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Preparation of highly enantiomerically enriched cyclobutane and cyclobutene diols

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Abstract—Cyclobutene (+)-**9**, (+)-**12**, (+)-**13**, (+)-**15**, and cyclobutane (+)-**19**, (+)-**22**, (+)-**23**, (+)-**25** diols were obtained in high enantiomeric excesses from monoacetates (−)-**23** or (+)-**16**. An alternative method for obtaining (+)-**22** and (+)-**25** involved the resolution of cyclobutane 1,2-dicarboxylic acid.

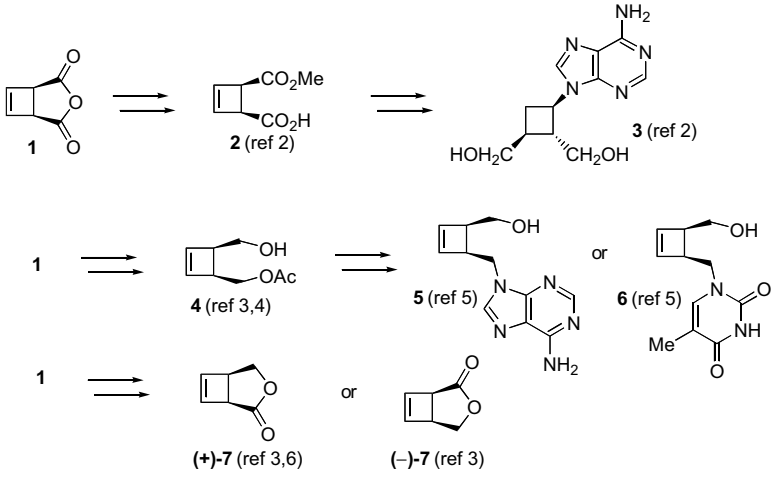
1. Introduction

Chiral cyclobutene compounds derived from anhydride **1**,[1] such as monoester **2**,[2] and monoacetate **4**,[3,4] have been used in the efficient syntheses of optically active nucleoside analogues **3**,[2] **5**,[5] and **6**.[5] Lactone **7**, which is equally available from **1** in both enantiomeric forms,[3,6] also proved to be an intermediate in nucleoside synthesis[7] (Scheme 1).

Other chiral cyclobutene and cyclobutane compounds, can be used as building blocks in asymmetric synthesis or find application in obtaining asymmetric reagents or catalysts. This is the reason why we envisaged preparing several diols, which can be interesting in their own right, or after substitution by amino or phosphino groups.

2. Results and discussion

The starting material for the cyclobutene series was monoacetate (−)-**4** obtained by enzymatic acetylation of



Scheme 1.

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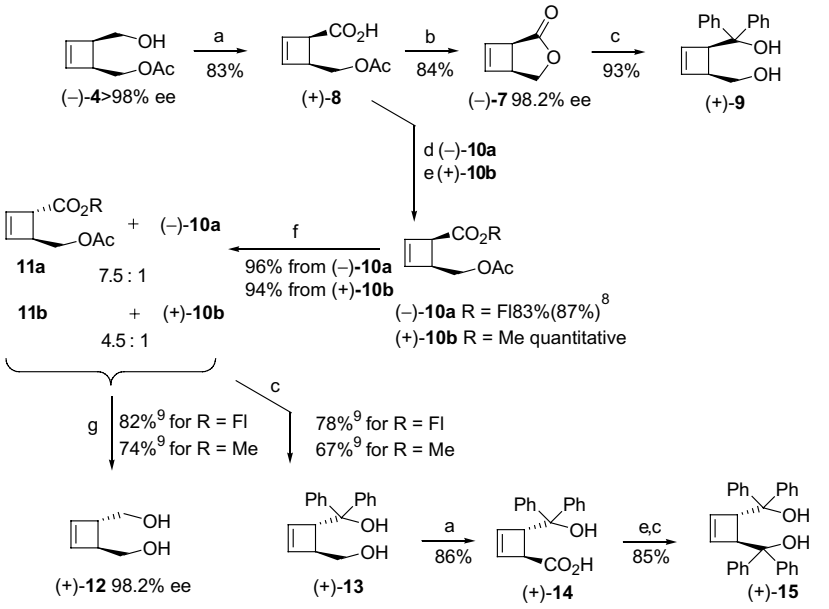
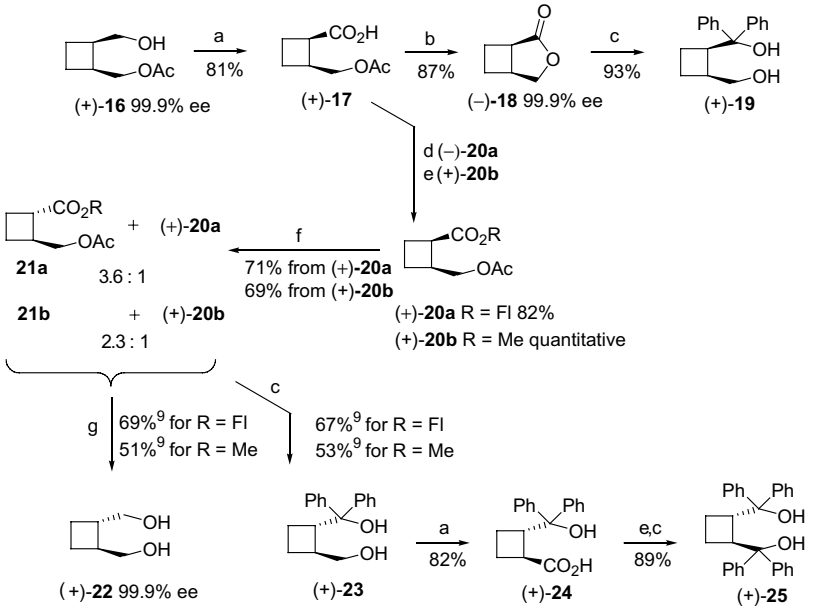
the corresponding diol.[4] It was oxidized to the acid (+)-**8**,[3] which was esterified with 9-fluorenol or diazomethane to yield (−)-**10a** or (+)-**10b**, respectively (Scheme 2). We then subjected both esters to epimerization in the presence of DBU. As expected, the *trans*/*cis* ratio, in favor of the *trans*-isomer, was higher from the more crowded compound (−)-**10a**. These mixtures were reduced with $LiAlH_4$ leading to both diols. The *trans*-isomer (+)-**12** was then easily separated from the *cis*-one. Similarly, reactions with PhMgBr led to compound (+)-**13**. The *cis*-isomer, (+)-**9** was available from lactone (−)-**7**[3] (Scheme 2).[8,9] We thought that it would also be interesting to prepare a cyclobutene analogue (+)-**15** of TADDOL. As a result we oxidized (+)-**13** to the acid (+)-**14**: esterification with CH_2N_2 followed by reaction with PhMgBr gave the expected product.

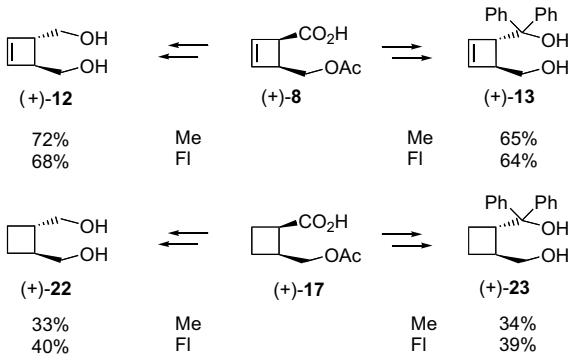
These methods were approximately the same for the cyclobutane series (Scheme 3).[8,9] However, in this case, epimerization with DBU did not work with the less acidic compounds (+)-**20a** and (+)-**20b** and so the reaction was carried out with 2 equiv of $(i\mathrm{Pr})_2\mathrm{NLi}$ followed by protonation. The optimal result for the latter step was obtained with AcOH in THF. Although in



Scheme 2. (a) CrO_3, H_2SO_4, H_2O (addition of the alcohol to the reagent); (b) (1) LiOH/THF, H_2O, (2) 3 M H_2SO_4; (c) PhMgBr, THF; (d) 9-fluorenol, DIC, CH_2Cl_2; (e) CH_2N_2; (f) DBU, CH_2Cl_2, rt, 8 days; (g) $LiAlH_4$, THF.



Scheme 3. (a) CrO_3, H_2SO_4, H_2O (addition of the alcohol to the reagent); (b) (1) LiOH/THF, H_2O, (2) 3 M H_2SO_4; (c) PhMgBr, THF; (d) 9-fluorenol, DIC, DMAP, CH_2Cl_2; (e) CH_2N_2; (f) (1) LDA, THF, (2) AcOH, THF; (g) $LiAlH_4$, THF.



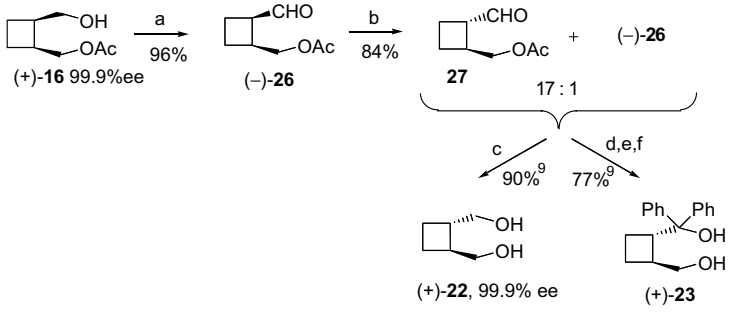
Scheme 4. Overall yields from (+)-**8** and (+)-**17**.

these reactions, several unidentified by-products were formed, however mixtures of **21a** and (−)-**20a** or **21b** and (+)-**20b**, used for the following step, could be obtained by column chromatography.

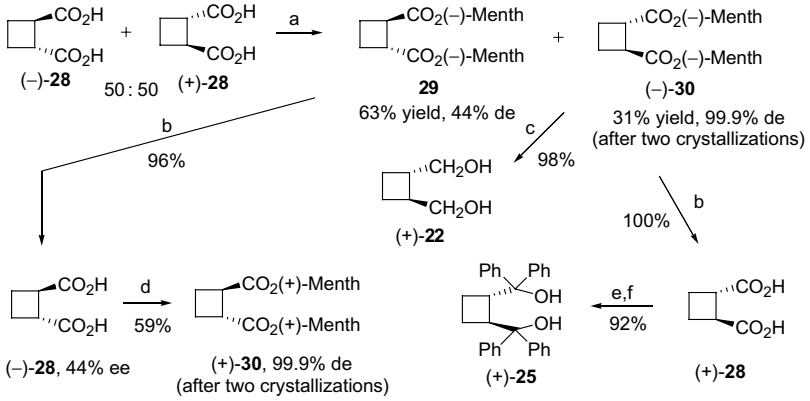
Eight diols were prepared in high enantiomeric purities. The *cis*-products (+)-**9** and (+)-**19** were obtained in a direct way, whereas obtaining the *trans*-products (+)-**12**, (+)-**13**, (+)-**22**, (+)-**23** then (+)-**15** and (+)-**25** involved a succession of esterification then epimerization steps. Compound (+)-**25** has already been obtained by a method involving epimerization of another chiral cyclobutane compound.[10] Overall yields depended upon several parameters: in the case of (+)-**12** and (+)-**13** they were higher via the methyl esters and in the case of (+)-**22** and (+)-**23**. They were higher via the 9-fluorenyl esters (Scheme 4).

We also tested an alternative method based on mild oxidation to (+)-**16**, followed by epimerization according to a known procedure.[11] Interestingly, this led to a large amount of the predominant *trans*-isomer **27**, an excellent precursor for alcohols (+)-**22** and (+)-**23** (Scheme 5). This method was more efficient than the previous one in the case of these compounds. Unfortunately it did not work in the cyclobutene series due to the instability of the intermediate aldehyde.[12]

A third methodology was based on the resolution of the diacid **28** (Scheme 6). One method has been reported using diastereomer salts formed by treatment with quinine or cinchonidine;[13] however the yields and enantiomeric excesses have not been indicated in the corresponding publications. A second method has also been described for obtaining (−)-**30** by reaction of (−)-menthyl succinate with 1,2-dibromoethane;[14] however the diastereomeric excess was not measured and the reaction led to a mixture of the *cis*- and *trans*-isomers. We then tried to carry out the resolution by preparing (−)-menthyl esters. We thus obtained a mixture of **29** and (−)-**30** in 97% yield with respect to the (−)-menthol. Both products could not be separated by chromatography but two successive crystallizations in methanol



Scheme 5. (a) DMSO, oxalyl chloride, Et_3N, CH_2Cl_2; (b) Et_3N; (c) $LiAlH_4$, THF; (d) CrO_3, H_2SO_4, H_2O (addition of the alcohol to the reagent); (e) CH_2N_2; (f) PhMgBr, THF.



Scheme 6. (a) (−)-Menthol, *p*TsOH, toluene, reflux; (b) LiOH, MeOH, H_2O; (c) $LiAlH_4$, THF; (d) (+)-menthol, *p*TsOH, toluene, reflux; (e) CH_2N_2; (f) PhMgBr, THF.

led to isolation of (−)-**30** in 31% yield and 99.9% diastereomeric excess. The absolute configuration and diastereomeric excess were determined thanks to a reduction into (+)-**22**. After separation of the pure (−)-**30**, compound **29** was recovered in 63% yield. The diastereomeric ratio (44%) was measured either from the inverse gate decoupling ^{13}C NMR spectrum or by reduction into (−)-**22** followed by measurement of the enantiomeric excess of the latter. Saponification followed by esterification with (+)-menthol led to (+)-**30** in 59% yield and 99.9% ee after two successive crystallizations. Obviously reduction into the alcohol (+)-**22** (or its enantiomer) was not the only way of measuring the diastereomeric excesses of the esters, but it was a useful method of obtaining this alcohol. On the other hand, the menthyl esters proved to react poorly with phenyl magnesium bromide. Therefore, to obtain (+)-**25**, the menthyl ester (−)-**30** was saponified, then esterified with diazomethane before reaction with phenyl magnesium bromide. Finally the method worked very well in obtaining (+)-**22** and (+)-**28** and it might also be used to prepare their enantiomers.

3. Conclusion

In conclusion we prepared several diols in efficient ways. In the case of the cyclobutene compounds (+)-**9**, (+)-**12**, (+)-**13**, and (+)-**15** we propose the method corresponding to Scheme 2, preferably via the methyl ester (+)-**10b**. Diol (+)-**19** is available by reaction with lactone (−)-**18** (Scheme 3). Obtaining diols (+)-**22** and (+)-**25** is efficient via diester (−)-**30** (Scheme 6) and the enantiomers might be available from (+)-**30**. Another good method for preparing (+)-**22** is via the aldehyde **27**, which is also a good intermediate for the preparation of (+)-**23**. In the case of these last three diols, the method corresponding to Scheme 3 is a less efficient alternative.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker AC 400 spectrometer at 400 and 100.6 MHz, respectively. All melting points are uncorrected. Elemental analyses were performed by the service of microanalyses, CNRS, ICSN, Gif sur Yvette. High resolution mass spectra were recorded on a Varian Mat 311 or ZabSpec TOF Micromass spectrometer at the CRMPO, Rennes. Infrared spectra were measured with an FT infrared spectrometer Genesis Matteson instrument. Enantiomeric excesses were determined by gas phase chromatography with a Hewlett-Packard HP 6890 Series apparatus equipped either with a Restek-β Dex Sm (25 m × 0.25 mm) column or with a R+βDEXCST (25 m × 0.25 mm) column.

4.2. (1*R*,5*S*)-3-Oxabicyclo[3.2.0]hept-6-en-2-one, (−)-7[3]

Jones' reagent was prepared from 26.7 g of CrO_3 and 23 mL of 18 M H_2SO_4 and the solution made up to 100 mL with acetone. Compound (−)-**4**[4] of 98.2% ee (1.401 g, 9 mmol) in acetone (30 mL) was then added dropwise to a solution of Jones' reagent previously prepared (9 mL) in acetone (30 mL) and stirred at −10 °C for 1 h. The reaction was allowed to proceed for 0.5 h after which isopropanol was added dropwise at the same temperature until discoloration. After 0.5 h stirring at room temperature, Celite (1 g) was added. After filtration over Celite, washing with acetone (3 × 30 mL) and evaporation, CH_2Cl_2 (100 mL) and an aqueous solution of 10% HCl saturated with NaCl (50 mL) were added to the residue. Decantation, extraction with CH_2Cl_2 (3 × 50 mL), drying of the combined organic phases with $MgSO_4$, and evaporation, afforded the acid (+)-**8**[3] as a colorless oil (1.271 g 83%). $[\alpha]_D^{20} = +118.5$ (*c* 1.1, $CHCl_3$), 98.2% ee [presumed identical to the ee of the precursor (−)-**4**]. ^1H NMR ($CDCl_3$) δ 2.02 (s, 3H), 2.65 (s, 1H), 3.50 (ddd, 1H, $J = 6.9$, 5.9, 4.9 Hz), 3.81 (dd, 1H, $J = 4.9$, 0.9 Hz), 4.19 (dd, 1H, $J = 11.8$, 5.9 Hz), 4.41 (dd, 1H, $J = 11.8$, 6.9 Hz), 6.17 (d, 1H, $J = 2.9$ Hz), 6.19 (dd, 1H, $J = 2.9$, 0.9 Hz). ^{13}C NMR ($CDCl_3$) δ 20.6, 45.5, 47.3, 63.5, 134.8, 138.9, 171.1, 177.1. IR (ν cm^{-1}) 3467, 1741, 1704, 1386, 1367, 1273, 1037. Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.19, H, 5.81. Acid (+)-**8** (680 mg, 4 mmol) was added to an ice-cooled solution of 1:1 THF/water mixture (8 mL). Lithium hydroxide (576 mg, 24 mmol) was then added portionwise and the reaction mixture stirred for 26 h at room temperature. The THF was evaporated, after which 20 mL of 3 M H_2SO_4 was added at 0 °C and NaCl then added until saturation. After 3 h stirring at 0 °C, extraction of the aqueous phase with CH_2Cl_2 (5 × 30 mL), washing of the combined organic phases with brine (30 mL), drying over $MgSO_4$, and evaporation led to an oil. Purification by column chromatography on silica gel (CH_2Cl_2/Et_2O, 10:0 → 9:1) provided lactone (−)-**7** as an oil (371 mg, 84%). $[\alpha]_D^{20} = -338$ (*c* 1, $CHCl_3$), 98.2% ee (determined by GPC). ^1H NMR ($CDCl_3$) δ 3.62 (m, 1H), 3.66 (d, 1H, $J = 3.5$ Hz), 4.29 (m, 2H), 6.33 (d, 1H, $J = 3.0$ Hz), 6.37 (d, 1H, $J = 3.0$ Hz). ^{13}C NMR ($CDCl_3$) δ 41.2, 46.5, 68.0, 139.0, 141.5, 177.3. IR (ν cm^{-1}) 3056, 1758, 1560, 1373, 1168.

4.3. (+)-(1*R*,4*S*)-4-(Hydroxymethylcyclobut-2-enyl)diphenylmethanol, (+)-9

A solution of (−)-**7** (370 mg, 3.36 mmol) in dry THF (7 mL) was added dropwise at 0 °C under nitrogen to a stirred 1 M THF solution of PhMgBr (13.5 mL, 13.5 mmol). After 15 min stirring at room temperature, and 30 min at 40 °C, the mixture was hydrolyzed at 0 °C with 10 mL of an aqueous solution of saturated NH_4Cl. THF was evaporated and 40 mL of water added. Extraction with CH_2Cl_2 (3 × 60 mL), washing of the combined organic phases with brine (50 mL), drying over $MgSO_4$, and evaporation, left a solid, which slowly crystallized at room temperature after solubilization in 20 mL of cyclohexane at 60 °C. Compound (+)-**9** was thus obtained as white crystals (829 mg, 3.12 mmol, 93%). Mp 127–128 °C (C_6H_{12}); $[\alpha]_D^{20} = +126$ (*c* 1, $CHCl_3$), 98.2 ee [presumed identical to the ee of the precursor (−)-**7**]. ^1H NMR ($CDCl_3$) δ 2.93 (s, 1H), 3.21–3.29 (m, 2H), 3.59 (dd, 1H, $J = 11.9$, 5.9 Hz), 4.16 (d,

1H, $J = 1.9$ Hz), 6.10 (d, 1H, $J = 2.9$ Hz), 6.18 (d, 1H, $J = 2.9$ Hz), 7.14–7.34 (m, 6H), 7.42–7.46 (m, 2H), 7.53–7.58 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 49.7, 56.5, 60.1, 76.1, 125.8, 125.9, 126.5, 126.8, 128.0, 128.3, 137.1, 137.5, 146.5, 147.0; IR (ν cm^{-1}) 3270, 3006, 1320, 1130. Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.16, H, 6.37.

4.4. (−)-(1*R*,4*S*)-4-Acetoxymethylcyclobut-2-ene carboxylic acid 9*H*-fluoren-9-yl ester, (−)-10a

A solution of DIC (1.2 mL, 7.7 mmol) in dry CH_2Cl_2 (8 mL) was added slowly at 0 °C to a stirred suspension of fluorenol (1.400 g, 7.7 mmol), DMAP (40 mg), and (+)-**8** (1.191 g, 7 mmol) in dry CH_2Cl_2 (14 mL). After 4 h at room temperature, oxalic acid (100 mg) was added. The reaction mixture then stirred for 3 h. Evaporation, then purification by column chromatography on silica gel (C_6H_{12}/Et_2O, 90:10 → 70:30) afforded (−)-**10a** as a paste (2.031 g, 87%). $[\alpha]_D^{20} = -2$ (c 1, $CHCl_3$), 98.2% ee [presumed identical to the ee of the precursor (−)-**4**]. ^{1}H NMR ($CDCl_3$) δ 1.85 (s, 3H), 3.46 (m, 1H), 3.89 (dt, 1H, $J = 4.7$, 1.0 Hz), 4.26 (dd, 1H, $J = 11.4$, 5.6 Hz), 4.37 (dd, 1H, $J = 11.4$, 6.9 Hz), 6.18 (dt, 1H, $J = 2.9$, 1.0 Hz), 6.21 (m, 1H), 6.80 (s, 1H), 7.30 (tdd, 2H, $J = 7.4$, 7.4, 2.8 Hz), 7.41 (m, 2H), 7.55 (m, 1H), 7.67 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 20.6, 45.9, 47.7, 63.6, 75.4, 120.0, 126.1, 127.9, 129.5, 135.2, 138.8, 141.0, 141.8, 170.9, 172.3; IR (ν cm^{-1}) 3009, 2978, 1743, 1738, 1410. Anal. Calcd for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.27, H, 5.37.

4.5. (+)-(1*R*,4*S*)-4-Acetoxymethylcyclobut-2-ene carboxylic acid methyl ester, (+)-10b

A solution of diazomethane in Et_2O was added with stirring to a solution of (+)-**8** (1.270 g, 7.47 mmol) in Et_2O (10 mL). Addition was stopped when the yellow coloration began to persist. The reaction mixture was stirred for 5 min, then acetic acid (90 μL, 1.5 mmol) was added. After 10 min stirring, the solution was evaporated affording (+)-**10b** as an oil (1.373 g, 7.46 mmol, quant). $[\alpha]_D^{20} = +4.2$ (c 1.1, $CHCl_3$), 98.2% ee [presumed identical to the ee of the precursor (−)-**4**]. ^{1}H NMR ($CDCl_3$) δ 2.02 (s, 3H), 3.46 (ddd, 1H, $J = 6.9$, 5.4, 4.9 Hz), 3.70 (s, 3H), 3.77 (m, 1H), 4.15 (dd, 1H, $J = 11.3$, 5.4 Hz), 4.32 (dd, 1H, $J = 11.3$, 6.9 Hz), 6.16 (d, 1H, $J = 3.4$ Hz), 6.17 (d, 1H, $J = 3.4$ Hz); ^{13}C NMR ($CDCl_3$) δ 20.2, 45.3, 47.3, 51.7, 63.6, 135.2, 138.7, 170.8, 171.9; IR (ν cm^{-1}) 3015, 2970, 1743, 1739, 1560. Anal. Calcd for $C_9H_{12}O_4$: C, 55.80; H, 7.02. Found: C, 55.66, H, 7.12.

4.6. (1*S*,4*S*)-4-Acetoxymethylcyclobut-2-ene carboxylic acid 9*H*-fluoren-9-yl ester, 11a

DBU (0.37 mL, 3 mmol) was added dropwise at 0 °C while stirring to a solution of (−)-**10a** (335 mg, 1 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture, sheltered from light was then stirred for 15 days at room temperature. Evaporation, addition of Et_2O (10 mL), washing with a 0.3 M aqueous solution of NH_4Cl (10 mL), water (10 mL) then brine (10 mL), drying over $MgSO_4$ then evaporation, provided a mixture of **11a** and (−)-**10a** in a 7.5:1 ratio, respectively, (322 mg, 96%) which was used as such in the following step. Data for **11a**: ^{1}H NMR ($CDCl_3$) δ 1.91 (s, 3H), 3.37 (m, 1H), 3.54 (m, 1H), 4.18 (dd, 1H, $J = 11.3$, 5.6 Hz), 4.22 (dd, 1H, $J = 11.3$, 7.0 Hz), 6.18 (d, 1H, $J = 2.8$ Hz), 6.21 (dd, 1H, $J = 2.8$, 0.9 Hz), 6.81 (s, 1H), 7.28–7.32 (m, 2H), 7.50–7.56 (m, 2H), 7.57–7.59 (m, 1H), 7.67 (d, 1H, $J = 7.5$ Hz).

4.7. (1*S*,4*S*)-4-Acetoxymethylcyclobut-2-ene carboxylic acid methyl ester, 11b

The previous experimental procedure was applied to the synthesis of **11b**, starting from (+)-**10b** (1.503 g, 8.1 mmol). After 8 days a mixture of **11b** and (−)-**10b** in a 4.5:1 ratio, respectively, (1.404 g, 94%). was obtained. It was used as such in the following step. Data for **11b**: ^{1}H NMR ($CDCl_3$) δ 2.06 (s, 3H), 3.30 (ddd, 1H, $J = 6.6$, 5.7, 1.6 Hz), 3.41 (dd, 1H, $J = 1.6$, 0.9 Hz), 3.70 (s, 3H), 4.16 (dd, 1H, $J = 11.3$, 5.7 Hz), 4.26 (dd, 1H, $J = 11.3$, 6.6 Hz), 6.14 (d, 1H, $J = 2.8$ Hz), 6.20 (dd, 1H, $J = 2.8$, 0.9 Hz).

4.8. (+)-(1*S*,4*S*)-(4-Hydroxymethylcyclobut-2-enylmethanol, (+)-12[2]

A 1:4.5 mixture of (+)-**10b** and **11b** (920 mg, 5 mmol) was dissolved in dry THF (10 mL) and this solution added dropwise under nitrogen, at 0 °C and with stirring, to a suspension of $LiAlH_4$ (380 mg, 10 mmol) in dry THF (10 mL). The reaction mixture was refluxed for 15 min, cooled to 0 °C, hydrolyzed by an aqueous solution of 2 M KOH (2.3 mL), stirred for 3 h then filtered on a sintered glass funnel. Washing of the solid with hot THF (4×4 mL), evaporation of the combined organic phases then column chromatography on silica gel (CH_2Cl_2/AcOEt 5:5 → 0:10) successively led to the *cis*-diol and then to (+)-**12** (423 mg, 74%) as oils. $[\alpha]_D^{20} = +4.1$ (c 1, $CHCl_3$), ee 98.2% [deduced from the ee of the reduction product, which was determined by GPC]. This product was obtained by the same experimental method as for (−)-**4**. ^{1}H NMR ($CDCl_3$) δ 2.69 (dd, 2H, $J = 9.7$, 4.7 Hz), 3.56 (dd, 2H, $J = 10.9$, 9.7 Hz), 3.79 (dd, 2H, $J = 10.9$, 4.7 Hz), 3.85 (br s, 2H), 6.11 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 49.4, 64.2, 137.0; IR (ν cm^{-1}) 3210, 1565, 1420. The same alcohol can also be obtained in 82% yield by reduction of the (−)-**10a** and **11a** mixture with $LiAlH_4$.

4.9. (+)-(1*S*,4*S*)-(4-Hydroxymethylcyclobut-2-enyl)diphenylmethanol, (+)-13

Reaction of the (−)-**10a** and **11a** or (+)-**10b** and **11b** mixture with PhMgBr [see preparation of (+)-**9**] provided crude mixtures of (+)-**9** and (+)-**13.** Purification by column chromatography on silica gel (C_6H_{12}/Et_2O

90:10 → 70:30), successively provided (+)-**13** then (+)-**9**. Compound (+)-**13** was thus obtained as an oil in 78% and 67% yield, respectively. $[\alpha]_D^{20} = +75$ (*c* 1, $CHCl_3$), 98.2% ee [presumed identical to the ee of the precursor (−)-**4**]. ^{1}H NMR ($CDCl_3$) δ 2.75 (s, 1H), 2.87 (m, 1H), 3.47 (m, 2H), 3.69 (s, 1H), 6.20 (dd, 1H, $J = 2.9$, 0.9 Hz), 6.25 (dd, 1H, $J = 2.9$, 0.7 Hz), 7.18–7.34 (m, 6H), 7.42–7.49 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 46.4, 55.8, 63.9, 76.8, 125.7, 126.5, 127.0, 128.0, 128.1, 137.0, 140.4, 145.8 et 145.8; IR (ν cm^{-1}) 3200, 3008, 2975, 1610, 1420. Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.16, H, 6.67.

4.10. (+)-(1*S*,4*S*)-(4-Hydroxydiphenylmethyl)cyclobut-2-ene carboxylic acid, (+)-14

Oxidation of (+)-**13** [see preparation of (+)-**8**] yielded (+)-**14** as an oil (86%). An analytical sample was obtained by column chromatography on silica gel (C_6H_{12}/Et_2O, 90:10 → 75:25). $[\alpha]_D^{20} = +170$ (*c* 1, $CHCl_3$), ee 98.2% [presumed identical to the ee of the precursor (−)-**4**]. ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 1H), 3.55 (m, 1H), 4.20 (m, 1H), 6.19 (ddd, 1H, $J = 2.8$, 1.2, 0.7 Hz), 7.18–7.33 (m, 6H), 7.41–7.44 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 46.7, 55.3, 77.0, 125.8, 126.1, 127.2, 128.2, 137.5, 139.0, 144.8, 145.3, 178.1; IR (ν cm^{-1}) 3400, 1708, 1420,1166. Anal. Calcd for $C_{18}H_{16}O_3$, $0.2H_2O$: C, 76.15; H, 5.82. Found: C, 76.40, H, 5.78.

4.11. (1*S*,4*S*)-[4-(Hydroxydiphenylmethyl)cyclobut-2-enyl]diphenylmethanol, (+)-15

Reaction of (+)-**14** with CH_2N_2 [see preparation of (+)-**10b**] led to the corresponding methyl ester as a yellow oil (quant). $[\alpha]_D^{20} = +176$ (*c* 1, $CHCl_3$), 98.2% ee [presumed identical to the ee of the precursor (−)-**4**]. ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 2H), 3.54 (m, 1H), 3.57 (s, 3H), 4.19 (m, 1H), 6.19 (dt, 1H, $J = 2.9$, 1.0 Hz), 6.28 (ddd, 1H, $J = 2.9$, 1.0, 0.5 Hz), 7.19–7.33 (m, 6H), 7.41–7.46 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 46.7, 52.1, 55.3, 77.0, 125.8, 126.1, 127.2, 128.2, 137.5, 139.0, 144.8, 145.3, 178.1; IR (ν cm^{-1}) 3220, 1740, 1420, 1320, 1160. Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.38, H, 6.12. Reaction of this ester with PhMgBr [see preparation of (+)-**9**] yielded (+)-**15** as a white solid in 85% yield. Mp 135–140 °C (dec); $[\alpha]_D^{20} = +76$ (*c* 1, $CHCl_3$), ee 98.2% [presumed identical to the ee of the precursor (−)-**4**]. ^{1}H NMR ($CDCl_3$) δ 3.59 (s, 2H), 5.52 (br s, 2H), 6.13 (s, 2H), 6.76–6.79 (m, 4H), 6.90 (tt, 2H, $J = 7.4$, 1.1 Hz), 7.14–7.41 (m, 14H); ^{13}C NMR ($CDCl_3$) δ 50.0, 78.2,0, 125.8, 126.1, 127.6, 127.7, 128.2, 128.3, 139.0, 144.7, 145.5; IR (ν cm^{-1}) 3215, 3006, 1610, 1332. Anal. Calcd for $C_{30}H_{26}O_2$: C, 86.09; H, 6.26. Found: C, 86.14, H, 6.31.

4.12. (1*R*,5*S*)-3-Oxabicyclo[3.2.0]hept-6-en-2-one, (−)-18[15]

Compound (+)-**16**[4] was oxidized into acid (+)-**17** with Jones' reagent [see preparation of (+)-**8**]. This acid was obtained in 81% yield as an oil. $[\alpha]_D^{20} = +9.1$ (*c* 1, $CHCl_3$), ee 99.9% (determined by GPC). ^{1}H NMR ($CDCl_3$) δ 1.80–1.90 (m, 1H), 2.03 (s, 3H), 2.10–2.17 (m, 2H), 2.34–2.43 (m, 1H), 2.95–3.04 (m, 1H), 3.28–3.36 (m, 1H), 4.21 (dd, 1H, $J = 11.3$, 6.5 Hz), 4.27 (dd, 1H, $J = 11.3$, 7.3 Hz), 9.80 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.7, 21.0, 21.5, 36.3, 39.3, 64.6, 171,2, 179.2; IR (ν cm^{-1}) 3390, 1740, 1702. Anal. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 7.02. Found: C, 55.66, H, 7.12. Lactone (−)-**18** was then obtained from (+)-**17** [see preparation of (−)-**7**] in 87% yield as an oil. $[\alpha]_D^{20} = -62$ (*c* 1.3, $CHCl_3$), 99.9% ee (determined by GPC). ^{1}H NMR ($CDCl_3$) δ 2.08–2.21 (m, 2H), 2.37–2.45 (m, 1H), 2.50–2.61 (m, 1H), 3.08–3.14 (m, 1H), 3.16–3.22 (m, 1H), 4.23 (m, 1H), 4.36 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 23.4, 25.3, 34.3, 38.1, 74.1, 180.8; IR (ν cm^{-1}) 2975, 2880, 1759.

4.13. (+)-(1*R*,2*S*)-(2-Hydroxymethylcyclobutyl)diphenylmethanol, (+)-19

Reaction of (−)-**18** with PhMgBr [see preparation of (+)-**9**] led to (+)-**19** as white crystals in 93% yield. Mp 136–137 °C (C_6H_{12}); $[\alpha]_D^{20} = +72$ (*c* 1, $CHCl_3$), 99.9% ee [presumed identical to the ee of the precursor (−)-**18**]. ^{1}H NMR ($CDCl_3$) δ 1.66–1.82 (2m, 2H), 2.01 (m, 1H, $J = 11.2$, 8.9 Hz), 2.20 (br s, 1H), 2.33 (m, 1H, $J = 9.9$, 1.1 Hz), 2.76 (m, 1H), 3.53 (dd, 1H, $J = 11.9$, 3.0 Hz), 3.63 (m, 2H), 4.77 (br s 1H), 7.15 (m, 1H), 7.20–7.26 (m, 4H), 7.30–7.35 (m, 4H), 7.51–7.54 (m, 1H); ^{13}C NMR ($CDCl_3$) δ. 19.9, 21.3, 40.0, 45.7, 62.4, 125.7, 126.1, 126.3, 126.6, 127.8, 128; IR (ν cm^{-1}) 3285, 2970, 2920, 2875, 1410, 1150. Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.56. Found: C, 80.69, H, 7.64.

4.14. (+)-(1*R*,2*S*)-2-Acetoxymethylcyclobutane carboxylic acid 9*H*-fluoren-9-yl ester, (+)-20a

Esterification of (+)-**17** with fluorenol [see preparation of (−)-**10a**] provided compound (−)-**20a** as a paste in 82% yield. $[\alpha]_D^{20} = +16$ (*c* 1, $CHCl_3$), 99.9% ee [presumed identical to the ee of the precursor (+)-**16**]. ^{1}H NMR ($CDCl_3$) δ 1.90 (s, 3H), 1.91 (m, 1H), 2.16 (m, 2H), 2.47 (m, 1H), 2.97 (m, 1H), 3.39 (m, 1H), 4.26 (d, 2H, $J = 6.8$ Hz), 6.78 (s, 1H), 7.30 (dd, 1H, $J = 7.5$, 2.5 Hz), 7.41 (td, 2H, $J = 7.5$, 0.6 Hz), 7.57 (td, 2H, $J = 7.7$, 0.6 Hz), 7.66 (d, 2H, $J = 7.5$ Hz); ^{13}C NMR ($CDCl_3$) δ 20.6, 21.2, 21.5, 36.1, 39.4, 64.5, 75.2, 119.8, 125.9, 126.0, 127.7 127.8, 129.3, 140.9, 141.8, 141.9, 170.8, 174.0; IR (ν cm^{-1}) 3007, 2948, 1736, 1731, 1452, 1365, 1240, 1170, 1039, 762, 742. Anal. Calcd for $C_{21}H_{20}O_4$: C, 74.98; H, 5.99. Found: C, 75.16, H, 6.17.

4.15. (−)-(1*R*,2*S*)-2-Acetoxymethylcyclobutane carboxylic acid methyl ester, (+)-20b

Esterification of (+)-**17** with diazomethane [see preparation of (+)-**10b**] quantitatively led to compound (+)-**20b** as a yellow oil. $[\alpha]_D^{20} = +38$ (*c* 1, $CHCl_3$), 99.9% ee [presumed identical to the ee of the precursor (+)-**16**]. ^{1}H NMR ($CDCl_3$) δ 1.77–1.86 (m, 1H), 2.02 (s, 3H), 2.05–

2.15 (m, 2H), 2.35–2.44 (m, 1H), 2.90–3.00 (m, 1H), 3.25–3.33 (m, 1H), 3.67 (s, 3H), 4.15 (dd, 1H, $J = 11.3$, 6.4 Hz), 4.20 (dd, 1H, $J = 11.3$, 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 20.9, 21.4, 21.6, 38.2, 38.2, 51.1, 64.6, 170.1, 179.3; IR (ν cm^{-1}) 2985, 2970, 1742, 1738, 1440. Anal. Calcd for $C_9H_{14}O_4$: C, 58.08; H, 7.58. Found: C, 58.05, H, 7.63.

4.16. (1*S*,2*S*)-2-Acetoxymethylcyclobutane carboxylic acid 9*H*-fluoren-9-yl ester, 21a

Epimerization of (+)-**20a** with LDA [see preparation of **21b**] provided a mixture of (+)-**20a** and **21a**, which were not separated. The ratio 1:3.6, respectively, was deduced from the ^{1}H NMR spectrum of the crude product and from the ratio of both alcohols [*cis*-(2-hydroxymethylcyclobutyl)methanol and (+)-**22**] obtained after reduction (see below).

4.17. (1*S*,2*S*)-2-Acetoxymethylcyclobutane carboxylic acid methyl ester, 21b

A solution of (+)-**20b** (1.029 g, 6 mmol) in THF (10 mL) was added at −78 °C to a solution of LDA in THF prepared from 1.8 mL (15.6 mmol) of *i*Pr$_2$NH, 9.4 mL of a 1.6 M solution of *n*BuLi in hexane (15 mmol) and THF (40 mL). After 1 h stirring at this temperature, hydrolysis with 10 mL of a 2 M solution of AcOH in THF followed by evaporation led to an oil, which was dissolved in CH_2Cl_2 (200 mL). Washing with an aqueous solution of saturated NH_4Cl (100 mL), water (100 mL) then brine (100 mL), drying over $MgSO_4$, and evaporation, provided a mixture of **21b** and (+)-**20b** in a 2.3:1 ratio, respectively. Purification by column chromatography on silica gel (CH_2Cl_2/Et_2O 10:1 → 8/2) provided the mixture of both products in the same ratio (712 mg, 69%). Data for **21b**: ^{1}H NMR ($CDCl_3$) δ 1.72–1.83 (m, 1H), 1.97 (dddd, 1H, $J = 17.3$, 9.1, 3.2, 0.9 Hz), 2.07 (s, 3H), 2.06–2.23 (2 m, 2H), 2.81–2.91 (m, 1H), 2.91–2.99 (m, 1H), 3.68 (s, 3H), 4.05 (dd, 1H, $J = 11.3$, 5.5 Hz), 4.11 (dd, 1H, $J = 11.3$, 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 20.7, 20.9, 21.5, 37.6, 51.6, 66.3, 171.1, 174.6; IR (cm^{-1}) 2980, 2920, 2870, 1741, 1739, 1410. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.09, H, 7.65.

4.18. (+)-(1*S*,2*S*)-(2-Hydroxymethylcyclobutyl)methanol, (+)-22

This alcohol was prepared by reduction with $LiAlH_4$ of the (+)-**20a** and **21a** or (+)-**20b** and **21b** mixtures [see preparation of (+)-**12**] or of the **27** and (−)-**26** mixture or of (−)-**30**. It was obtained as an oil. Yields are given in the schemes. $[\alpha]_D^{20} = +4.8$ (c 1, $CHCl_3$), 99.9% ee (determined by GPC). ^{1}H NMR ($CDCl_3$) δ 1.56–1.68 (m, 2H), 1.82–1.95 (m, 2H), 2.19–2.30 (m, 2H), 3.05 (br s, 2H), 3.40 (dd, 2H, $J = 11.1$, 5.4 Hz), 3.67 (dd, 2H, $J = 11.1$, 9.1 Hz); IR (ν cm^{-1}) 3240, 2950, 2875, 1420, 1210.

4.19. (+)-(1*S*,2*S*)-(2-Hydroxymethylcyclobutyl)diphenylmethanol, (+)-23

This alcohol was prepared by reaction with PhMgBr of the (−)-**20a** and **21a** or (−)-**20b** and **21b** mixtures [see preparation of (+)-**9**] or from the **27** and (−)-**26** mixture. It was obtained as an oil. Yields are given in the schemes. $[\alpha]_D^{20} = +99$ (c 1, $CHCl_3$), 99.9% ee [presumed identical to the ee of the precursor (+)-**16**]. ^{1}H NMR ($CDCl_3$) δ 1.91–2.42 (m, 6H), 3.11 (dd, 1H, $J = 11.5$, 5.4 Hz), 3.20 (br s, 1H), 3.63 (dd, 1H, $J = 11.5$, 6.7 Hz), 4.21 (br s, 1H), 7.15–7.34 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 23.2, 24.5, 38.7, 45.7, 68.6, 89.5, 26.1, 126.2, 126.9, 127.0, 127.2, 143.1, 143.6; IR (ν cm^{-1}) 3300, 2970, 1420, 1170. Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.56. Found: C, 80.69, H, 7.64.

4.20. (+)-(1*S*,2*S*)-(2-Hydroxydiphenylmethyl)cyclobutane carboxylic acid, (+)-24

Oxidation of (+)-**23** [see preparation of (+)-**8**] yielded (+)-**24** as an oil (82%). An analytical sample was obtained by column chromatography on silica gel (C_6H_{12}/Et_2O, 90:10 → 75:25). $[\alpha]_D^{20} = +93$ (c 1, $CHCl_3$), 99.9% ee [presumed identical to the ee of the precursor (+)-**16**]. ^{1}H NMR ($CDCl_3$) δ 2.01–2.07 (m, 2H), 2.19–2.25 (m, 2H), 2.28–2.38 (m, 1H), 3.31 (br s, 1H), 3.58–3.63 (m, 1H), 7.22–7.42 (m, 5H), 7.42 (dd, 2H $J = 7.2$, 7.2 Hz), 7.58 (dd, 1H, $J = 7.1$, 7.1 Hz), 7.91 (d, 2H, $J = 7.1$ Hz); ^{13}C NMR ($CDCl_3$) δ 21.8, 22.9, 44.1, 46.1, 79.5, 125.9, 126.0, 126.1, 127.3, 128.1, 144.7, 145.2, 178.2.; IR (ν cm^{-1}) 3430, 1709, 1424,1170. Anal. Calcd for $C_{18}H_{18}O_3$, 0.2 H_2O: C, 75.61; H, 6.49. Found: C, 75.77, H, 6.78.

4.21. (1*S*,2*S*)-[(2-Hydroxydiphenylmethyl)cyclobutyl]-diphenyl-methanol, (+)-25[10]

Reaction of (+)-**24** with CH_2N_2 [see preparation of (+)-**10b**] led to the corresponding methyl ester as an oil (quant). $[\alpha]_D^{20} = +135$ (c 1, $CHCl_3$), 99.9% ee [presumed identical to the ee of the precursor (+)-**16**]. ^{1}H NMR ($CDCl_3$): δ 1.99–2.05 (m, 2H), 2.18–2.25 (m, 2H), 2.27–2.35 (m, 1H), 3.47 (br s, 1H), 3.58–3.63 (m, 1H), 3.59 (s, 3H), 7.22–7.42 (m, 5H), 7,42 (dd, 2H, $J = 7.2$, 7.2 Hz), 7.58 (dd, 1H, $J = 7.1$, 7.1 Hz), 7.93 (d, 2H, $J = 7.1$ Hz); ^{13}C NMR ($CDCl_3$) δ 21.9, 22.8, 44.0, 45.8, 50.8, 79.4, 125.9, 126.0, 126.1, 127.3, 128.1, 144.7, 145.2, 175.7; IR (ν cm^{-1}) 3210, 2970, 1741, 1445, 1355, 1154. Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.89, H, 6.89. Reaction of this ester with PhMgBr [see preparation of (+)-**9**] yielded (+)-**25** as a white solid in 85% yield. Mp 181–182 °C (C_6H_{12}); $[\alpha]_D^{20} = +189$ (c 2, $CHCl_3$), 99.9% ee [presumed identical to the ee of the precursor (+)-**16**]. ^{1}H NMR ($CDCl_3$) δ 1.65–1.77 (m, 2H), 1.83–1.95 (m, 2H), 3.21–3.28 (m, 2H), 3.52 (br s, 2H), 7.16–7.36 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 21.7, 44.1, 79.4, 126.7, 127.6, 128.0, 128.1, 145.0, 146.5; IR (ν cm^{-1}) 3217, 2975, 2910, 2874, 1615, 1430, 1142. Anal. Calcd for $C_{30}H_{28}O_2$: C, 85.68; H, 6.71. Found: C, 85.71, H, 6.73. The same alcohol was also obtained by reaction of the dimethyl ester derived from (+)-**28** with PhMgBr.

4.22. (1*R*,2*S*)-(2-Hydroxymethyl)cyclobutane carbaldehyde, (−)-26

A solution of DMSO (2 mL, 28.2 mmol) in CH_2Cl_2 (68 mL) was cooled to −78 °C under nitrogen after which oxalyl chloride (1.20 mL, 14 mmol) was added

dropwise with stirring. After 5 min, a solution of compound (+)-**16**[4] (1.563 g, 9.9 mmol) in CH_2Cl_2 (48 mL) was added dropwise. After 1 h between −50 °C and −78 °C, dry Et_3N (7 mL, 50 mmol) was added. The reaction mixture was then warmed to room temperature and stirred for a further 30 min. Adding of CH_2Cl_2 (300 mL), washing with a 0.3 M aqueous solution of NH_4Cl (2×100 mL), water (2×100 mL) then brine (100 mL), drying over $MgSO_4$ then evaporation, led to (−)-**26** as an oil. $[\alpha]_D^{20} = -31.5$ (*c* 1, $CHCl_3$), 99.9% ee [presumed identical to the ee of the precursor (+)-**16**]. ^1H NMR ($CDCl_3$) δ 1.72–1.81 (m, 1H), 1.98–2.06 (m, 1H), 2.03 (s, 3H), 2.12–2.21 (m, 1H), 2.41–2.49 (m, 1H), 2.99–3.12 (m, 1H), 3.30–3.36 (m, 1H), 4.12 (dd, 1H, $J = 11.4$, 8.1 Hz), 4.19 (dd, 1H, $J = 11.4$, 5.5 Hz), 9.85 (d, 1H, $J = 1.8$ Hz); ^{13}C NMR ($CDCl_3$) δ 18.3, 20.8, 21.2, 37.2, 47.1, 64.2, 170.7, 202.4; IR (ν cm^{-1}) 1741, 1725, 1360, 1237.

4.23. (1*S*,2*S*)-(2-Hydroxymethyl)cyclobutane carbaldehyde, 27

Oxygen was removed by argon from 90 mL of dry Et_3N, then (−)-**26** (1.407 g, 9 mmol) added. Stirring under argon for 10 days, evaporation and purification by column chromatography on silica gel (CH_2Cl_2/Et_2O 99:1 → 80:20) led to a (1:17) mixture of (−)-**26** and **27** (1.182 g, 84%). Data for **27**: ^1H NMR ($CDCl_3$) δ 1.56–1.76 (m, 2H), 1.94–2.02 (m, 1H), 2.04 (s, 3H), 2.07–2.16 (m, 1H), 2.25–2.36 (m, 1H), 2.46–2.62 (m, 3H), 4.01 (dd, 1H, $J = 11.2$, 7.0 Hz), 4.07 (dd, 1H, $J = 11.2$, 5.8 Hz), 9.72 (d, 1H, $J = 1.8$ Hz); ^{13}C NMR ($CDCl_3$) δ 20.9, 21.7, 24.8, 33.1, 40.4, 50.1, 67.3, 171.1, 201.5.

4.24. Intermediates between 27 and (+)-23

Oxidation of the (−)-**26** and **27** mixture with Jones' reagent [see preparation of (−)-**8**] led to the corresponding acids. ^1H NMR ($CDCl_3$) of the major isomer (93% yield): δ 1.71–1.82 (m, 1H), 1.96 (dddd, 1H, $J = 17.3$, 9.1, 3.2, 0.9 Hz), 2.07 (s, 3H), 2.05–2.21 (2 m, 2H), 2.79–2.89 (m, 1H, $J = 8.8$, 6.1 Hz), 2.89–2.97 (m, 1H, $J = 8.9$ Hz), 3.68 (s, 3H), 4.05 (dd, 1H, $J = 11.3$, 5.5 Hz), 4.11 (dd, 1H, $J = 11.3$, 6.0 Hz). Esterification of these acids with CH_2N_2 [see preparation of (+)-**10b**] provided the corresponding methyl esters **21b** in quantitative yield.

4.25. (−)-(1*S*,2*S*)-Cyclobutane-1,2-dicarboxylic acid di(−)-menthyl ester, (−)-30[13] and (1*R*,2*R*)-cyclobutane-1,2-dicarboxylic acid di(−)-menthyl ester, 29

A racemic mixture of diacid (±)-**28** (10.00 g, 69.4 mmol), (−)-menthol (20.6 g, 131.9 mmol) and *p*TsOH (900 mg) was heated at reflux in toluene (150 mL) with stirring. A small amount of water was removed by azeotropic distillation with a Dean–Stark apparatus. The reaction was allowed to proceed for 21 h and the mixture cooled and evaporated at reflux. The oily residue was dissolved in CH_2Cl_2 (600 mL) and the organic phase was successively washed with an aqueous solution of 10% K_2CO_3 (200 mL) water (200 mL) and brine (200 mL), dried over $MgSO_4$, and evaporated to yield a mixture of **29** and (−)-**30** (25.24 g, 97%) as an oil. After dilution with MeOH (150 mL) and cooling to −25 °C overnight, a mixture of crystals, an oil and a solution were obtained. Warming to 4 °C for 8 h led to solubilization of the oily fraction. The mixture was then alternately cooled (−25 °C) and warmed (4 °C) over a week. The crystals were then filtered at −25 °C on a sintered glass funnel and washed with cold methanol (−25 °C, 20 mL). Two recrystallizations (heating with 30 mL in dry MeOH, 7 h at room temperature, one night at 4 °C, 3 h at −25 °C), washing (10 mL of MeOH, −25 °C) and drying under reduced pressure, yielded (−)-**30** as crystals (8.07 g, 31%). Mp 53–54 °C (MeOH); $[\alpha]_D^{20} = -69$ (*c* 1, $CHCl_3$), 99.9% de [presumed identical to the ee of the reduction product (+)-**22**]. ^1H NMR ($CDCl_3$) δ 0.75 (d, 6H, $J = 6.9$ Hz), 0.81–1.11 (m, 4H), 0.88 (d, 6H, $J = 7.1$ Hz), 0.90 (d, 6H, $J = 6.9$ Hz), 1.37 (ddt, 2H, $J = 12.9$, 9.3, 3.1 Hz), 1.42–1.56 (m, 2H), 1.64–1.71 (m, 4H), 1.83 (dtd, 2H, $J = 13.9$, 6.9, 2.7 Hz), 1.94–2.08 (m, 2H, $J = 11,9$ Hz), 2.13–2.17 (m, 4H), 3.32–3.37 (m, 2H), 4.62 (td, 2H, $J = 11.9$, 4.4 Hz); ^{13}C NMR ($CDCl_3$) 16.4, 20.8, 21.8, 22.1, 23.5, 26.3, 31.4, 34.3, 40.92, 40.94, 74.4, 173.2; IR (ν cm^{-1}) 2995, 2930, 2870, 2850, 1740, 1430, 1320, 1260. Anal. Calcd for $C_{24}H_{42}O_4$: C, 72.99; H, 10.64. Found C, 73.06, H, 10.54. The other organic fractions were combined and evaporated affording **29** (16.4 g, 63%). The de (44%) was deduced from the inverse gate decoupling ^{13}C NMR spectrum.

4.26. (1*S*,2*S*)-Cyclobutane (1,2)-dicarboxylic acid, (+)-28[13]

Water (8 mL), LiOH (360 mg) and MeOH (4 mL) were successively added to a solution of diester (−)-**30** (3.948 g, 10 mmol) in THF (8 mL). The reaction mixture was heated at reflux for 6 h then cooled. Organic solvents were evaporated and water (20 mL) added to the resulting aqueous solution. Extraction with Et_2O (4×30 mL) and removal of the organic phase, acidification of the aqueous phase by a 6 M aqueous solution of HCl until pH 2, addition of NaCl until saturation, extraction with Et_2O (5×30 mL), drying over $MgSO_4$ then evaporation provided (+)-**28** as a white powder (1.366 g, 95%) (when the residue was oily, 10 mL of toluene was added, then crystallization occurred during evaporation). Mp 128–130 (Et_2O); $[\alpha]_D^{20} = +155$ (*c* 1, EtOH), 99.9% ee (determined by GPG). ^1H NMR (acetone-d_6) δ 2.12–2.17 (m, 4H), 3.35–3.39 (m, 2H), 10.1 (very br s, 2H); ^{13}C NMR (acetone-d_6) δ 22.2, 40.7, 175.0.

4.27. (1*R*,2*R*)-Cyclobutane (1,2)-dicarboxylic acid, (−)-28

The mixture of both diastereomers **29** (16.4 g, 41.55 mmol) was saponified with LiOH [see preparation of (+)-**28**]. Compound (−)-**28** was thus obtained as a white powder [5.736 g, 96%, 44% ee (determined by GPC)].

4.28. (1*R*,2*R*)-Cyclobutane-1,2-dicarboxylic acid di(+)-menthyl ester, (+)-30

Diacid (−)-**28** (5.736 g, 39.8 mmol) was esterified with (+)-(menthol) (11.82 mg, 75.9 mmol) [see preparation of (−)-**30**]. A mixture of both esters was obtained. It was crystallized by the same procedure as for (−)-**30**, to give diester (+)-**30** (9.269 g, 59%). $[\alpha]_D^{20} = +69$ (*c* 1, $CHCl_3$), 99.9% de.

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