Synthesis of Enantiomerically Pure Functionalized *cis*- and *trans*-2-Aminocyclohexanecarboxylic Acid Derivatives

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Introduction

The enantioselective synthesis of β-amino acids has always attracted considerable attention,[1] because this substructure is present in many natural products[2,3] and biologically active peptides,[4] as well as in other bioactive compounds,[5] and they are useful starting materials in the synthesis of β-lactam antibiotics.[6] Moreover, the β-amino acid moiety is currently gaining increasing importance as a result of the recent advances in the chemistry of β-peptides (oligomers of β-amino acids), which have been reported to adopt predictable and reproducible folding patterns[7,8] and to form self-assembling transmembrane ion channels.[9]

On the other hand, in the recent years we have been exploring some of the synthetic applications of compounds derived from chiral 2-amino-1,3-butadienes.[10] In a previous paper, we demonstrated that functionalized 4-nitrocyclohexanones can be prepared with very high enantiomeric excesses from the reaction of chiral 2-aminodienes with conjugated nitroalkenes bearing aryl or alkyl substituents (Scheme 1).[11]

Nitro compounds **1** may be regarded as precursors of enantiomerically pure *cis*- and *trans*-2-aminocyclohexanecarboxylic acid (ACHC) derivatives **I** and **II** (Figure 1): reduction of the nitro group would afford the amino function, and oxidation of either the C3 or C5 substituent

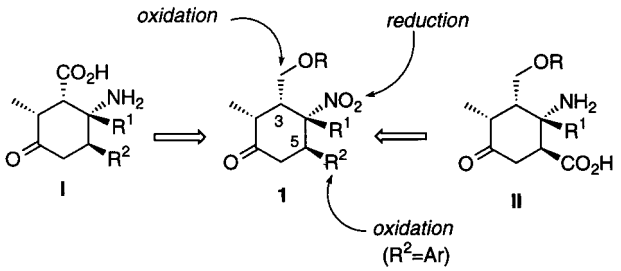
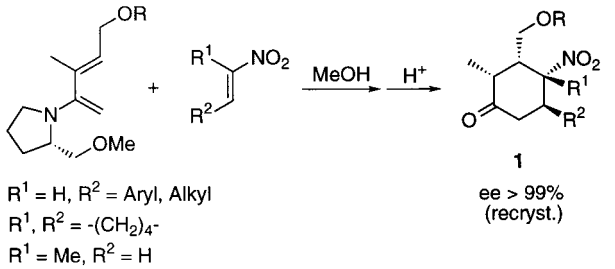


Figure 1.

Scheme 1



would lead to the carboxylic functionality. The apparently simple sequence required for those transformations together with the increasing interest of β-amino acids prompted us to develop a synthetic route to these compounds starting from 4-nitrocyclohexanones **1**. As an extension of our previous work,[11c] in this paper we report our studies toward the synthesis of functionalized enantiomerically pure cis- and *trans*-2-ACHC derivatives from 4-nitrocyclohexanones **1**.

Results and Discussion

Synthesis of cis-β-Amino Acid Derivatives I. Two different approaches can be designed for the synthesis of cis-β-amino acid derivatives **I** from nitrocyclohexanones **1** depending on the sequence chosen for the synthetic transformations (reduction of the nitro group and oxidation of the hydroxy substituent). Both strategies were explored independently, to find out that the sequence that involved the oxidation of the hydroxy group in first place required less number of steps and provided higher overall yield.[12] The synthetic sequence applied is depicted in Scheme 2. First of all, the hydroxy group of **1a** (protected as a TBDMS ether in the starting cyclohexanone) was deprotected under acidic conditions leading to nitro hydroxy ketone **2a** along with its intramolecular hemiketal **3a** (ratio **2a**/**3a**, 1:3). Nevertheless, oxidation of the mixture with Jones reagent went to completion, and after diazomethane esterification of the crude, the desired nitro ester **4a** was isolated as a single compound in good yield. Finally, hydrogenation of the nitro group in the presence of Raney nickel[13] proceeded smoothly to obtain the cis-β-amino ester **5a** in 80% overall yield (4 steps).

The same strategy was applied to 4-nitrocyclohexanone **1b** (Scheme 2). This time, upon desilylation with aqueous

(1) For a review on recent stereoselective synthetic approaches to β-amino acids, see: Cole, D. C. *Tetrahedron* **1994**, *32*, 9517−9582.
(2) Goto, T.; Toya, Y.; Ohgi, T.; Kondo, T. *Tetrahedron Lett.* **1982**, *23*, 1271.
(3) Katayama, N.; Nozaki, Y.; Tsubotani, S.; Kondo, M.; Harada, S.; Ono, H. *J. Antibiot.* **1990**, *43*, 10.
(4) Drey, C. N. C. In *Chemistry and Biochemistry of the Amino acids*; Barret, G. C., Ed.; Chapman and Hall: New York, 1985; Chapter 3.
(5) For the applications of β-amino acids as peptidomimetics, see: Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244−1267.
(6) For a review in the field of β-lactam antibiotics, see: Dürckheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180−202.
(7) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015−2022.
(8) Apella, D. H.; Christianson, L. A.; Klein, D. A.; Powell, D. R.; Huang, X.; Barchi, Jr. J. J.; Gellman, S. H. *Nature* **1997**, 387, 381−384.
(9) Clark, T. D.; Buehler, L. K.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1998**, *120*, 651−656.
(10) (a) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C.; Fernández, M.; Cabal, M. P.; Trujillo, J. *Chem. Eur. J.* **1996**, *2*, 805−811. (b) Enders, D.; Meyer, O.; Raabe, G. *Liebigs Ann.* **1996**, 1023−1035 and references therein.
(11) (a) Barluenga, J.; Aznar, F.; Valdés, C.; Martín, A.; García-Granda, S.; Martín, E. *J. Am. Chem. Soc.* **1993**, *115*, 4403−4404. (b) Enders, D.; Meyer, O.; Raabe, G. *Synthesis* **1992**, 1242−1244. (c) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C. *J. Org. Chem.* **1997**, *62*, 6746−6753.
(12) Spectroscopic data for the alternative approach are included as Supporting Information.
(13) Moffett, R. B. *Organic Syntheses*; Rabjohn, N., Ed.; John Wiley: New York; Collect. Vol. IV, p 1963, 357−359.

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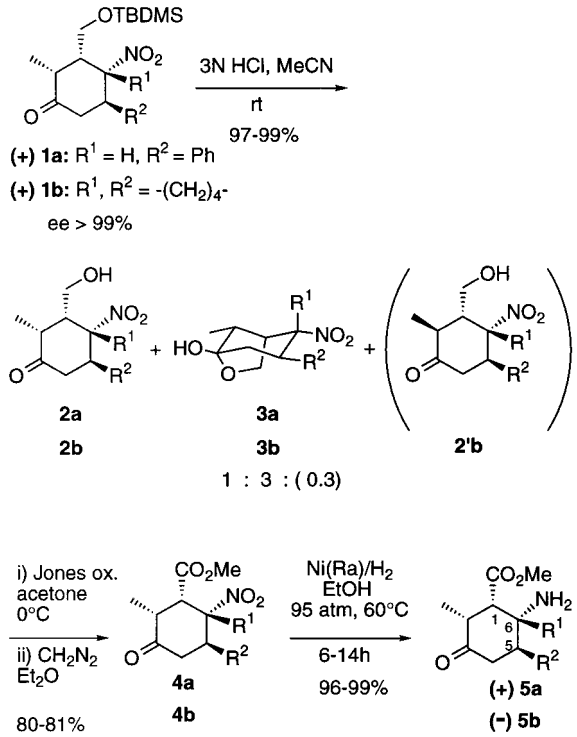
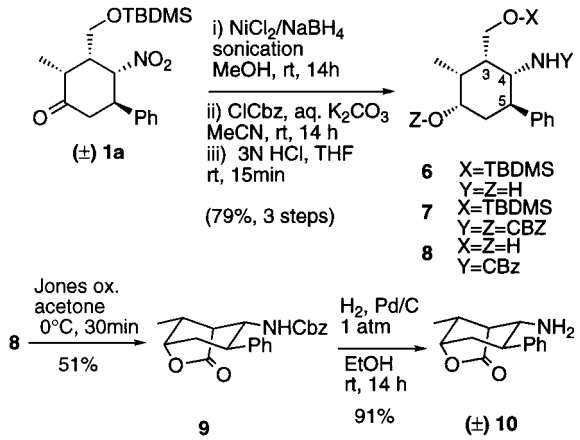
Scheme 2



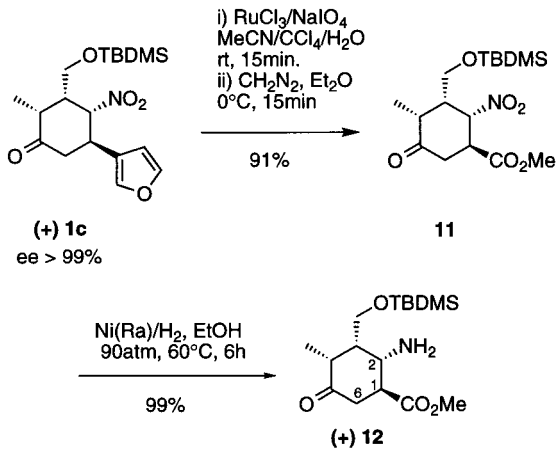
HCl, a small amount of the C3 epimer **2′b** was observed along with nitrohydroxyketone **2b** and its intramolecular hemiketal **3b**, (ratio **2b**/**3b**/**2′b**, 1:3:0.3). Again, oxidation of the mixture with Jones reagent and subsequent treatment of the crude acid with diazomethane afforded nitro ester **4b**, which was easily separated from the minor C3 epimer **4′b** by column chromatography. The tertiary nitro group could then be cleanly reduced by hydrogenation with Raney nickel employing longer reaction times (14 h), leading to cis-*β*-amino ester **5b** with 85% overall yield. It is worth pointing out that amino ester **5b** features a very rigid structure, as a result of the amino group being positioned in a tertiary carbon atom, which may be of interest in the design of *β*-peptides with predefined conformations.

Interestingly, bicyclic lactone **10**, a different *β*-amino acid derivative, was prepared when the sequence of synthetic transformations was inverted and the reduction of the nitro group was carried out applying Ganem's reduction procedure (Scheme 3).[14] Thus, when **(±)-1a** was treated with $NiCl_2$ and $NaBH_4$ in methanol, amino alcohol **6** was obtained as a single diastereoisomer.[15] The amino group was protected by treatment of crude **6** with excess benzyl chloroformate to produce the benzoylation of both the amino and hydroxy groups to furnish carbamate **7**.[16] At this point, the analysis of the ^{1}H NMR spectrum revealed that the reduction step had taken place with no epimerization: C*H*−NH appears as a ddd (J_{H4-H5} = 12.5 Hz, J_{H3-H4} = 6.9 Hz, J_{H4-NH} = 6.9 Hz), where the large coupling constant J_{H4-H5} = 12.5 Hz

Scheme 3



Scheme 4



indicates the equatorial arrangement of the amino group. Under the acidic conditions required for the hydrolysis of the silyl group, the benzoyl carbamate was cleanly cleaved, leading to diol **8** as the unique reaction product. Oxidation of **8** with Jones reagent then afforded bicyclic lactone **9**, the lactonization process being favored by the cis diaxial arrangement of both substituents at C1 and C3. Finally, hydrogenation of the Cbz protecting group gave amine **10** with 37% overall yield based on nitrocyclohexanone **1a**. It is worth noting that amino lactone **10** is a conformationally rigid nitrogenated analogue of *trans*-2-phenylcyclohexanol, a chiral auxiliary widely used in asymmetric synthesis. Therefore, this simple approach would be useful in the preparation of a new class of rigid chiral auxiliaries.

Synthesis of trans-*β*-Amino Acid Derivatives II. Once we had completed the synthesis of *cis*-ACHC esters, we turned our attention to the trans derivatives. The conversion of the substituent at C5 of 4-nitrocyclohexanones **1** into a carboxylic group would give *β*-amino esters with trans relative configuration. To accomplish this chemical transformation, compound **1c**, derived from *β*-(3-furyl)nitroethylene, was used as starting material. The furan ring was oxidized employing the Sharpless procedure,[17] followed by esterification with diazometane to obtain *β*-nitro ester **11** in very high yield (Scheme 4). Catalytic hydrogenation of the nitro group then afforded trans-*β*-amino ester **12** with 99% yield (91% overall yield

(14) Osby, J. O.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 6413−6416.

(15) This synthetic study was carried out on racemic **1**, obtained by cycloaddition of *β*-nitrostyrene with the appropriate 2-morpholino-1,3-butadiene.

(16) Under the reaction conditions studied, it was not possible to protect exclusively the amino group in the presence of the secondary alcohol, although the monoprotected compound could be isolated with low yields when the reaction was carried out in the presence of smaller amounts of CbzCl.

(17) Carlsen, P. H. J.; Katsuki, T.; Martín, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.

for the three steps). Again, no epimerization was observed during the process, as deduced by the analysis of the coupling constants in the ^{1}H NMR spectrum. Thus, the signal assigned to H_1 (C*H*−COOMe) appears as a triplet of doublets at 4.18 ppm ($J_{H1-H6ax} = J_{H1-H2} = 12.0$ Hz, $J_{H1-H6eq} = 6.2$ Hz); the presence of a large coupling constant between H_1 and H_2 (C*H*−NH_2) clearly indicates the equatorial−equatorial trans arrangement of both the amino and carboxylate substituents.

In conclusion, we have described some very simple syntheses of enantiomerically pure substituted *cis*- and *trans*-2-aminocyclohexanecarboxylic esters from 4-nitrocyclohexanones derived from the asymmetric cycloaddition of 2-aminodienes and nitroolefins. It is interesting to note that these compounds present the β-amino ester moiety in a conformationally restricted environment, which is an important feature to be employed in the fields of peptidomimetics and β-peptides. Furthermore, given the wide scope of the cycloaddition reaction, the method presented herein would allow for the preparation of a large variety of cyclic β-amino acid derivatives with different substituents.

Experimental Section

General. The same experimental techniques were used as reported previously (see ref 11c). Nitrocyclohexanones **1** were prepared as described in ref 11c.

Desilylation of 1. Synthesis of the Mixture of Nitro Alcohols 2 and Hemiketals 3. To a solution of nitroketone **1** (0.55 mmol) in 20 mL of THF were added 15 mL of 3 N aqueous HCl, and the mixture was vigorously stirred for 90 min at room temperature. Brine (15 mL) and EtOAc (30 mL) were then added to the reaction mixture. The layers were separated, and the aqueous layer was extracted with additional EtOAc (3 × 20 mL). The organic layers were combined, washed with brine (15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (SiO_2, hexane/EtOAc, 1:1) to obtain a mixture of compounds **2** and **3** which was employed for the next step. The following were prepared with this procedure:

(2*R*,3*S*,4*R*,5*R*)-3-(Hydroxymethyl)-2-methyl-4-nitro-5-phenylcyclohexanone (2a) and (1*S*,3*R*,4*R*,5*S*,8*R*)-1-Hydroxy-8-methyl-4-nitro-3-phenylbicyclo[3.2.1]octan-7-one (3a). Nitro compound **1a** (208 mg) was employed to obtain 144 mg of a white solid existing as a 3:1 mixture of compounds **2a** and **3a** in 99% yield: $R_f = 0.23$ (SiO_2, hexane/EtOAc 2:1); mp = 169−170 °C; $[\alpha]^{15}_D = +9.5$ (*c* 0.4, MeOH); ee > 99%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.24 (m, 5H) × 2, 5.43 (dd, J = 12.3, 4.1 Hz, 1H, **2a**), 4.89 (dd, J = 11.7, 1.2 Hz, 1H, **3a**), 4.37 (td, J = 12.3, 6.0 Hz, 1H, **2a**), 4.28 (d, J = 9.4 Hz, 1H, **3a**), 4.10 (dd, J = 9.4, 4.1 Hz, 1H, **3a**), 3.91−3.60 (m, 2H, **2a**), 3.91−3.82 (m, 1H, **3a**), 2.82−2.66 (m, 3H, **2a**), 2.82−2.66 (m, 1H, **3a**), 2.47 (dd, J = 15.8, 12.3 Hz, 1H, **2a**), 2.27 (dd, J = 12.9, 7.0 Hz, 1H, **3a**), 2.08 (q, J = 7.0 Hz, 1H, **3a**), 2.00 (t, J = 12.9 Hz, 1H, **3a**), 1.22 (d, J = 6.5 Hz, 3H, **2a**), 1.15 (d, J = 7.0 Hz, 3H, **3a**) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 207.9 (**2a**), 141.0 (**2a**), 139.7 (**3a**), 129.7 (**3a**), 129.6 (**2a**), 128.4 (**2a**), 128.3 (**3a**), 127.8 × 2, 106.1 (**3a**), 92.1 (**3a**), 91.8 (**2a**), 66.1 (**3a**), 58.2 (**2a**), 48.5 (**3a**), 47.4 (**2a**), 47.3 (**2a**), 46.2 (**3a**), 45.3 (**2a**), 44.7 (**3a**), 43.9 (**2a**), 42.7 (**3a**), 12.2 (**2a**), 12.0 (**3a**) ppm. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.77; H, 6.38; N, 5.06.

(1*S*,3*S*,8*R*,9*S*,12*R*)-1-Hydroxy-12-methyl-8-nitrotricyclo[7.2.1.0^{3,8}]dodecan-11-one (3b) and (3*R*,4*S*,5*R*,10*S*)-4-(Hydroxymethyl)-3-methyl-5-nitro-2-decalone (2b). Nitro compound **1b** (196 mg) was employed to obtain 128 mg of a white solid consisting in a 3:1 mixture of compounds **2b** and **3b** in 97% yield: $R_f = 0.24$ (SiO_2, hexane/EtOAc, 2:1); mp = 126−128 °C; $[\alpha]^{15}_D = -31.4$ (*c* 1.0, CH_2Cl_2); ee > 99%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.99 (dd, J = 9.4, 4.6 Hz, 1H, **3b**), 3.80 (dd, J = 12.3, 3.5 Hz, 1H, **2b**), 3.67 (d, J = 9.4 Hz, 1H, **3b**), 3.63−3.52 (m, 1H, **2b**), 3.37 (d, J = 12.3 Hz, 1H, **2b**), 3.15−3.02 (m, 1H, **3b**), 2.76 (quint, J = 7.0 Hz, 1H, **3b**), 2.58−1.21 (m, 12H, **2b**; 11H **3b**), 1.18 (d, J = 6.8 Hz, 3H, **2b**), 1.09 (d, J = 7.0 Hz, 3H, **3b**) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.9 (**2b**), 105.7 (**3b**), 95.1 (**2b**), 94.6 (**3b**), 66.1 (**3b**), 58.9 (**2b**), 53.0 (**3b**), 52.9 (**2b**), 42.3 (**2b**), 42.2 (**2b**), 41.0 (**3b**), 40.6 (**3b**), 34.9 (**2b**), 32.1 (**3b**), 30.7 (**2b**), 30.3 (**3b**), 26.5 (**2b**), 25.8 (**3b**), 22.3 (**2b**), 22.0 (**3b**), 20.3 (**3b**), 18.8 (**2b**), 11.8 (**2b**), 11.6 (**3b**) ppm. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.73; H, 7.96; N, 5.73.

Oxidation of the Mixture of 2 and 3. Synthesis of Nitro Esters 4. The mixture of compounds **2** and **3** (0.53 mmol) was dissolved in 8 mL of acetone and cooled to 0 °C. A solution of Jones reagent was then added dropwise with stirring until the orange color of the CrO_3 solution remained. The stirring was then continued for 30 min, and ethanol was added dropwise until the solution turned colorless. The solution was separated from the viscous green residue and filtered through Celite, and the green residue and the Celite were washed with additional acetone. The filtrates were combined and concentrated under reduced pressure. The resulting oil was redissolved in EtOAc, (20 mL) and washed with brine. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude acid obtained was dissolved in 10 mL of Et_2O and treated with a solution of freshly prepared diazomethane in Et_2O. After 15 min, the excess of diazomethane was destroyed by the addition of acetic acid until the yellow color due to diazomethane disappeared. The mixture was washed with brine, the aqueous layer was extracted with Et_2O (2 × 20 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford a solid that was purified by flash chromatography. The following compounds were prepared with this method:

(+)-Methyl (1*S*,2*R*,5*R*,6*R*)-2-Methyl-6-nitro-3-oxo-5-phenylcyclohexane-1-carboxylate (4a). A mixture of **2a** and **3a** (140 mg) afforded 124 mg of **4a** as a white solidin 80% yield: $R_f = 0.37$ (SiO_2, hexane/EtOAc 2:1); mp = 143−144 °C; $[\alpha]^{15}_D = +157.0$ (*c* 0.8, CH_2Cl_2); ee > 99%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41−7.24 (m, 5H), 5.37 (dd, J = 12.3, 4.6 Hz, 1H), 4.22 (td, J = 12.3, 5.5 Hz, 1H), 3.77 (s, 3H), 3.70 (t, J = 4.6 Hz, 1H), 2.89 (dd, J = 15.6, 5.5 Hz, 1H), 2.78 (qdd, J = 6.7, 4.6, 0.9 Hz, 1H), 2.60 (ddd, J = 15.6, 12.3, 0.9 Hz, 1H), 1.17 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 204.4, 170.1, 137.7, 129.0, 128.0, 127.0, 88.8, 52.5, 51.2, 45.5, 43.9, 42.7, 11.5 ppm. Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.48; H, 6.17; N, 4.96.

(+)-Methyl (1*S*,2*R*,9*R*,10*S*)-2-Methyl-9-nitro-3-oxobicyclo[4.4.0]decane-1-carboxylate (4b). A mixture of **2b**, **3b**, and **2′b** (118 mg) afforded 107 mg of **4b** as a white solid in 81% yield: $R_f = 0.19$ (SiO_2, hexane/EtOAc 4:1); mp = 147−148 °C; $[\alpha]^{15}_D = +58.3$ (*c* 1.1, CH_2Cl_2); ee > 99%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.65 (s, 3H), 3.54−3.40 (m, 1H), 3.27 (d, J = 6.8 Hz, 1H), 2.66 (quint, J = 6.8 Hz, 1H), 2.60−2.50 (m, 3H), 2.22 (ddd, J = 14.5, 12.7, 4.1 Hz, 1H), 1.88−1.26 (m, 6H), 1.07 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 206.1, 169.8, 92.4, 58.9, 52.5, 42.3, 41.6, 33.7, 29.4, 26.1, 22.0, 18.2, 11.8 ppm. Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.60; H, 6.75; N, 5.02.

Hydrogenation of the Nitro Group of Nitro Esters 4. Synthesis of Amino Esters 5. A mixture of nitro compound **4** (0.40 mmol) and Raney nickel (120 mg) in 50 mL of absolute EtOH was hydrogenated at a pressure of 90 atm and 60 °C for 6 h. The mixture was then cooled to room temperature and filtered through Celite, and the catalyst and the Celite were washed with additional EtOH (3 × 5 mL). The combined filtrates were concentrated under reduced pressure, and the residue was redissolved in CH_2Cl_2 (20 mL) and filtered again through Celite. The solvent was removed under reduced pressure to afford amino ester **5** as a white solid. The following compounds were preapred with this procedure:

(+)-Methyl (2*R*,1*S*,6*R*,5*R*)-6-Amino-2-methyl-3-oxo-5-phenylcyclohexane-1-carboxylate (5a). Hydrogenation of 117 mg of nitro ester **4a** afforded 104 mg of amino ester **5a** as a white solid with a reaction time of 6 h in 100% yield: $R_f = 0.40$ (SiO_2, CH_2Cl_2/MeOH 20:1); mp = 136 °C (dec); $[\alpha]^{15}_D = +66.9$ (*c* 1.4, CH_2Cl_2); ee > 99%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38−7.20 (m, 5H), 3.72 (s, 3H), 3.70 (dd, J = 12.0, 5.6 Hz, 1H), 3.35 (td, J = 12.0, 5.6 Hz, 1H), 3.28 (t, J = 5.6 Hz, 1H), 2.75 (qd, J = 6.8, 5.6 Hz, 1H), 2.64 (dd, J = 15.0, 5.6 Hz, 1H), 2.53 (ddd, J = 15.0,

12.0, 0.9 Hz, 1H), 1.07 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 207.8, 172.5, 141.3, 128.9, 127.4, 127.2, 55.4, 54.9, 51.6, 47.3, 46.4, 44.2, 11.9 ppm. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.95; H, 7.33; N, 5.36. Found: C, 68.85; H, 7.69; N, 5.46.

(−)-Methyl (1*S*,2*R*,9*R*,10*S*)-9-Amino-2-methyl-3-oxobicyclo[4.4.0]decane-1-carboxylate (5b). Hydrogenation of 94 mg of nitroester **4b** using 100 mg of Raney nickel afforded 80 mg of amino ester **5b** as a white solid with a reaction time of 14 h in 96% yield: R_f = 0.21 (SiO_2, CH_2Cl_2/MeOH 40:1); mp = 105−107 °C; $[\alpha]^{15}_D$ = −17.2 (*c* 1.0, CH_2Cl_2); ee > 99%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.66 (s, 3H), 2.78 (d, J = 6.5 Hz, 1H), 2.66 (quint, J = 6.5 Hz, 1H), 2.54−2.05 (m, 4H), 1.88−1.24 (m, 7H), 0.98 (d, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.3, 172.8, 62.8, 51.9, 51.3, 42.1, 41.8, 38.6, 33.4, 25.9, 21.0, 19.3, 12.1 ppm. Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85. Found: C, 64.85; H, 8.49; N, 5.63.

Reduction of the Nitro Group of 1a with Ni_2B. Synthesis of (±)-(1*S,2*R**,3*S**,4*R**,5*R**)-4-Amino-3-(*tert*-butyldimethylsilyloxymethyl)-2-methyl-5-phenylcyclohexanol (6).** A suspension of $NiCl_2$ (33 mg, 0.28 mmol) in 10 mL of MeOH was sonicated for 15 min followed by the addition of $NaBH_4$ (29 mg, 0.84 mmol), and the sonication was maintained for 30 min. A solution of nitro compound **1a** (190 mg, 0.5 mmol) in 5 mL of MeOH was then added to the mixture. Ten minutes later the sonicator was turned off, and the mixture was stirred at room temperature. $NaBH_4$ was then added in four portions (4 × 190 mg, 4 × 5 mmol) distributed in a period of 6 h. Finally, the solvent was removed under reduced pressure and the black slurry was redissolved in H_2O (10 mL) and EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with more EtOAc (3 × 15 mL). The organics were combined, washed with brine, dried under Na_2SO_4, and concentrated under reduced pressure. The crude amino alcohol was then purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH 20:1) to obtain 166 mg of **6** as a white solid in 95% yield: mp = 90−94 °C; R_f = 0.29 (SiO_2, CH_2Cl_2/MeOH 19:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.14 (m, 5H), 4.08 (dd, J = 11.2, 2.6 Hz, 1H), 3.75 (dd, J = 11.2, 2.2 Hz, 1H), 3.66 (q, J = 3.0 Hz, 1H), 3.05−2.95 (m, 2H), 2.12 (quintd, J = 7.3, 3.0 Hz, 1H), 2.01 (dt, J = 14.2, 3.0 Hz, 1H), 1.94−1.90 (m, 1H), 1.72−1.62 (m, 1H), 1.15 (d, J = 7.3 Hz, 3H), 0.99 (s, 9H), 0.20 (s, 3H), 0.18 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 128.6, 127.6, 126.3, 68.6, 57.7, 56.4, 45.4, 44.1, 42.2, 38.3, 25.7, 18.0, 15.9, −5.6, −6.0 ppm. Anal. Calcd for $C_{20}H_{35}NO_2Si$: C, 63.29; H, 8.76; N, 3.69. Found: C, 63.33; H, 8.86; N, 3.82.

Protection of Amino alcohol 8 with Cbz. Synthesis of (±)-(1*S,2*R**,3*S**,4*R**,5*R**)-4-(*N*-Benzyloxycarbonylamino)-1-(benzyloxycarbonyloxy)-3-(*tert*-butyldimethylsilyloxymethyl)-2-methyl-5-phenylcyclohexane (7).** Benzyl chloroformate (0.22 mL, 1.56 mmol) was added to a solution of 136 mg (0.39 mmol) of amino alcohol **6** in 10 mL of CH_3CN and 5 mL of saturated aqueous solution of K_2CO_3, and the mixture was stirred vigorously at room temperature for 14 h. The reaction was diluted with 20 mL of EtOAc, the layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in a vacuum. The resulting oil was purified by column chromatography (SiO_2, hexane/EtOAc 4:1) affording 200 mg of **7** as a colorless oil in 83% yield: R_f = 0.35 (SiO_2, hexane/EtOAc 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.15 (m, 15H), 5.00 (d, J = 12.7 Hz, 1H), 4.94 (d, J = 12.7 Hz, 1H), 4.58 (d, J = 6.9 Hz, 1H), 4.51 (d, J = 10.8 Hz, 1H), 4.06 (dt, J = 12.5, 6.9 Hz, 1H), 3.88 (dd, J = 11.2, 2.8 Hz, 1H), 3.79 (dd, J = 11.2, 2.4 Hz, 1H), 3.72−3.64 (m, 1H), 3.18 (td, J = 12.5, 3.4 Hz, 1H), 2.35−2.29 (m, 1H), 2.23−2.14 (m, 1H), 2.09 (dt, J = 13.8, 3.4 Hz, 1H), 1.72 (td, J = 13.8, 12.6 Hz, 1H), 1.16 (d, J = 6.9 Hz, 3H), 1.00 (s, 9H), 0.17 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 155.3 (×2), 142.4, 141.1, 136.2, 128.2, 128.1, 127.9, 127.8, 127.3, 127.0, 126.7, 126.3, 126.2, 68.0, 65.7, 64.1, 58.3, 55.6, 42.7, 42.5, 39.7, 36.9, 25.4, 17.6, 15.4, −6.0, −6.3 ppm.

Deprotection of 6. Synthesis of Diol (±)-(1*S,2*R**,3*S**,4*R**,5*R**)-4-(*N*-Benzyloxycarbonylamino)-3-(hydroxymethyl)-2-methyl-5-phenylcyclohexanol (8).** The procedure is identical to that described for the deprotection of silyl ethers **1** employing compound **7** (173 mg, 0.28 mmol). The residue was purified by a short flash chromatography (SiO_2, hexane/EtOAc 1:1) to obtain 103 mg of diol **8** as a colorless oil in 100% yield: R_f = 0.16 (SiO_2, hexane/EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27−7.03 (m, 10H), 5.28 (d, br, J = 9.0 Hz, 1H), 4.87 (s, 2H), 4.15−4.02 (m, 1H), 3.83 (dd, J = 12.5, 1.7 Hz, 1H), 3.81−3.70 (m, 1H), 3.75 (d, J = 12.5 Hz, 1H), 3.24 (td, J = 12.8, 3.4 Hz, 1H), 2.21−2.09 (m, 2H), 2.05 (dt, J = 12.8, 3.4 Hz, 1H), 1.73 (td, J = 12.8, 2.6 Hz, 1H), 1.13 (d, J = 6.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 142.9, 136.4, 128.5, 128.3, 127.7, 127.4, 127.3, 126.5, 68.4, 66.1, 56.7, 55.5, 43.0, 42.4, 40.5, 37.2, 15.8 ppm; HRMS (EI) calcd for $C_{22}H_{27}NO_4$ 369.1940, found 369.1940.

Oxidation of Diol 7. Synthesis of (±)-(1*S,2*R**,3*R**,5*S**,8*R**)-2-(Benzyloxycarbonylamino)-8-methyl-6-oxa-3-phenylbicyclo[3.2.1]octa-7-one (9).** The procedure is identical to that described above for the oxidation of nitro alcohols **2** but employing 92 mg of **8** (0.25 mmol). The reaction crude was purified by flash chromatography (SiO_2, hexane/EtOAc 2:1) and afforded 92 mg of lactone **9** as a white solid in 51% yield: mp = 145−154 °C; R_f = 0.25 (SiO_2, hexane/EtOAc 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39−7.17 (m, 10H), 5.09 (d, br, J = 9.1 Hz, 1H), 4.96 (s, 2H), 4.54 (d, J = 4.4 Hz, 1H), 4.24 (ddd, J = 12.3, 9.1, 2.6 Hz, 1H), 2.81 (td, J = 12.3, 6.7 Hz, 1H), 2.78 (d, J = 2.6 Hz, 1H), 2.41 (ddd, J = 14.1, 6.7, 4.4 Hz, 1H), 2.32 (q, J = 6.8 Hz, 1H), 1.79 (dd, J = 14.1, 12.3 Hz, 1H), 1.19 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 155.5, 139.6, 135.9, 128.7, 128.3, 127.9, 127.7, 127.6, 127.3, 82.1, 66.6, 53.8, 51.6, 43.5, 42.4, 37.7, 16.2 ppm. Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 71.91; H, 6.05; N, 3.68.

Deprotection of the Cbz Group of 9. Synthesis of (±)-(1*S,2*R**,3*R**,5*S**,8*R**)-2-Amino-8-methyl-6-oxa-3-phenylbicyclo[3.2.1]octa-7-one (10).** A flask containing lactone **11** (40 mg, 0.11 mmol) and Pd/C 10% (43 mg, 0.04 mmol) and capped with a rubber septum was evacuated and filled with nitrogen with a needle and a balloon. Absolute EtOH (10 mL) was added with a syringe, and the mixture was stirred vigorously at room temperature overnight. The reaction was filtered through Celite, and the Celite washed with EtOH (2 × 5 mL). The solvents were removed under reduced pressure to afford 23 mg of pure amino lactone **10** after filtration through a short flash chromatographic column (SiO_2, hexane/EtOAc 2:1) (yield 91%): R_f = 0.24 (SiO_2, CH_2Cl_2/EtOAc 1:2); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.56−7.34 (m, 5H), 4.70 (d, J = 4.1 Hz, 1H), 3.85 (dd, J = 11.5, 2.0 Hz, 1H), 3.00 (d, J = 2.0 Hz, 1H), 2.96 (td, J = 11.5, 6.2 Hz, 1H), 2.72 (q, J = 6.9 Hz, 1H), 2.28 (ddd, J = 13.5, 6.2, 4.1 Hz, 1H), 1.95 (dd, J = 13.5, 11.5 Hz, 1H), 1.16 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.1, 139.3, 128.8, 128.6, 127.5, 82.1, 53.1, 49.6, 42.6, 41.0, 36.7, 16.1 ppm; HRMS (EI) calcd for $C_{14}H_{17}NO_2$ 231.1259, found 231.1259.

Oxidation of the Furan Ring of 1c. Synthesis of Nitro Ester (+)-Methyl (1*S*,2*S*,3*S*,4*R*)-3-(*tert*-Butyldimethylsilyloxymethyl)-4-methyl-2-nitro-5-oxocyclohexane-1-carboxylate (11). To a solution of nitrocyclohexanone **1c** (202 mg, 0.55 mmol) in CH_3CN (4 mL) were added 4 mL of CCl_4, 6 mL of H_2O, and 1.75 g (8.19 mmol) of $NaIO_4$. The biphasic mixture was vigorously stirred, and 11 mg of $RuCl_3 \cdot xH_2O$ was added in one portion. After 15 min the mixture was diluted with 25 mL of EtOAc, and the supernatant organic layer was decanted carefully; this operation was repeated three times. The combined organic layers were treated with Na_2SO_4 and charcoal, filtered through Celite, and concentrated under reduced pressure. The residue was dissolved in 15 mL of Et_2O and treated with a solution of freshly prepared diazomethane in Et_2O. After 15 min, the excess of diazomethane was destroyed by the addition of acetic acid until the yellow color of diazomethane disappeared. The mixture was washed with brine, the aqueous layer was extracted with Et_2O (2 × 20 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The solid was purified by flash chromatography (SiO_2, hexane/EtOAc 2:1) to afford 180 mg of nitro ester **11** as a pale yellow solid in 91% yield: R_f = 0.53 (SiO_2, hexane/EtOAc 2:1); mp = 74−76 °C; $[\alpha]^{15}_D$ = +14.7 (*c* 1.3, CH_2Cl_2); ee > 99%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.32 (dd, J = 12.0, 4.7 Hz, 1H), 4.18 (td, J = 12.0, 6.2 Hz, 1H), 3.77 (dd, J = 11.5, 3.2 Hz, 1H), 3.76 (s, 3H), 3.47 (dd, J = 11.5, 0.9 Hz, 1H), 2.90−2.82 (m, 1H), 2.82 (dd, J = 15.6, 6.2 Hz, 1H), 2.60 (q, J = 6.8 Hz, 1H), 2.32 (dd, J = 15.6, 12.0 Hz, 1H), 1.21 (d, J = 6.8 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 203.7, 172.4, 85.7, 57.9, 52.5, 45.4, 43.7, 41.8, 39.9, 25.4, 17.9, 11.4, −6.3, −6.4 ppm; HRMS (EI) calcd for $C_{15}H_{26}NO_6Si$ (M − CH_3) 344.1529, found 344.1529.

Catalytic Hydrogenation of the Nitro Group of Ester 11. Synthesis (+)-Methyl (1*S*,2*S*,3*S*,4*R*)-3-(*tert*-Butyldimethylsilyloxymethyl)-2-amino-4-methyl-5-oxocyclohexane-1-carboxylate (12). The procedure is identical to that described above for nitro compound **1a**, but applied to 165 mg (0.46 mmol) of nitro ester **11** with 160 mg of Raney nickel. The resulting yellowish oil consisted in essentially pure amino ester **12** that was filtered through a short chromatographic column (SiO_2, CH_2Cl_2/MeOH 20:1) to obtain 150 mg (yield 99%): $R_f = 0.23$ (SiO_2, CH_2Cl_2/MeOH 20:1); $[\alpha]^{18}_D = +12.3$ (*c* 1.1, CH_2Cl_2); ee > 99%; ^{1}H NMR (200 MHz, $CDCl_3$) 4.00 (dd, $J = 10.9$, 0.9 Hz, 1H), 3.74 (s, 3H), 3.70 (dd, $J = 10.9$, 3.8 Hz, 1H), 3.67−3.54 (m, 1H), 3.27 (td, $J = 12.0$, 6.2 Hz, 1H), 2.56 (dd, $J = 15.8$, 6.2 Hz, 1H), 2.53 (quint, d, $J = 6.8$ Hz, 1H), 2.43 (ddd, $J = 15.8$, 12.0, 0.9 Hz, 1H), 2.10−2.01 (m, 1H), 1.14 (d, $J = 6.8$ Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.1, 174.5, 57.2, 53.1, 51.9, 48.4, 47.8, 44.9, 41.1, 25.5, 17.9, 11.6, −6.1, −6.2 ppm; HRMS (EI) calcd for $C_{16}H_{31}NO_4Si$ 329.2022, found 329.2019.

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Supporting Information Available: Copies of ^{13}C NMR and DEPT 3 spectra of selected compounds (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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