mixture was stirred overnight at room temperature. Afterwards, the reaction mixture was filtered under $N_2$ and concentrated under reduced pressure. The resulting oil was extracted once with dry *n*-hexane (150 mL), and the organic solution was kept at −20 °C for 10 h. The clear solution was transferred to another schlenk flask, to eliminate the oil formed at low temperature, and concentrated in vacuo. The resulting chiral diene was purified by distillation at high vacuum ($10^{-3}$ mbar).

**(*E*)-*N*-(2-Methyl-1-methylene-4-trimethylsilyloxy-2-butenyl)-2-(*S*)-methoxymethylpyrrolidine (1a)**: 3-Methyl-5-trimethylsilyloxy-3-penten-1-yne (5.9 g) was employed. Yield 60% (6.0 g). Yellow oil; b.p. 92–96 °C ($10^{-3}$ mbar); $[\alpha]_{589}^{20} = +58.1$ ($c = 2.4$ in $CH_2Cl_2$); for spectroscopic data, see reference [12].

**(*E*)-*N*-(2-Methyl-1-methylene-4-methoxy-2-butenyl)-2-(*S*)-methoxymethylpyrrolidine (1b)**: 5-Methoxy-3-methyl-3-penten-1-yne (3.9 g) was employed. Yield 67% (5.3 g). Yellowish oil; b.p. 82–88 °C ($10^{-3}$ mbar); $[\alpha]_{589}^{20} = +91.8$ ($c = 2.4$ in $CH_2Cl_2$); for spectroscopic data, see reference [12].

**(*E*)-*N*-(2-Methyl-1-methylene-4-methoxymethoxy-2-butenyl)-2-(*S*)-methoxymethylpyrrolidine (1c)**: 5-Methoxymethoxy-3-methyl-3-penten-1-yne (4.9 g) was employed. Yield 57% (5.1 g). Yellowish oil; b.p. 102–103 °C ($10^{-3}$ mbar); $[\alpha]_{589}^{20} = +129.3$ ($c = 3.7$ in $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$, RT, $CHCl_3$): $\delta = 5.57$ (t, $^3J$(H,H) = 6.9 Hz, 1H; =CH), 4.50 (s, 2H; $OCH_2O$), 4.01 (d, $^3J$(H,H) = 6.9 Hz, 2H; =CHC$H_2$), 3.71 (s, 1H; =C$H_2$), 3.54 (s, 1H; =C$H_2$), 3.47–2.78 (m, 5H; pyrrolidine), 3.27 (s, 3H; $OCH_3$), 3.18 (s, 3H; $OCH_3$), 1.92–1.65 (m, 4H; pyrrolidine), 1.70 (s, 3H; =$CCH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$, RT, $CDCl_3$): $\delta$ = 155.0 (=CN), 138.7 (=CMe), 124.3 (=CH), 95.1 ($OCH_2O$), 83.3 (=$CH_2$), 73.0 ($CH_2OMe$), 63.1 (=CH$CH_2O$), 58.5 ($OCH_3$), 56.6 (CHN), 54.7 ($OCH_3$), 48.8 ($CH_2$), 28.5 ($CH_2$), 23.0 ($CH_2$), 16.2 (=$CCH_3$).

**(*E*)-*N*-[2-Methyl-1-methylene-4-(*tert*-butyldimethylsilyl)oxy-2-butenyl]-2-(*S*)-methoxymethylpyrrolidine (1d)**: 5-(*tert*-Butyldimethylsilyl)oxy-3-methyl-3-penten-1-yne (7.4 g) was employed. Yield 45% (5.1 g). Yellow oil; b.p. 94–97 °C ($10^{-4}$ mbar); $[\alpha]_{589}^{20} = +86.5$ ($c = 0.7$ in $CH_2Cl_2$); $^1$H NMR (200 MHz, $CDCl_3$, RT, $CHCl_3$): $\delta = 5.59$ (t, $^3J$(H,H) = 6.0 Hz, 1H; =CH), 4.16 (d, $^3J$(H,H) = 6.0 Hz, 2H; $CH_2OSi$), 3.72 (s, 1H; =C$H_2$), 3.55 (s, 1H; =C$H_2$), 3.57–2.77 (m, 5H; pyrrolidine), 3.21 (s, 3H; $OCH_3$), 1.97–1.65 (m, 4H; $CH_2$), 1.68 (s, 3H; =$CCH_3$), 0.82 [s, 9H; $C(CH_3)_3$], −0.01 [s, 6H; $Si(CH_3)_2$]; $^{13}$C NMR (50.3 MHz, $CDCl_3$, RT, $CDCl_3$): $\delta$ = 155.3 (=CN), 135.4 (=CMe), 128.5 (=CH), 83.2 (=$CH_2$), 73.1 ($CH_2OMe$), 60.0 ($CH_2OSi$), 58.6 ($CH_3O$), 56.7 (CHN), 48.8 ($CH_2$), 28.6 ($CH_2$), 25.7 [$SiC(CH_3)_3$], 23.1 ($CH_2$), 18.0 [$SiC(CH_3)_3$], 16.3 ($CH_3C$), −4.6 [$Si(CH_3)_2$]; HREIMS calculated for $C_{18}H_{35}NO_2Si$ 325.243708; found 325.243042.

**General preparative procedure for 4-piperidones 4 and 6:** To a solution of a chiral diene **1** (1.5 mmol) in dry THF (30 mL) at RT was added a solution of $ZnCl_2$ in diethyl ether (1 M, 3 mL, 3.0 mmol). The mixture was stirred for 10 min at this temperature and then cooled to −80 °C. A solution of the imine **2** (3.0 mmol) in dry THF (10 mL) was added dropwise. The reation mixture was stirred at this temperature for 8 h before it was allowed to reach room temperature (over 8 h). The reaction was quenched with 5 mL of saturated aqueous $NaHCO_3$ and 15 mL of ethyl acetate (EtOAc). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (2 × 10 mL), dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The resulting crude product was separated by column chromatography ($SiO_2$, hexane/EtOAc), unless $R^1$ = TMS in the chiral diene **1**. In these cases, the crude product was treated at this stage with anhydrous $Na_2CO_3$ (100 mg) in MeOH (8 mL) for 6 h; the solvent was removed under reduced presure, and $H_2O$ (10 mL) and EtOAc (10 mL) were added to the solid obtained. The basic aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous $Na_2SO_4$, and concentrated in vacuo. The desilylated 4-piperidone obtained was then purified by column chromatography ($CH_2Cl_2$/EtOAc).

**(2*R*,3*S*,6*S*)-6-(3-Furyl)-2-hydroxymethyl-3-methyl-4-piperidone (4a)**: The reaction was performed as described in the general procedure with **1a** (425 mg) and *N*-trimethylsilyl-3-furylaldimine (502 mg). After extractive workup, the crude product was treated with $Na_2CO_3$ in MeOH to complete desilylation and epimerization, to yield, after silica gel chromatography ($CH_2Cl_2$/EtOAc 4:1), 160 mg (51%) of 4-piperidone **4a**. Yellowish oil; $R_f = 0.14$ ($SiO_2$, $CH_2Cl_2$/EtOAc 1:1); $[\alpha]_{589}^{20} = -54.2$ ($c = 0.8$ in $CH_2Cl_2$); *ee* > 98% (by HPLC, hexane/isopropanol 8:1, $t_{R\,major} = 15.5$ min, $t_{R\,minor} = 19.9$ min); $^1$H NMR (200 MHz, $CDCl_3$, RT, $CHCl_3$): $\delta = 7.38–7.36$ (m, 2H; 3-furyl), 6.42–6.41 (m, 1H; 3-furyl), 3.96 (dd, $^3J$(H,H) = 10.5 Hz, $^3J$(H,H) = 4.5 Hz, 1H; CHAr), 3.82 (dd, $^2J$(H,H) = 11.1 Hz, $^3J$(H,H) = 2.8 Hz, 1H; $CH_2O$), 3.62 (dd, $^2J$(H,H) = 11.1 Hz, $^3J$(H,H) = 6.3 Hz, 1H; $CH_2O$), 2.72 (ddd, $^3J$(H,H) = 10.7 Hz, $^3J$(H,H) = 6.3 Hz, $^3J$(H,H) = 2.8 Hz, 1H; C$HCH_2O$), 2.56 (t, $^2J$(H,H) = 10.5 Hz, $^3J$(H,H) = 10.5 Hz, 1H; C$H_2$CHAr ax.), 2.52 (dd, $^2J$(H,H) = 10.5 Hz, $^3J$(H,H) = 4.5 Hz, 1H; C$H_2$CHAr eq.), 2.40 (d, $^3J$(H,H) = 10.7 Hz, $^3J$(H,H) = 6.7 Hz, 1H; CHMe), 1.01 (d, $^3J$(H,H) = 6.7 Hz,



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3H; $CH_3$); $^{13}C$ NMR (50.3 MHz, $CDCl_3$, RT, $CDCl_3$): $\delta$ = 209.5 (CO); 143.3 (3-furyl); 138.7 (3-furyl); 126.8 (3-furyl); 108.5 (3-furyl); 63.5 ($CH_2OH$); 63.4 (CHN); 52.4 (CHN); 48.6 ($CH_2CO$); 46.3 (CHMe); 9.4 ($CH_3$); HREIMS calculated for $C_{11}H_{15}NO_3$ 209.105193; found 209.104379.

**(2*R*,3*S*,6*S*)-6-(3-Furyl)-2-(methoxy)methyl-3-methyl-4-piperidone (4b)**: Pyrrolidine **1b** (338 mg) was treated with *N*-trimethylsilyl-3-furylaldimine (502 mg); the resulting crude product was purified by silica gel chromatography (hexane/EtOAc 4:1) to yield 77 mg (23%) as a mixture of epimers, 60 mg (18%) of 4-piperidone **4b**. Yellowish oil; $R_f$ = 0.31 ($SiO_2$, hexane/EtOAc 1:1); $[\alpha]_{589}^{20}$ = −75.3 (*c* = 0.6 in $CH_2Cl_2$); *ee* = 86% (determined by HPLC on derivative **7b**); $^1H$ NMR (200 MHz, $CDCl_3$, RT, $CHCl_3$): $\delta$ = 7.38–7.37 (m, 2H; 3-furyl), 6.43–6.41 (m, 1H; 3-furyl), 3.94 (dd, $^3J$(H,H) = 10.5 Hz, $^3J$(H,H) = 4.5 Hz, 1H; CHAr), 3.60 (dd, $^2J$(H,H) = 9.2 Hz, $^3J$(H,H) = 2.9 Hz, 1H; $CH_2O$), 3.43 (dd, $^2J$(H,H) = 9.2 Hz, $^3J$(H,H) = 7.3 Hz, 1H; $CH_2O$), 3.37 (s, 3H; $OCH_3$), 2.79 (ddd, $^3J$(H,H) = 10.5 Hz, $^3J$(H,H) = 7.3 Hz, $^3J$(H,H) = 2.9 Hz, 1H; $CHCH_2O$), 2.65–2.50 (m, 2H; $CH_2CHAr$), 2.36 (d, $^3J$(H,H) = 10.5 Hz, $^3J$(H,H) = 6.7 Hz, 1H; CHMe), 1.03 (d, $^3J$(H,H) = 6.7 Hz, 3H; $CH_3CH$); $^{13}C$ NMR (50.3 MHz, $CDCl_3$, RT, $CDCl_3$): $\delta$ = 209.4 (CO), 143.3 (3-furyl), 138.7 (3-furyl), 127.2 (3-furyl), 108.6 (3-furyl), 74.2 ($CH_2OMe$), 62.0 ($OCH_3$), 59.1 (CHN), 52.5 (CHN), 49.2 ($CH_2CO$), 47.0 (CHMe), 9.6 ($CH_3CH$); HREIMS calculated for $C_{12}H_{17}NO_3$ 223.120843, found 223.119844.

**(2*R*,3*S*,6*S*)-6-(3-Furyl)-2-methoxymethoxymethyl-3-methyl-4-piperidone (4c)**: Pyrrolidine **1c** (383 mg) was treated with *N*-trimethylsilyl-3-furylaldimine (502 mg); the resulting crude product was purified by silica gel chromatography (hexane/EtOAc 5:1) to yield 125 mg (33%) as a mixture of epimers, 99 mg (26%) of 4-piperidone **4c**. Yellowish oil; $R_f$ = 0.23 ($SiO_2$, hexane/EtOAc 2:1); $[\alpha]_{589}^{20}$ = −5.3 (*c* = 0.6 in $CH_2Cl_2$); *ee* = 82% (determined by HPLC on derivative **7c**); $^1H$ NMR (200 MHz, $CDCl_3$, RT, $CHCl_3$): $\delta$ = 7.35–7.33 (m, 2H; 3-furyl), 6.39–6.38 (m, 1H; 3-fuyl), 4.59 (s, 2H; $OCH_2O$), 3.91 (dd, $^3J$(H,H) = 10.7 Hz, $^3J$(H,H) = 4.3 Hz, 1H; CHAr), 3.73 (dd, $^2J$(H,H) = 9.7 Hz, $^3J$(H,H) = 2.7 Hz, 1H; $CH_2O$), 3.56 (dd, $^2J$(H,H) = 9.7 Hz, $^3J$(H,H) = 7.2 Hz, 1H; $CH_2O$), 3.30 (s, 3H; $OCH_3$), 2.77 (ddd, $^3J$(H,H) = 10.5 Hz, $^3J$(H,H) = 7.2 Hz, $^3J$(H,H) = 2.7 Hz, 1H; $CHCH_2O$), 2.61–2.44 (m, 2H; $CH_2CHAr$), 2.35 (d, $^3J$(H,H) = 10.5 Hz, $^3J$(H,H) = 6.4 Hz, 1H; CHMe), 0.99 (d, $^3J$(H,H) = 6.4 Hz, 3H; $CH_3CH$); $^{13}C$ NMR (75 MHz, $CDCl_3$, RT, $CDCl_3$): $\delta$ = 208.6 (CO), 142.8 (3-furyl), 138.3 (3-furyl), 126.9 (3-furyl), 108.3 (3-furyl), 96.1 ($OCH_2O$), 68.8 ($CHCH_2O$), 61.5 ($OCH_3$), 54.8 (CHN), 52.1 (CHN), 48.7 ($CH_2CO$), 46.4 (CHMe), 9.2 ($CH_3CH$); HREIMS calculated for $C_{13}H_{19}NO_4$ 253.131408; found 253.132239.

**(2*R*,3*S*,6*S*)-2-(*tert*-Butyldimethylsilyloxy)methyl-6-(3-furyl)-3-methyl-4-piperidone (4d)**: Pyrrolidine **1d** (488 mg) was treated with *N*-trimethylsilyl-3-furylaldimine (502 mg); the resulting crude product was purified by silica gel chromatography (hexane/EtOAc 10:1) to yield 140 mg (30%) as a mixture of epimers, 87 mg (18%) of 4-piperidone **4d**. Yellowish oil; $R_f$ = 0.39 ($SiO_2$, hexane/EtOAc 4:1); $[\alpha]_{589}^{20}$ = −32.3 (*c* = 0.5 in $CHCl_3$); *ee* = 77% (determined by HPLC on the desilylated derivative, see product **4a** for the conditions used); $^1H$ NMR (300 MHz, $CDCl_3$, RT, $CHCl_3$): $\delta$ = 7.39–7.38 (m, 2H; 3-furyl), 6.40-6.39 (m, 1H; 3-furyl), 3.96 (dd, $^3J$(H,H) = 11.6 Hz, $^3J$(H,H) = 3.0 Hz, 1H; CHAr), 3.87 (dd, $^2J$(H,H) = 9.9 Hz, $^3J$(H,H) = 3.0 Hz, 1H; $CH_2O$), 3.65 (dd, $^2J$(H,H) = 9.9 Hz, $^3J$(H,H) = 6.9 Hz, 1H; $CH_2O$), 2.70 (ddd, $^3J$(H,H) = 10.3 Hz, $^3J$(H,H) = 6.9 Hz, $^3J$(H,H) = 3.0 Hz, 1H; $CHCH_2O$), 2.62 (dd, $^2J$(H,H) = 13.3 Hz, $^3J$(H,H) = 3.0 Hz, 1H; $CH_2CO$ eq.), 2.46 (ddd, $^2J$(H,H) = 13.3 Hz, $^3J$(H,H) = 11.6 Hz, $^4J$(H,H) = 1.3 Hz, 1H; $CH_2CO$ ax.), 2.41–2.25 (m, 1H; CHMe), 1.03 (d, $^3J$(H,H) = 6.2 Hz, 3H; $CH_3CH$), 0.89 [s, 9H; $(CH_3)_3C$], 0.08 [s, 6H; $(CH_3)_2Si$]; $^{13}C$ NMR (75 Hz, $CDCl_3$, RT, $CDCl_3$): $\delta$ = 209.8 (CO), 143.3 (3-furyl), 138.4 (3-furyl), 127.5 (3-furyl), 108.5 (3-furyl), 64.7 ($CH_2O$), 63.7 (CHN), 52.6 (CHN), 49.4 ($CH_2CO$), 46.8 (CHMe), 25.8 [$(CH_3)_3C$], 18.2 [$C(CH_3)_3$], 9.5 ($CH_3CH$), −5.5 [$(CH_3)_2Si$]; HREIMS calculated for $C_{17}H_{29}NSiO_3$ 323.191673; found 323.192144.

**(2*R*,3*S*,6*S*)-2-Hydroxymethyl-6-(*p*-methoxyphenyl)-3-methyl-4-piperidone (4e)**: Pyrrolidine **1a** (425 mg) was treated with *N*-trimethylsilyl-*p*-methoxyphenylaldimine (623 mg). After extractive workup, the crude product was treated with $Na_2CO_3$ in MeOH to complete desilylation and epimerization, to yield, after silica gel chromatography ($CH_2Cl_2$/EtOAc 3:1), 161 mg (43%) of 4-piperidone **4e**. Yellowish oil; $R_f$ = 0.27 ($SiO_2$, $CH_2Cl_2$/EtOAc 1:1); $[\alpha]_{589}^{20}$ = −76.6 (*c* = 2.3 in $CH_2Cl_2$); *ee* = 90% (by HPLC, hexane/ethanol 5:1, $t_{Rmajor}$ = 11.0 min, $t_{Rminor}$ = 15.1 min); $^1H$ NMR (200 MHz, $CDCl_3$, RT, $CHCl_3$): $\delta$ = 7.20 (d, $^3J$(H,H) = 8.6 Hz, 2H; $C_6H_4OMe$), 6.78 (d, $^3J$(H,H) = 8.6 Hz, 2H; $C_6H_4OMe$), 3.83 (dd, $^3J$(H,H) = 10.2 Hz, $^3J$(H,H) = 4.8 Hz, 1H; CHAr), 3.72 (dd, $^2J$(H,H) = 11.1 Hz, $^3J$(H,H) = 2.9 Hz, 1H; $CH_2O$), 3.70 (s, 3H; $CH_3O$), 3.54 (dd, $^2J$(H,H) = 11.1 Hz, $^3J$(H,H) = 6.0 Hz, 1H; $CH_2O$), 2.83–2.70 (m, 1H; $CHCH_2O$), 2.67–2.39 (m, 3H; $CH_2CHAr$ and CHMe), 0.95 (d, $^3J$(H,H) = 6.4 Hz, 3H; $CH_3CH$); $^{13}C$ NMR (75 Hz, $CDCl_3$, RT, $CDCl_3$): $\delta$ = 209.9 (CO), 159.1 ($C_6H_4OMe$), 134.1 ($C_6H_4OMe$), 127.5 ($C_6H_4OMe$), 113.9 ($C_6H_4OMe$), 63.8 ($CH_2OH$), 63.6 ($CH_3O$), 60.2 (CHN), 55.2 (CHN), 49.8 ($CH_2CO$), 46.1 (CHMe), 9.5 ($CH_3CH$); HREIMS calculated for $C_{14}H_{19}NO_3$ 249.136493, found 249.136607.

**(2*R*,3*S*,6*S*)-2-(*tert*-Butyldimethylsilyloxy)methyl-6-(*p*-methoxyphenyl)-3-methyl-4-piperidone (4f)**: Pyrrolidine **1d** (488 mg) was treated with *N*-trimethylsilyl-*p*-methoxyphenylaldimine (623 mg); the resulting crude product was purified by silica gel chromatography (hexane/EtOAc 8:1) to yield 158 mg (29%) as a mixture of epimers, 125 mg (23%) of 4-piperidone **4f**. Yellowish oil; $R_f$ = 0.34 ($SiO_2$, hexane/EtOAc 4:1); $[\alpha]_{589}^{20}$ = −76.6 (*c* = 1.1 in $CH_2Cl_2$); *ee* = 84% (determined by HPLC on the desilylated derivative, see product **4e** for the conditions used); $^1H$ NMR (200 MHz, $CDCl_3$, RT, $CHCl_3$): $\delta$ = 7.31 (d, $^3J$(H,H) = 8.6 Hz, 2H; $C_6H_4OMe$), 6.89 (d, $^3J$(H,H) = 8.6 Hz, 2H; $C_6H_4OMe$), 3.93 (dd, $^2J$(H,H) = 9.8 Hz, $^3J$(H,H) = 5.1 Hz, 1H; $CH_2O$), 3.88 (dd, $^3J$(H,H) = 7.0 Hz, $^3J$(H,H) = 2.9 Hz, 1H; CHAr), 3.80 (s, 3H; $CH_3O$), 3.65 (dd, $^2J$(H,H) = 9.8 Hz, $^3J$(H,H) = 7.6 Hz, 1H; $CH_2O$), 2.74 (ddd, $^3J$(H,H) = 10.5 Hz, $^3J$(H,H) = 7.6 Hz, $^3J$(H,H) = 2.9 Hz, 1H; $CHCH_2O$), 2.60–2.49 (m, 2H; $CH_2CO$), 2.35 (d, $^3J$(H,H) = 10.5 Hz, $^3J$(H,H) = 6.7 Hz, 1H; CHMe), 1.04 (d, $^3J$(H,H) = 6.7 Hz, 3H; $CH_3CH$), 0.88 [s, 9H; $(CH_3)_3C$], 0.10 [s, 6H; $(CH_3)_2Si$]; $^{13}C$ NMR (50.3 MHz, $CDCl_3$, RT, $CDCl_3$): $\delta$ = 210.0 (CO), 158.8 ($C_6H_4OMe$), 134.8 ($C_6H_4OMe$), 127.1 ($C_6H_4OMe$), 113.8 ($C_6H_4OMe$), 65.1 ($CH_2O$), 63.8 ($CH_3O$), 60.0 (CHN), 55.0 (CHN), 50.5 ($CH_2CO$), 46.6 (CHMe), 25.7 [$(CH_3)_3C$], 18.1 [$C(CH_3)_3$], 9.4 ($CH_3CH$), −5.4 [$(CH_3)_2Si$]; HREIMS calculated for $C_{20}H_{33}NSiO_3$ 363.222973; found 363.223715.

**(2*R*,3*S*,6*S*)-2-Hydroxymethyl-3-methyl-6-phenyl-4-piperidone (4g)**: Pyrrolidine **1a** (425 mg) was treated with *N*-trimethylsilylbenzaldimine (532 mg); after extractive workup, the crude product was treated with $Na_2CO_3$ in MeOH to complete desilylation and epimerization, to yield after silica gel chromatography ($CH_2Cl_2$/EtOAc 4:1) 214 mg (65%) of 4-piperidone **4g**. $[\alpha]_D^{20}$ = −78.0 (*c* = 6.0 in $CHCl_3$); *ee* = 95% (determined by NMR over Mosher's derivative, see product **13**); for spectroscopic data, see reference [10].

**(2*R*,3*S*,6*S*)-2-Methoxymethoxymethyl-3-methyl-6-phenyl-4-piperidone (4h)**: Pyrrolidine **1c** (383 mg) was treated with *N*-trimethylsilylbenzaldimine (532 mg); the resulting crude product was purified by silica gel chromatography (hexane/EtOAc 5:1) to yield 138 mg (35%) as a mixture of epimers, 107 mg (27%) of 4-piperidone **4h**. Yellowish oil; $R_f$ = 0.34 ($SiO_2$, hexane/EtOAc 2:1); $[\alpha]_{589}^{20}$ = −92.9 (*c* = 1.3 in $CH_2Cl_2$); *ee* = 87% (by HPLC, hexane/ethanol 350:1, $t_{Rmajor}$ = 34.2 min, $t_{Rminor}$ = 32.2 min); $^1H$ NMR (200 MHz, $CDCl_3$, RT, $CHCl_3$): $\delta$ = 7.40–7.26 (m, 5H; $C_6H_5$), 4.64 (s, 2H; $OCH_2O$), 4.04 (dd, $^3J$(H,H) = 11.8 Hz, $^3J$(H,H) = 3.5 Hz, 1H; CHAr), 3.81 (dd, $^2J$(H,H) = 10.1 Hz, $^3J$(H,H) = 2.9 Hz, 1H; $CH_2O$), 3.65 (dd, $^2J$(H,H) = 10.1 Hz, $^3J$(H,H) = 7.5 Hz, 1H; $CH_2O$), 3.35 (s, 3H; $OCH_3$), 2.96 (ddd, $^3J$(H,H) = 10.5 Hz, $^3J$(H,H) = 7.5 Hz, $^3J$(H,H) = 2.9 Hz, 1H; $CHCH_2O$), 2.70 (ddd, $^2J$(H,H) = 13.7 Hz, $^3J$(H,H) = 11.8 Hz, $^4J$(H,H) = 1.0 Hz, 1H; $CH_2CHAr$ ax.), 2.59 (dd, $^2J$(H,H) = 13.7 Hz, $^3J$(H,H) = 3.5 Hz, 1H; $CH_2CHAr$ eq.), 2.62–2.45 (m, 1H; CHMe), 1.08 (d, $^3J$(H,H) = 6.6 Hz, 3H; $CH_3CH$); $^{13}C$ NMR (75 Hz, $CDCl_3$, RT, $CDCl_3$): $\delta$ = 209.3 (CO), 142.3 ($C_6H_5$), 128.5 ($C_6H_5$), 127.6 ($C_6H_5$), 126.3 ($C_6H_5$), 96.4 ($OCH_2O$), 69.5 ($CHCH_2O$), 62.0 ($OCH_3$), 60.7 (CHN), 55.2 (CHN), 50.2 ($CH_2CO$), 46.8 (CHMe), 9.5 ($CH_3CH$); HREIMS calculated for $C_{15}H_{21}NO_3$ 263.152143, found 263.152143.

**(2*R*,3*S*,6*S*)-2-(*tert*-Butyldimethylsilyloxy)methyl-3-methyl-6-phenyl-4-piperidone (4i)**: Pyrrolidine **1d** (488 mg) was treated with *N*-trimethylsilylbenzaldimine (532 mg); the resulting crude product was purified by silica gel chromatography (hexane/EtOAc 15:1) to yield 140 mg (28%) as a mixture of epimers, 110 mg (22%) of 4-piperidone **4i**. Yellowish oil; $R_f$ = 0.53 ($SiO_2$, hexane/EtOAc 4:1); $[\alpha]_{589}^{20}$ = −62.4 (*c* = 0.4 in $CH_2Cl_2$); *ee* = 84% (determined by HPLC on the desilylated derivative, hexane/isopropanol 4:1, $t_{Rmajor}$ = 20.5 min, $t_{Rminor}$ = 28.2 min); $^1H$ NMR (200 MHz, $CDCl_3$, RT, $CHCl_3$): $\delta$ = 7.44–7.27 (m, 5H; Ph), 4.01 (dd, $^3J$(H,H) = 10.4 Hz, $^3J$(H,H) = 4.1 Hz, 1H; CHAr), 3.93 (dd, $^2J$(H,H) = 9.9 Hz, $^3J$(H,H) = 2.5 Hz, 1H; $CH_2O$), 3.70 (dd, $^2J$(H,H) = 9.9 Hz, $^3J$(H,H) = 7.7 Hz, 1H; $CH_2O$), 2.79 (ddd, $^3J$(H,H) = 10.3 Hz, $^3J$(H,H) = 7.7 Hz, $^3J$(H,H) = 2.5 Hz, 1H; $CHCH_2O$), 2.67–2.47 (m, 2H; $CH_2CO$), 2.39 (d, $^3J$(H,H) = 10.3 Hz, $^3J$(H,H) = 6.4 Hz, 1H; CHMe), 1.08 (d, $^3J$(H,H) = 6.4 Hz, 3H; $CH_3CH$), 0.91 [s, 9H; $(CH_3)_3C$], 0.10 [s, 6H; $(CH_3)_2Si$]; $^{13}C$ NMR (50.3 MHz, $CDCl_3$, RT, $CDCl_3$): $\delta$ = 209.8 (CO), 142.6 (Ph), 128.5 (Ph), 127.5 (Ph), 126.0 (Ph), 65.2 ($CH_2O$), 63.8 (CHN), 60.5 (CHN), 50.5 ($CH_2CO$), 46.7 (CHMe), 25.7 [$(CH_3)_3C$], 18.1 [$C(CH_3)_3$], 9.5 ($CH_3CH$), −5.4 [$(CH_3)_2Si$]; HREIMS calculated for $C_{19}H_{31}NSiO_2$ 333.212408; found 333.213336.

**(2*R*,3*S*,6*S*)-6-(*o*-Bromophenyl)-2-methoxymethyl-3-methyl-4-piperidone (4j)**: Pyrrolidine **1b** (338 mg) was treated with *N*-trimethylsilyl-*o*-bromophenylaldimine (769 mg); the resulting crude product was purified by silica gel chromatography (hexane/EtOAc 8:1) to yield 295 mg (63%) of 4-piperidone **4j**. $[\alpha]_D^{20}$ = −77.0 (*c* = 3.0 in $CHCl_3$); *ee* = 86% (determined by HPLC on derivative **7j**); for spectroscopic data, see reference [10].

**(2*R*,3*S*,6*S*)-6-(*o*-Bromophenyl)-2-(*tert*-butyldimethylsilyloxy)methyl-3-methyl-4-piperidone (4k)**: Pyrrolidine **1d** (488 mg) was treated with *N*-trimethylsilyl-*o*-bromophenylaldimine (769 mg); the resulting crude product was purified by silica gel chromatography (hexane/EtOAc 15:1) to yield 198 mg (32%) as a mixture of epimers, 136 mg (22%) of 4-piperidone **4k**. Yellowish oil; $R_f$ = 0.38 ($SiO_2$, hexane/EtOAc 8:1); $[\alpha]_{589}^{20}$ = −70.1 (*c* = 1.1 in $CH_2Cl_2$); *ee* = 53% (by HPLC, hexane/ethanol 350:1, $t_{Rmajor}$ = 8.2 min, $t_{Rminor}$ = 9.7 min); $^1H$ NMR (200 MHz, $CDCl_3$, RT, $CHCl_3$): $\delta$ = 7.61 (dd, $^3J$(H,H) = 7.9 Hz, $^4J$(H,H) = 1.6 Hz, 1H; $C_6H_4$), 7.55 (dd, $^3J$(H,H) = 7.9 Hz, $^4J$(H,H) = 1.3 Hz, 1H; $C_6H_4$), 7.35 (ddd, $^3J$(H,H) = 7.9 Hz, $^3J$(H,H) = 7.3 Hz, $^4J$(H,H) = 1.3 Hz, 1H; $C_6H_4$), 7.14 (ddd, $^3J$(H,H) = 7.9 Hz, $^3J$(H,H) = 7.3 Hz, $^4J$(H,H) = 1.6 Hz, 1H; $C_6H_4$), 4.35 (dd, $^3J$(H,H) = 11.8 Hz,

$^3J$(H,H) = 2.9 Hz, 1H; CHAr), 3.90 (dd, $^2J$(H,H) = 9.9 Hz, $^3J$(H,H) = 2.9 Hz, 1H; $CH_2O$), 3.64 (dd, $^2J$(H,H) = 9.9 Hz, $^3J$(H,H) = 8.0 Hz, 1H; $CH_2O$), 2.82 (ddd, $^3J$(H,H) = 10.8 Hz, $^3J$(H,H) = 8.0 Hz, $^3J$(H,H) = 2.9 Hz, 1H; $CHCH_2O$), 2.72 (dd, $^2J$(H,H) = 13.3 Hz, $^3J$(H,H) = 2.9 Hz, 1H; $CH_2CO$ eq.), 2.43 (ddd, $^2J$(H,H) = 13.3 Hz, $^3J$(H,H) = 11.9 Hz, $^4J$(H,H) = 1.0 Hz, 1H; $CH_2CO$ ax.), 2.40–2.23 (m, 1H; CHMe), 1.06 (d, $^3J$(H,H) = 6.6 Hz, 3H; $CH_3CH$), 0.89 [s, 9H; $(CH_3)_3C$], 0.08 [s, 6H; $(CH_3)_2Si$]; $^{13}C$ NMR (50.3 Hz, $CDCl_3$, RT, $CDCl_3$): $\delta$ = 208.3 (CO), 141.0 ($C_6H_4$), 132.6 ($C_6H_4$), 128.6 ($C_6H_4$), 127.7 ($C_6H_4$), 127.1 ($C_6H_4$), 122.6 ($C_6H_4$), 65.2 ($CH_2O$), 63.3 (CHN), 58.6 (CHN), 47.7 ($CH_2CO$), 46.4 (CHMe), 25.6 [$(CH_3)_3C$], 18.0 [$C(CH_3)_3$], 9.3 ($CH_3CH$), −5.5 [$(CH_3)_2Si$]; HREIMS calculated for $C_{19}H_{30}BrNO_2Si$ 411.122931; found 411.122388.

**(2*S**,3*R**,6*S**)- and (2*S**,3*S**,6*S**)-2-Methoxymethyl-3-methyl-1,6-diphenyl-4-piperidone (6 and 6′)**: Pyrrolidine **1b** (338 mg) and *N*-benzylideneaniline (544 mg) were employed; the resulting crude product was purified by $SiO_2$ chromatography (hexane/EtOAc 10:1) to yield 139 mg (30%) of 4-piperidone **6** and 70 mg (15%) of **6′**. *ee* = 35% (determined by $^1H$ NMR using Eu(hfc)$_3$ as shift reagent); for spectroscopic data, see reference [10].

**General procedure for the epimerization of 4′:** To a solution of epimer **4′** (0.5 mmol) in THF (5 mL) at 0 °C was added sodium bis(trimethylsilyl)amide (0.5 mL, 0.5 mmol, 1 M solution in THF). The reaction mixture was allowed to reach RT. After 6 h, $H_2O$ (3 mL) and EtOAc (3 mL) were added to quench the reaction. The aqueous layer was extracted with EtOAc (2 × 3 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL), dried, and concentrated. The resulting oil consisted essentially of the corresponding thermodynamic isomer **4** and was obtained in good yields; for example, following this procedure **4′d** led to **4d** in 92% yield, and **4′i** led to **4i** in 91% yield.

**General procedure for the desilylation of 4-piperidones 4d, 4f, and 4i:** The cycloadducts were treated with a large excess of 3 N aqueous HCl in MeCN for 2 h. Water and EtOAc were added to the reaction mixture and layers were separated. The organic phase was washed with 1 N HCl (10 mL), and KOH pellets were added to the combined acidic aqueous phase until it turned basic. Then, it was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with brine, dried, and concentrated to give the desilylated 4-piperidone essentially pure. **4d** gave **4a** in 88% yield, **4f** gave **4e** in 95% yield, and **4i** yielded **4g** in 90% yield.

**General procedure for the reduction of 4b, 4c, and 4j:** A solution of K-Selectride in THF (1 M, 0.8 mL, 0.8 mmol) was diluted with 5 mL of dry THF and cooled at −80 °C. The piperidone **4** (0.4 mmol) in 3 mL of THF was added dropwise at this temperature, and stirring was continued for an additional 6 h. Then the reaction was warmed to 0 °C and quenched with $H_2O$ (0.5 mL), EtOH (1.0 mL), 3 N aq. KOH (1.5 mL, 10 min stirring), $H_2O_2$ 30% v/v (1.0 mL, 20 min stirring), and saturated aqueous $K_2CO_3$ (7.5 mL). This mixture was extracted with EtOAc (2 × 8 mL), the combined organic layers were washed, dried and concentrated. The resulting orange syrup obtained was purified by column chromatography (hexane/EtOAc/$NEt_3$ or hexane/EtOAc).

**(2*R*,3*S*,4*R*,6*S*)-6-(3-Furyl)-4-hydroxy-2-methoxymethyl-3-methylpiperidine (7b)**: The reaction was performed as described in the general procedure with 89 mg of **4b**; the resulting crude product was purified by silica gel chromatography (hexane/EtOAc/$NEt_3$ 2:1:0.02) to yield 66 mg (73%) of 4-hydroxypiperidine **7b**. White solid; m.p. 70–73 °C; $R_f$ = 0.26 ($SiO_2$, hexane/EtOAc/$NEt_3$ 1:1:0.02); $[\alpha]_{589}^{20}$ = −53.2 (*c* = 0.4 in $CH_2Cl_2$); *ee* = 86% (by HPLC, hexane/ethanol 20:1, $t_{R\,major}$ = 13.1 min, $t_{R\,minor}$ = 11.6 min); $^1H$ NMR (300 MHz, $CDCl_3$, RT, $CHCl_3$): $\delta$ = 7.35–7.33 (m, 2H; 3-furyl), 6.40–6.39 (m, 1H; 3-furyl), 4.07 (dd, $^3J$(H,H) = 12.0 Hz, $^3J$(H,H) = 2.6 Hz, 1H; CHAr), 3.94–3.88 (m, 1H; $CHOH$), 3.51 (dd, $^2J$(H,H) = 9.5 Hz, $^3J$(H,H) = 2.6 Hz, 1H; $CH_2O$), 3.32 (s, 3H; $OCH_3$), 3.28 (t, $^2J$(H,H) = 9.5 Hz, $^3J$(H,H) = 9.0 Hz, 1H; $CH_2O$), 3.01 (ddd, $^3J$(H,H) = 10.8 Hz, $^3J$(H,H) = 9.0 Hz, $^3J$(H,H) = 2.6 Hz, 1H; $CHCH_2O$), 1.94 (dt, $^2J$(H,H) = 13.3 Hz, $^3J$(H,H) = 3.0 Hz, $^3J$(H,H) = 2.6 Hz, 1H; $CH_2CHAr$ eq.), 1.73 (ddd, $^2J$(H,H) = 13.3 Hz, $^3J$(H,H) = 12.0 Hz, $^3J$(H,H) = 2.6 Hz, 1H; $CH_2CHAr$ ax.), 1.54 (dd, $^3J$(H,H) = 10.8 Hz, $^3J$(H,H) = 6.9 Hz, $^3J$(H,H) = 2.6 Hz, 1H; CHMe), 0.94 (d, $^3J$(H,H) = 6.9 Hz, 3H; $CH_3CH$); $^{13}C$ NMR (75 Hz, $CDCl_3$, RT, $CDCl_3$): $\delta$ = 142.7 (3-furyl), 138.6 (3-furyl), 128.5 (3-furyl), 109.1 (3-furyl), 74.8 ($CH_2OMe$), 70.2 (CHOH), 58.9 ($OCH_3$), 55.5 (CHN), 46.1 (CHN), 40.8 ($CH_2CHOH$), 37.0 (CHMe), 14.1 ($CH_3CH$); HREIMS calculated for $C_{12}H_{19}NO_3$ 225.136493; found 225.135893.

**(2*R*,3*S*,4*R*,6*S*)-6-(3-Furyl)-4-hydroxy-2-methoxymethoxymethyl-3-methylpiperidine (7c)**: The reaction was performed as described in the general procedure with 101 mg of **4c**; the resulting crude product was purified by silica gel chromatography (hexane/EtOAc/$NEt_3$ 2:1:0.02) to yield 71 mg (70%) of 4-hydroxypiperidine **7c**. White solid; m.p. 99–101 °C; $R_f$ = 0.24 ($SiO_2$, hexane/EtOAc/$NEt_3$ 1:1:0.02); $[\alpha]_{589}^{20}$ = −52.7 (*c* = 0.9 in $CH_2Cl_2$); *ee* = 82% (by HPLC, hexane/ethanol 20:1, $t_{R\,major}$ = 13.8 min, $t_{R\,minor}$ = 12.3 min); $^1H$ NMR (300 MHz, $CDCl_3$, RT, $CHCl_3$): $\delta$ = 7.37–7.35 (m, 2H; 3-furyl), 6.42–6.41 (m, 1H; 3-furyl), 4.64 (d, $^2J$(H,H) = 6.7 Hz, 1H; $OCH_2O$), 4.61 (d, $^2J$(H,H) = 6.7 Hz, 1H; $OCH_2O$), 4.11 (dd, $^3J$(H,H) = 12.0 Hz, $^3J$(H,H) = 2.6 Hz, 1H; CHAr), 4.00–3.87 (m, 1H; $CHOH$), 3.71 (dd, $^2J$(H,H) = 9.5 Hz, $^3J$(H,H) = 3.0 Hz, 1H; $CH_2O$), 3.43 (dd, $^2J$(H,H) = 9.5 Hz, $^3J$(H,H) = 9.0 Hz, 1H; $CH_2O$), 3.35 (s, 3H; $OCH_3$), 3.04 (ddd, $^3J$(H,H) = 11.0 Hz, $^3J$(H,H) = 9.0 Hz, $^3J$(H,H) = 3.0 Hz, 1H; $CHCH_2O$), 1.99 (dt, $^2J$(H,H) = 13.3 Hz, $^3J$(H,H) = 2.6 Hz, $^3J$(H,H) = 2.6 Hz, 1H; $CH_2CHAr$ eq.), 1.76 (ddd, $^2J$(H,H) = 13.3 Hz, $^3J$(H,H) = 12.0 Hz, $^3J$(H,H) = 2.6 Hz, 1H; $CH_2CHAr$ ax.), 1.59 (dd, $^3J$(H,H) = 11.0 Hz, $^3J$(H,H) = 6.9 Hz, $^3J$(H,H) = 2.6 Hz, 1H; CHMe), 0.99 (d, $^3J$(H,H) = 6.9 Hz, 3H; $CH_3CH$); $^{13}C$ NMR (75 MHz, $CDCl_3$, RT, $CDCl_3$): $\delta$ = 142.6 (3-furyl), 138.5 (3-furyl), 128.6 (3-furyl), 108.9 (3-furyl), 96.4 ($OCH_2O$), 69.8 (CHOH), 69.7 ($CHCH_2O$), 55.4 ($OCH_3$), 55.0 (CHN), 46.1 (CHN), 40.9 ($CH_2CHOH$), 37.0 (CHMe), 13.9 ($CH_3CH$); HREIMS calculated for $C_{13}H_{21}NO_4$ 255.147058; found 255.147149.

**(2*R*,3*S*,4*R*,6*S*)-6-(*o*-Bromophenyl)-4-hydroxy-2-methoxymethyl-3-methylpiperidine (7j)**: The reaction was performed as described in the general procedure with 125 mg of **4j**; the resulting crude product was purified by silica gel chromatography (hexane/EtOAc 6:1) to yield 113 mg (90%) of 4-hydroxypiperidine **7j**. $R_f$ = 0.34 ($SiO_2$, hexane/EtOAc, 5:1); $[\alpha]_{Na}^{20}$ = −61.5 (*c* = 0.6, $CH_2Cl_2$); *ee* = 82% (by HPLC, hexane/ethanol 22.5:1, $t_{R\,major}$ = 15.6 min, $t_{R\,minor}$ = 13.4 min); $^1H$ NMR (300 MHz, $CDCl_3$, RT, $CHCl_3$): $\delta$ = 7.57–7.18 (m, 2H; *o*-BrPh), 7.07–6.66 (m, 2H; *o*-BrPh), 4.46 (dd, $^3J$(H,H) = 11.6 Hz, $^3J$(H,H) = 2.2 Hz, 1H; CHAr), 3.94–3.89 (m, 1H; $CHOH$), 3.49 (dd, $^2J$(H,H) = 9.0 Hz, $^3J$(H,H) = 2.6 Hz, 1H; $CH_2O$), 3.27 (s, 3H; $OCH_3$), 3.31–3.22 (m, 1H; $CH_2O$), 3.08 (ddd, $^3J$(H,H) = 10.3 Hz, $^3J$(H,H) = 10.3 Hz, $^3J$(H,H) = 2.6 Hz, 1H; $CHCH_2O$), 2.02 (ddd, $^2J$(H,H) = 13.3 Hz, $^3J$(H,H) = 3.4 Hz, $^3J$(H,H) = 3.4 Hz, 1H; $CH_2CHAr$), 1.62 (ddd, $^2J$(H,H) = 13.3 Hz, $^3J$(H,H) = 11.6 Hz, $^3J$(H,H) = 2.6 Hz, 1H; $CH_2CHAr$), 1.62–1.50 (m, 1H; CHMe), 0.94 (d, $^3J$(H,H) = 6.9 Hz, 3H; $CH_3CH$); $^{13}C$ NMR (75 MHz, $CDCl_3$, RT, $CDCl_3$): $\delta$ = 142.3 (*o*-BrPh), 132.4 (*o*-BrPh), 128.2 (*o*-BrPh), 127.8 (*o*-BrPh), 127.4 (*o*-BrPh), 123.2 (*o*-BrPh), 74.5 (CHOH), 70.1 ($CH_2OMe$), 58.6 ($OCH_3$), 55.6 (CHN), 53.2 (CHN), 39.7 (CHMe), 36.7 ($CH_2CHOH$), 13.9 ($CH_3CH$); $C_{14}H_{20}BrNO_2$ (314.2): calcd C 53.51, H 6.41, N 4.45; found C 53.62, H 6.37, N 4.29.

**(2*R*,3*S*,4*R*,6*S*)-2-(*p*-Bromobenzoyloxymethyl)-6-(3-furyl)-3-methyl-4-piperidone (8)**: Compound **4a** (544 mg, 2.6 mmol) was dissolved in dry pyridine (10 mL). A few crystals of DMAP were added, and *p*-bromobenzoyl chloride (1.14 g, 5.2 mmol) was then added in one portion. The dense suspension was stirred at RT for 10 min. $H_2O$ (10 mL) and EtOAc (20 mL) were added to quench the reaction; the aqueous layer was extracted with EtOAc (2 × 10 mL); the combined organic layers were washed with saturated $NaHCO_3$ aqueous solution (10 mL), brine (10 mL), dried, and concentrated. The resulting oil consisted essentially in the ester **8** (1 g, quantitative) and was used in the following step without further purification. Brownish oil; $R_f$ = 0.82 ($SiO_2$, $CH_2Cl_2$/EtOAc 2:1); $[\alpha]_{589}^{20}$ = −36.4 (*c* = 0.5 in $CH_2Cl_2$); $^1H$ NMR (300 MHz, $CDCl_3$, RT, $CHCl_3$): $\delta$ = 7.80 (d, $^3J$(H,H) = 7.7 Hz, 2H; *p*-BrPh), 7.48 (d, $^3J$(H,H) = 7.7 Hz, 2H; *p*-BrPh), 7.35 (s, 1H; 3-furyl), 7.32 (s, 1H; 3-furyl), 6.37 (s, 1H; 3-furyl), 4.59 (dd, $^2J$(H,H) = 11.4 Hz, $^3J$(H,H) = 1.7 Hz, 1H; $CH_2O$), 4.29 (dd, $^2J$(H,H) = 11.4 Hz, $^3J$(H,H) = 6.9 Hz, 1H; $CH_2O$), 3.95 (dd, $^3J$(H,H) = 10.8 Hz, $^3J$(H,H) = 3.5 Hz, 1H; CHAr), 2.97 (ddd, $^3J$(H,H) = 9.4 Hz, $^3J$(H,H) = 6.9 Hz, $^3J$(H,H) = 1.7 Hz, 1H; $CHCH_2O$), 2.59–2.42 (m, 2H; $CH_2CO$), 2.39 (d, $^3J$(H,H) = 9.4 Hz, $^3J$(H,H) = 6.4 Hz, 1H; CHMe), 1.08 (d, $^3J$(H,H) = 6.4 Hz, 3H; $CH_3$); $^{13}C$ NMR (75 Hz, $CDCl_3$, RT, $CDCl_3$): $\delta$ = 208.0 (CO), 165.2 (COO), 143.1 (3-furyl), 138.5 (3-furyl), 131.5 (Ph), 130.8 (Ph), 128.3 (Ph), 128.0 (Ph), 127.0 (3-furyl), 108.4 (3-furyl), 66.7 ($CH_2O$), 60.9 (CHN), 52.2 (CHN), 48.9 ($CH_2CO$), 46.7 (CHMe), 9.5 ($CH_3$); HREIMS calculated for $C_{18}H_{18}BrNO_4$ 391.041931, found 391.040191.

**(2*R*,3*S*,4*R*,6*S*)-2-(*p*-Bromobenzoyloxymethyl)-6-(3-furyl)-4-hydroxy-3-methylpiperidine (9)**: The procedure is analogous to the general procedure described for the reduction of the ketone group of **4b**, **4c**, and **4j**, except that K-Selectride (5.2 mL, 5.2 mmol) is added over a cooled solution of piperidone **8** (1 g, 2.6 mmol). If the order is inverted, the transesterified product is mainly obtained. Column chromatography of the resulting orange syrup ($CH_2Cl_2$/EtOAc 1:1) gave 297 mg of **9** (29%). Colorless oil; $R_f$ = 0.28 ($SiO_2$, $CH_2Cl_2$/EtOAc 1:1); $[\alpha]_{589}^{20}$ = −36.0 (*c* = 0.6 in $CHCl_3$); $^1H$ NMR (200 MHz, $CDCl_3$, RT, $CHCl_3$): $\delta$ = 7.86 (d, $^3J$(H,H) = 8.6 Hz, 2H; *p*-BrPh), 7.57 (d, $^3J$(H,H) = 8.6 Hz, 2H; *p*-BrPh), 7.37–7.36 (m, 2H; 3-furyl), 6.42–6.41 (m, 1H; 3-furyl), 4.56 (dd, $^2J$(H,H) = 11.1 Hz, $^3J$(H,H) = 2.8 Hz, 1H; $CH_2O$), 4.23–4.13 (m, 2H; $CH_2O$ + $CHOH$), 4.02–3.99 (m, 1H; CHAr), 3.25 (ddd, $^3J$(H,H) = 10.5 Hz, $^3J$(H,H) = 7.6 Hz, $^3J$(H,H) = 2.7 Hz, 1H; $CHCH_2O$), 2.06–1.57 (m, 5H; $CH_2CHAr$ + CHMe + NH + OH), 1.08 (d, $^3J$(H,H) = 7.0 Hz, 3H; $CH_3$); $^{13}C$ NMR (50.3 MHz, $CDCl_3$, RT, $CDCl_3$): $\delta$ = 165.5 (COO), 142.8 (3-furyl), 138.5 (3-furyl), 131.5 (Ph), 130.8 (Ph), 128.5 (Ph), 128.3 (Ph), 127.9 (3-furyl), 108.9 (3-furyl), 69.5 (CHOH), 67.7 ($CH_2O$), 54.7 (CHN), 45.9 (CHN), 40.7 ($CH_2CO$), 37.1 (CHMe), 14.2 ($CH_3$); HREIMS calculated for $C_{18}H_{20}BrNO_4$ 393.057581; found 393.056270. The transesterified product was also obtained in 8% yield.

**(2*R*,3*S*,4*R*,6*S*)-4-(*p*-Bromobenzoyloxy)-2-(*p*-bromobenzoyloxymethyl)-6-(3-furyl)-3-methylpiperidine (10)**: Compound **9** (297 mg, 0.75 mmol) was dissolved in dry THF (10 mL), and sodium bis(trimethylsilyl)amide (0.8 mL, 0.8 mmol, 1 M in THF) was added at RT; after 1 h of stirring, *p*-bromobenzoyl chloride (395 mg, 1.80 mmol) was added in one portion. The stirring was continued for 12 h, and the reaction mixture was quenched with $H_2O$ (5 mL) and $Et_2O$ (20 mL). The aqueous layer was extracted with $Et_2O$ (2 × 10 mL), and the combined organic layers were



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washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), dried, and concentrated. After column chromatography (hexane/EtOAc 5:1), 173 mg of **10** (40%) was obtained. Yellowish oil; $R_f = 0.22$ ($SiO_2$, hexane/EtOAc, 4:1); $[\alpha]_{589}^{20} = +16.3$ ($c = 0.3$ in $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$, RT, $CDCl_3$): $\delta = 7.95$ (d, $^3J(H,H) = 8.5$ Hz, 2H; *p*-BrPh), 7.89 (d, $^3J(H,H) = 8.5$ Hz, 2H; *p*-BrPh), 7.61 (d, $^3J(H,H) = 8.5$ Hz, 2H; *p*-BrPh), 7.59 (d, $^3J(H,H) = 8.5$ Hz, 2H; *p*-BrPh), 7.37 (s, 1H; 3-furyl), 7.36 (s, 1H; 3-furyl), 6.39 (s, 1H; 3-furyl), 5.41 (m, 1H; COOCH), 4.65 (dd, $^2J(H,H) = 11.1$ Hz, $^3J(H,H) = 2.8$ Hz, 1H; $CH_2O$), 4.24 (dd, $^2J(H,H) = 11.1$ Hz, $^3J(H,H) = 7.7$ Hz, 1H; $CH_2O$), 4.11 (dd, $^3J(H,H) = 11.6$ Hz, $^3J(H,H) = 2.3$ Hz, 1H; CHAr), 3.36 (ddd, $^3J(H,H) = 10.4$ Hz, $^3J(H,H) = 7.7$ Hz, $^3J(H,H) = 2.8$ Hz, 1H; $CHCH_2O$), 2.22 (dt, $^2J(H,H) = 14.1$ Hz, $^3J(H,H) = 2.8$ Hz, 1H; $CH_2CHAr$), 1.88–1.84 (m, 1H; CHMe), 1.84 (dt, $^2J(H,H) = 14.1$ Hz, $^3J(H,H) = 2.5$ Hz, 1H; $CH_2CHAr$), 1.06 (d, $^3J(H,H) = 6.9$ Hz, 3H; $CH_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$, RT, $CDCl_3$): $\delta = 165.7$ (COO), 165.1 (COO), 143.2, 138.8, 131.9, 131.8, 131.1, 129.2, 128.8, 128.3, 128.2, 128.1, 108.9 (aryl), 73.8 (COOCH), 67.5 ($COOCH_2$), 56.3 (CHN), 47.2 (CHN), 38.1 ($CH_2CHAr$), 36.5 (CHMe), 14.1 ($CH_3$); HREIMS calculated for $C_{25}H_{23}Br_2NO_5$ 574.994319; found 574.992198.

**(2*R*,3*S*,4*R*,6*S*)-1-Aza-4-hydroxy-3-methyl-2-phenyl-8-oxa-7-oxobicyclo[4.3.0]nonane (12)**: To a solution of piperidone **4g** (110 mg, 0.5 mmol) in THF (5 mL) was added triphosgene (150 mg, 0.5 mmol). The solution was cooled at 0 °C, and a solution of triethylamine (0.7 mL, 0.5 mmol) in THF (1 mL) was then slowly added. The mixture was stirred for 15 min and quenched with $H_2O$ (3 mL). The layers were separated, and the aqueous layer extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated. Flash chromatography ($SiO_2$, hexane/EtOAc 1:2) afforded (2*R*,3*S*,6*S*)-1-aza-3-methyl-6-phenyl-8-oxa-4,7-dioxobicyclo[4.3.0]nonane (122 mg, quantitative). Colorless oil; $R_f = 0.45$ ($SiO_2$, hexane/EtOAc, 1:2); $[\alpha]_D^{20} = -9.0$ ($c = 9.0$ in $CHCl_3$); *ee* = 95%; $^1H$ NMR (300 MHz, $CDCl_3$, RT, $CHCl_3$): $\delta = 7.2$ (m, 5H; Ph), 4.82 (dd, $^3J(H,H) = 6.2$ Hz, $^3J(H,H) = 6.0$ Hz, 1H; PhCH), 4.40 (m, 1H; $CH_2O$), 3.92 (m, 2H; $CH_2O + CH_2CHN$), 2.84 (dd, $^2J(H,H) = 15.2$ Hz, $^3J(H,H) = 6.0$ Hz, 1H; $CH_2CO$), 2.66 (dd, $^2J(H,H) = 15.2$ Hz, $^3J(H,H) = 6.2$ Hz, 1H; $CH_2CO$), 2.46 (dq, $^3J(H,H) = 10.7$ Hz, $^3J(H,H) = 6.5$ Hz, 1H; $CHCH_3$), 0.98 (d, $^3J(H,H) = 6.5$ Hz, 3H; $CH_3$).

K-selectride (0.7 mL, 0.7 mmol, 1 M in THF) was added to a solution of the bicyclic piperidone (122 mg, 0.50 mmol) in dry THF (5 mL) at −80 °C. After the mixture had been stirred at −80 °C for 70 min, the cold bath was removed, and $H_2O$ (0.2 mL) was added; the reaction mixture was stirred until the temperature rose to 0 °C. Then, EtOH (0.1 mL) and NaOH 3 N (0.2 mL) were added to the stirred mixture; after 5 min $H_2O_2$ 30% (0.5 mL) was slowly added. After 15 min, aqueous saturated $Na_2CO_3$ (1 mL) and EtOAc (5 mL) were added. The layers were separated and the aqueous layer extracted with EtOAc (2 × 5 mL). The organic layers were combined, washed with $H_2O$, and dried over $Na_2SO_4$. Solvents were removed under reduced pressure, and flash chromatography ($SiO_2$, $CH_2Cl_2$/EtOAc 4:1) gave 117 mg (95%) of alcohol **12**. Yellowish oil; $R_f = 0.43$ ($SiO_2$, $CH_2Cl_2$/EtOAc 4:1); $[\alpha]_{578}^{20} = -88.3$ ($c = 1.5$ in $CHCl_3$); *ee* = 95% (determined by means of Mosher's derivative, see product **13**); $^1H$ NMR (300 Hz, $CDCl_3$, RT, $CHCl_3$): $\delta = 7.20$ (m, 5H; Ph), 4.41 (dd, $^3J(H,H) = 12.0$ Hz, $^3J(H,H) = 3.4$ Hz, 1H; CHPh), 4.27 (m, 1H, $CH_2O$), 3.88 (ddd, $^3J(H,H) = 3.4$ Hz, $^3J(H,H) = 2.6$ Hz, $^3J(H,H) = 2.3$ Hz, 1H; CHOH), 3.72 (m, 2H; $CHCH_2O + CH_2O$), 1.93 (ddd, $^2J(H,H) = 14.2$ Hz, $^3J(H,H) = 3.4$ Hz, $^3J(H,H) = 3.4$ Hz, 1H; $CH_2CHPh$), 1.76 (ddd, $^2J(H,H) = 14.2$ Hz, $^3J(H,H) = 12.0$ Hz, $^3J(H,H) = 2.6$ Hz, 1H; $CH_2CHPh$), 1.66 (dq, $^3J(H,H) = 10.0$ Hz, $^3J(H,H) = 6.8$ Hz, $^3J(H,H) = 2.3$ Hz, 1H; $CHCH_3$), 0.93 (d, $^3J(H,H) = 6.8$ Hz, 3H; $CH_3$); $^{13}C$ NMR (75 Hz, $CDCl_3$, RT, $CDCl_3$): $\delta = 160.5$ (CO), 143.4 (Ph), 133.2 (Ph), 131.3 (Ph), 131.1 (Ph), 71.4 ($CH_2OCO$), 70.5 (CHOH), 59.7 (CHN), 55.3 (CHN), 44.9 ($CHCH_3$), 42.5 ($CH_2CHPh$), 14.6 ($CH_3$); $C_{14}H_{17}NO_3$ (247.3): calcd C 67.99, H 6.92, N 5.66; found C 67.73; H 6.80, N 5.91.

**(2*R*,3*S*,4*R*,6*S*)-1-Aza-4-[(*R*)-α-methoxy-α-phenyl-α-trifluoromethylacetoxy]-3-methyl-8-oxa-7-oxo-6-phenylbicyclo[4.3.0]nonane (13)**: To a solution of the alcohol **12** (117 mg, 0.5 mmol) in pyridine (0.2 mL) were added a small crystal of DMAP and (+)-MPTA chloride (105 μL, 0.55 mmol); the solution was allowed to stand at room temperature for 13 h. The solvent was evaporated, and the crude product was dissolved in diethyl ether (5 mL). The solution was washed with saturated aqueous $Na_2CO_3$ solution (2 × 5 mL) and brine, and dried over $Na_2SO_4$. Removal of the solvents afforded (*R*)-MPTA esters **13** (220 mg, quantitative) that were used for NMR measurements. Noncrystalline solid; $R_f = 0.47$ ($SiO_2$, hexane/EtOAc 1:1); mixture of two diastereoisomers, *de* = 95%; $^1H$ NMR (300 MHz, $CDCl_3$, RT, $CHCl_3$): $\delta = 7.50$–$7.00$ (m, 10H; aryl), 5.22 (m, 1H; CHOCO), 4.28 (dd, $^3J(H,H) = 7.8$ Hz, $^2J(H,H) = 7.8$ Hz, 1H; $CH_2O$), 3.84 (dd, $^3J(H,H) = 12.0$ Hz, $^3J(H,H) = 3.4$ Hz, 1H; CHAr), 3.79 (dd, $^3J(H,H) = 10.7$ Hz, $^2J(H,H) = 7.8$ Hz, 1H; $CH_2O$), 3.60–3.50 (m, 4H; $OCH_3 + CHN$), 2.10 (ddd, $^2J(H,H) = 14.6$ Hz, $^3J(H,H) = 3.4$ Hz, $^3J(H,H) = 3.4$ Hz, 1H; $CH_2CHPh$) 1.92–1.79 (m, 2H; $CHCH_3 + CH_2CHPh$), 0.89 (d, $^3J(H,H) = 6.9$ Hz, 3H; $CH_3CH$); $^{13}C$ NMR (75 MHz, $CDCl_3$, RT, $CDCl_3$): $\delta = 165.9$ (C=O ester), 157.1 (C=O carbamate), 138.1 (Car), 129.8 (CHar), 128.7 (CHar), 128.4 (CHar), 128.2 (CHar), 127.8 (CHar), 127.0 (CHar), 73.7 (CHO), 66.7 ($CH_2O$), 57.3 ($OCH_3$), 55.6 (CHN), 53.9 (CHN), 39.1 (CH), 37.6 ($CH_2$), 12.9 ($CH_3$); $C_{24}H_{24}F_3NO_5$ (463.5): calcd C 62.20, H 5.22, N 3.02; found C 62.41, H 5.32, N 3.21.

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[1] a) For a monograph on piperidone chemistry see: M. Rubiralta, E. Giralt, A. Diez, *Piperidine. Structure, Preparation, Reactivity and Synthetic Applications of Piperidine and its Derivatives*, Elsevier, Amsterdam, **1991**. b) M. Rubiralta, A. Diez, C. Vila, Y. Troin, M. Feliz, *J. Org. Chem.* **1991**, *56*, 6292–6298. c) D. L. Comins, D. H. LaMunyon, *ibid.* **1992**, *57*, 5807–5809. d) A. Diez, S. Mavel, J. C. Teulade, O. Chavignon, M. E. Sinibaldi, Y. Troin, M. Rubiralta, *Heterocycles* **1993**, *36*, 2451–2463. e) J. Gracia, N. Casamitjana, J. Bonjoch, J. Bosch, *J. Org. Chem.* **1994**, *59*, 3939–3951.

[2] a) F. Janssens, J. Torremans, P. A. J. Janssen, *J. Med. Chem.* **1986**, *29*, 2290–2297. b) J. R. Bagley, R. L. Wynn, F. G. Rudo, B. M. Doorley, H. K. Spencer, T. Spaulding, *ibid.* **1989**, *32*, 663–671. c) L. V. Kudzma, S. A. Severnak, M. J. Benvenga, E. F. Ezell, M. H. Ossipov, V. V. Knight, F. G. Rudo, H. K. Spencer, T. C. Spaulding, *ibid.* **1989**, *32*, 2534–2542.

[3] G. V. Grishina, V. M. Potapov, S. A. Abdulganeeva, T. A. Gudasheva, I. F. Leshcheva, N. M. Sergeev, T. A. Kudryavtseva, E. Y. Korchagina, *Khim Geterotzikl. Soedin.* **1983**, 1693–1694.

[4] G. V. Grishina, S. A. Abdulganeeva, V. M. Potapov, I. A. Ivanova, A. A. Espenbetov, Y. T. Strychkov, I. A. Grishina, A. I. Lutsenko, *Khim Geterotzikl. Soedin.* **1985**, 1656–1662.

[5] a) G. V. Grishina, E. L. Gaidarova, *Khim Geterotzikl. Soedin.* **1992**, 1072–1078. b) Idem, *Synlett*, **1992**, 89–93.

[6] M. Rubiralta, A. Diez, C. Vila, J. Castells, I. López, *Heterocycles* **1992**, *34*, 643–650.

[7] For some leading references see: a) D. L. Boger, S. M. Weinreb, *Hetero-Diels–Alder Methodology in Organic Synthesis*, Academic Press, Orlando, **1987**, pp. 35–71. b) S. M. Weinreb in *Comprehensive Organic Synthesis, Vol. 5*, **1991**, pp. 402–449. c) H. Waldmann, *Synthesis* **1994**, 535–551.

[8] a) W. Pfrengle, H. Kunz, *J. Org. Chem.* **1989**, *54*, 4261–4263. b) H. Waldmann, M. Braun, M. Dräger, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1468–1471. c) P. D. Bailey, R. D. Wilson, G. R. Brown, *J. Chem. Soc. Perkin Trans I*, **1991**, 1337–1340. d) A. K. McFarlane, G. Thomas, A. Whiting, *Tetrahedron Lett.* **1993**, *34*, 2379–2382. e) K. Ishimaru, K. Watanabe, Y. Yamamoto, K. Akiba, *Synlett*, **1994**, 495–498.

[9] a) K. Hattori, H. Yamamoto, *J. Org. Chem.* **1992**, *57*, 3264–3265. b) Idem, *Synlett*, **1993**, 129–130.

[10] J. Barluenga, F. Aznar, C. Valdés. M. P. Cabal, *J. Org. Chem.* **1993**, *58*, 3391–3396.

[11] a) J. Barluenga, F. Aznar, C. Valdés, A. Martín, S. García-Granda, E. Martín, *J. Am. Chem. Soc.* **1993**, *115*, 4403–4404. b) J. Barluenga, F. Aznar, A. Martín, S. Barluenga, S. García-Granda, A. A. Paneque-Quevedo, *J. Chem. Soc. Chem. Commun.* **1994**, 843–844. c) D. Enders, O. Meyer, G. Raabe, *Synthesis* **1992**, 1242–1244. d) D. Enders, O. Meyer, G. Raabe, J. Runsink, *ibid.* **1994**, 66–72.

[12] J. Barluenga, F. Aznar, C. Valdés, M. P. Cabal, *J. Org. Chem.* **1991**, *56*, 6166–6171.

[13] The isolation of the less favorable epimers **4'** has not been achieved, since they undergo partial interconversion to the more stable epimers **4** upon chromatography on silica gel. Nevertheless, the axial arrangement of the methyl group attached at C3 can be deduced from the analysis of the $^1H$ NMR spectra. For example, in compound **4'h** (see Table 1), the signal for H3 appears at $\delta = 2.49$, and the coupling constants with the methyl group [$^3J(H3,CH_3) = 7.3$ Hz] and with H2 [$^3J(H3,H2) = 3.2$ Hz] establish that it is equatorial and therefore that the methyl group is axial. In addition, a coupling through four bonds with equatorial H5 [$^4J(H3,H5) = 1.3$ Hz] is observed due to the planar W geometry.

[14] N. Harada, K. Nakanishi, *J. Am. Chem. Soc.* **1969**, *91*, 3989–3991.

[15] For a monograph on exciton CD spectroscopy see: N. Harada, K. Nakanishi, *Circular Dichroic Spectroscopy—Exciton Coupling in Organic Stereochemistry*, University Science Books, Mill Valley, CA, **1983**.

[16] MMX force field. PCMODEL-PI (v 4.0), Serena Software: P. O. Box 3076, Bloomington, IN 47402–3076.

[17] The strain energy differences, rotamer distributions, and especially dihedral angles O4-C4-C7-O7 found for the rotamers of compound **13** are of great interest for CD analysis.

[18] C-Nucleosil column, 7.250 × 10 mm i.d., 254 nm, 3 mL min$^{-1}$ and HPLC grade *n*-hexane/EtOAc (85:15) solvent system.

[19] J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512–519.

[20] For some recent examples: a) I. Othani, T. Kusumi, Y. Kashman, H. Kasikawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096. b) E. Finamore, L. Minale, R. Riccio, G. Rinaldo, F. Zollo, *J. Org. Chem.* **1991**, *56*, 1146–1153. c) J. Rodriguez, R. Riguera, C. Debitus, *ibid.* **1992**, *57*, 4624–4632.

[21] For TMS, see E. J. Corey, B. B. Snider *J. Am. Chem. Soc.* **1972**, *94*, 2549–2550. For methyl group see R. A. W. Johnstone, M. E. Rose *Tetrahedron* **1979**, *35*, 2169–2173. For MOM, see L. Banfi, A. Bernardi, L. Colombo, C. Gennari, C. Scolastico *J. Org. Chem.* **1984**, *49*, 3784–3790. For TBDMS, see E. J. Corey, A. Venkateswarlu *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.

[22] E. W. Colvin, D. McGarry, M. J. Nugent, *Tetrahedron* **1988**, *44*, 4157–4172.