Asymmetric Construction of Quaternary Carbons from Chiral Malonates: Selective and Versatile Total Syntheses of the Enantiomers of α- and β-Cuparenones from a Common Optically Active Precursor

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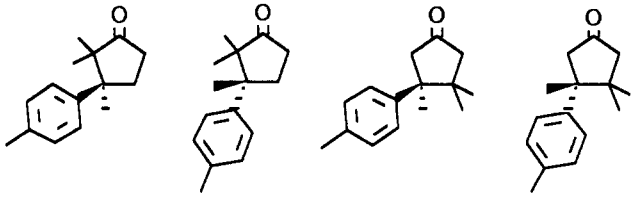
From a single chiron (*R*)-**4**, available with high enantiomeric purity (96%) by simple enzymatic hydrolysis (PLE) of a prochiral malonate, were prepared convenient precursors of the two enantiomers of α- and β-cuparenones (**1a,b** and **2a,b**). This versatile method also allows preparations of the enantiomer (*S*)-**4** and dimethyl 2-methyl-2-*p*-tolylsuccinate ((*S*)-**9a**), as well as the new butyrolactones (*R*)-**15**, (*R*)-**23**, and (*S*)-**25**, the new but-3-enolide (*S*)-**32**, and cyclopentenones (*S*)-**22** and (*S*)-**30**, all these compounds bearing an asymmetric quaternary carbon.

Asymmetric quaternary carbon centers are found in many naturally occurring compounds[1a] and convenient methods for their enantioselective construction have been only recently investigated.[1b] Prochiral malonic acid derivatives can provide versatile chiral building blocks[2] either through chemical transformations, i.e., by enantioselective alkylation of chiral half esters of monoalkyl malonic acids,[3] or through enzymatic conversions.[4]

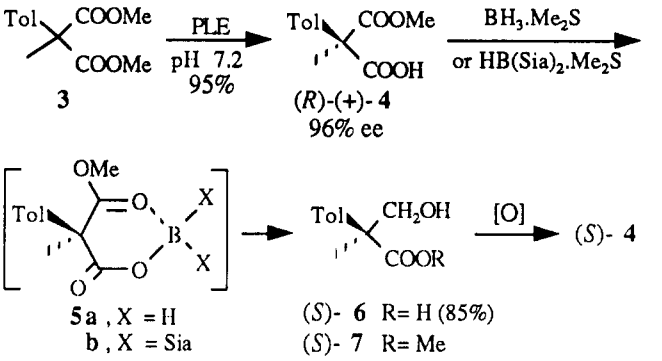
We report herein an enantioselective preparation of chiral α,α-disubstituted succinate derivatives and an efficient strategy for the construction of five-membered rings containing a chiral quaternary center. This approach provides a general pathway for the preparation of a wide variety of natural products containing a cyclopentane ring. It is illustrated by the syntheses of the γ-butyrolactones (*R*)-**15**, (*S*)-**25**, γ-lactol (*R*)-**19**, and but-3-enolide (*S*)-**32**, efficient precursors of the two enantiomers of α- and β-cuparenones (**1a,b** and **2a,b**).



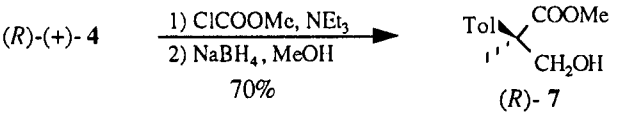
(+)-α-1a (-)-α-1b (-)-β-2a (+)-β-2b

These sesquiterpenes, first isolated from the essential oil of *Mayur Pankhi tree*,[5] have been detected in a number of essential oils.[6] Owing to the presence of two contiguous quaternary centers in the cyclopentanone ring, these compounds are the target of current synthetic efforts.[7-13]

Scheme I



Scheme II



The previous asymmetric syntheses of cuparenones involved either stereospecific rhodium-catalyzed intramolecular C-H insertion on an optically pure ternary center,[8] enantiocontrolled conjugate addition by chiral sulfoxide,[9] or alkylation of chiral bicyclic lactams derived from (*S*)-valinol.[1b] Enantioselective enzymatic hydrolysis of 1-acetoxydicyclopentadiene,[10] resolution of a disubstituted succinic acid with brucine,[11] Lewis acid induced ring contraction of an optically active epoxycyclohexanone,[12] or diastereoselective chiral olefin-ketene [2+2] cycloaddition[13] have been also used as key steps.

We had previously reported that the prochiral dimethyl malonate **3**, obtained in 78% yield from methyl *p*-tolylacetate by successive alkylations with methyl iodide and methyl chloroformate, underwent enantioselective enzymatic hydrolysis by pig liver esterase (PLE) to provide in 95% yield the acid ester (*R*)-(+)-**4** with 96% enantiomeric excess, determined from the ^{1}H NMR spectra of its salt with (*R*)-(+)-methylbenzylamine.[14]

Reduction of (*R*)-(+)-**4** with borane (BH_3·Me_2S) gave in 85% yield the β-hydroxy acid (*S*)-(-)-**6** *exclusively*. Es-

(1) (a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419. (b) Meyers, A. I.; Lefker, B. A. *J. Org. Chem.* **1986**, *51*, 1541.
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(6) Benesova, V. *Collect. Czech. Chem. Commun.* **1976**, 3812.
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(9) Posner, G. H.; Kogan, T. P.; Hulce, M. *Tetrahedron Lett.* **1984**, *25*, 383.
(10) Takano, S.; Inomato, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1989**, 271 and references cited therein.
(11) (a) Gharpure, M. M.; Rao, A. S. *Synth. Commun.* **1989**, *19*, 679. (b) *Ibid.* 1813.
(12) Asaoka, M.; Hayashibe, S.; Sonoda, S.; Takei, H. *Tetrahedron Lett.* **1990**, *31*, 4761.
(13) Greene, A. E.; Charbonnier, F.; Luche, J.; Moyano, A. *J. Am. Chem. Soc.* **1987**, *109*, 4752.
(14) (a) Fadel, A.; Canet, J. L.; Salaün, J. *Tetrahedron Lett.* **1989**, *30*, 6687. (b) Fadel, A. unpublished results. Dimethyl 2-(4-methoxyphenyl)-2-methylmalonate was hydrolyzed with PLE to give the corresponding (*R*)-(+)-malonic acid ester only with 84% ee (98% ee after recrystallization.

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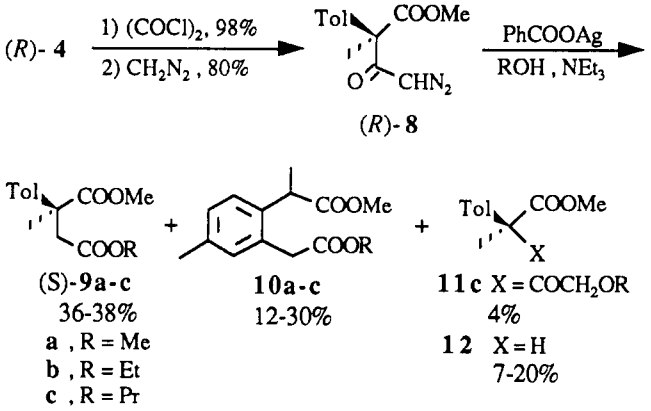
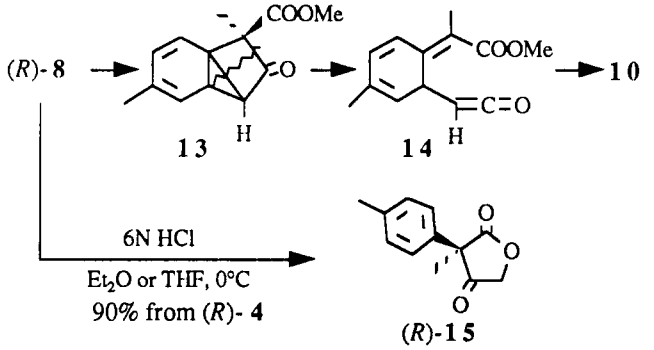
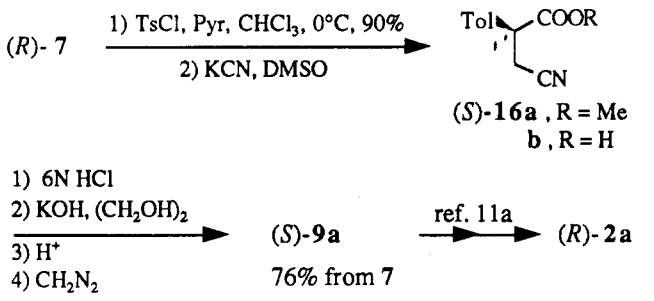
Scheme III



Scheme IV



Scheme V



terification with diazomethane (or acidified methanol) led to the β-hydroxy ester (*S*)-**7** which underwent oxidation by Jones' reagent to give the enantiomeric acid ester (*S*)-**4** in 86% overall yield. Formation of a six-membered ring intermediate **5** was considered to explain the abnormal behavior of the acid ester (*R*)-**4**, i.e., borane reduction of the ester function in the presence of a carboxylic acid group.[15a] Effectively no reduction occurred upon treatment of the acid ester (*R*)-**4** with disiamylborane (HB(Sia)$_2$·Me$_2$S).[16a,b] Although the cyclic intermediate **5b** (X = Sia) was likely formed, the lack of any transferable hydride on boron precludes reduction from taking place. Furthermore, addition of an excess of BH$_3$·Me$_2$S to **5b** or treatment with sodium borohydride in methanol at 20 °C did not give rise to any reduction product. Therefore, it was concluded that borane reduction of the activated ester group of (*R*)-**4** required an intramolecular hydride transfer within the cyclic boron complex **5a**.[14a]

On the other hand, reaction of the acid ester (*R*)-**4** with 1 equiv of methyl chloroformate in the presence of triethylamine gave a mixed anhydride which, upon reduction with sodium borohydride in methanol,[15b] gave the enantiomeric β-hydroxy ester (*R*)-(+)-**7** in 70% overall yield.

Therefore, both enantiomeric hydroxy esters (*S*)-**7** and (*R*)-**7** are now readily available from a common chiron, i.e., the methyl malonate monoester (*R*)-(+)-**4**. They constitute convenient sources of the quaternary stereogenic centers found in sesquiterpenes such as **1a,b** and **2a,b**.

(−)-β-Cuparenone (2a)

We first investigated the preparation of (−)-β-cuparenone (**2a**) from dimethyl 2-methyl-2-*p*-tolylsuccinate ((*S*)-**9a**). Thus, reaction of acid ester (*R*)-(+)-**4** with oxalyl chloride gave the corresponding acid chloride in 98% yield. Then treatment with diazomethane in the presence of NEt$_3$ (to avoid further lactonization which occurred readily in acidic medium) gave the expected diazoketone (*R*)-**8** in 80% yield. Unfortunately, this diazo ketone underwent Wolff rearrangement with poor yields. Thus, on heating in refluxing methanol, ethanol, or *n*-propanol in the presence of silver benzoate and triethylamine the expected succinates (*S*)-**9a–c** were formed with 36, 38, and 36% yield, respectively, besides the byproducts **10–12**.

The diester **10a–c** (12–30%) most likely arose from ring opening (retro [2+2] olefin-ketene cycloaddition)[17] of the cyclopropane **13**, which in turn results from a ketocarbene addition on the *p*-tolyl ring of (*R*)-**8**. Intermediate ketene **14** then underwent addition of methanol (ethanol or propanol) and aromatization (by 1,3-hydrogen shift) to form diesters **10a–c**. Formation of keto ether **11c** (X = COCH$_2$OR) arose from addition of propanol to the ketocarbene derived from (*R*)-**8**, while methyl 2-*p*-tolylpropionate (**12**) corresponds to a decarboxylation from the acid ester (*R*)-**4**.

Attempted photolytically induced[18] or silver oxide catalyzed[17a] Wolff reaction of diazo ketone (*R*)-**8** remained unsuccessful. While our work was in progress, the synthesis of α,α-disubstituted succinates based on the Wolff rearrangement of α-diazo ketones prepared from a malonic acid monoester was reported in 43–51% yield;[3] likely the *p*-tolyl ring as substituent of the α-diazo ketone (*R*)-**8** is responsible for the low yields obtained in this Arndt–Eistert synthesis. However, simple addition of an excess of 6 N hydrochloric acid to a solution of the α-diazo ketone (*R*)-**8** in ether or tetrahydrofuran at 0 °C gave 2-methyl-3-oxo-2-*p*-tolyl-4-butanolide ((*R*)-(+)-**15**) ([α]$_D$ = +11°, *c* 1, CHCl$_3$) in 90% overall yield from the acid ester (*R*)-**4** when the synthesis was performed in one pot. This oxo γ-lactone (*R*)-**15** constitutes a convenient precursor of (+)-β-cuparenone (**2b**) (vide infra).

On the other hand, reaction of β-hydroxy ester (*R*)-**7** with tosyl chloride (1.5 equiv) in chloroform containing 2 equiv of pyridine led to corresponding tosylate (90% yield). Then treatment with 2.5 equiv[19a] of potassium cyanide in

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(17) (a) Lokensgrad, J. P.; O'Dea, J.; Hill, E. A. *J. Org. Chem.* **1974**, *39*, 3355. (b) Smith, A. B., III; Toder, B. H.; Branca, S. J. *J. Am. Chem. Soc.* **1976**, *98*, 7456.

(18) For a review on photolysis Wolff rearrangement, see: Ando, W. In *The Chemistry of Diazonium and Diazo compounds*; Patai, S., Ed.; Wiley: New York, 1978; pp 458–475.

(19) (a) Treatment of the tosylate with 1 equiv of potassium cyanide in dimethyl sulfoxide (DMSO) at 100 °C for 12 h gave a mixture of nitriles (*S*)-**16** (30%) of retroaldol product, i.e., the methyl 2-*p*-tolylpropionate **12** (40%), and of the unreacted tosylate (30%). (b) The crude mixture was treated with a solution of potassium hydroxide (2 equiv) in ethylene glycol at reflux for 14 h to give, after acidification (1 N HCl), nitrile acid (*S*)-**16b**, exclusively; use of 12 equiv of potassium hydroxide in refluxing ethylene glycol led only to partial saponification of the nitrile group.

DMSO at 100 °C for 12 h gave a mixture of nitrile ester (*S*)-**16a** (R = Me) and nitrile acid (*S*)-**16b** (R = H). In order to obtain total hydrolysis of the nitrile function,[19b] the crude nitrile ester and acid mixture (*S*)-**16a,b** were successively heated at reflux in 6 N hydrochloric acid for 14 h and in ethylene glycol at reflux containing 10 equiv of potassium hydroxide for 14 h. Acidification to pH 2 with 6 N HCl and esterification of the resulting succinic acid with an excess of diazomethane (5 equiv) (or with acidic methanol)[11a] gave the expected dimethyl (*S*)-(+)-2-methyl 2-*p*-tolylsuccinate (**9a**) in 76% overall yield from hydroxy ester (*R*)-7. The enantiomeric excess of succinate (*S*)-**9a** determined from its 250-MHz ^{1}H NMR spectra recorded in the presence of a chiral shift reagent (Eu(hfc)$_3$), compared to the racemic succinate (±)-**9a** (prepared by alkylation of **12** with sodium iodoacetate), was 98% ee. While this work was in progress, the obtention of the dimethyl succinate (*S*)-**9a** was claimed from resolution of the corresponding racemic succinic acid with brucine followed by esterification. As reported this diester is a suitable precursor to (*R*)-(−)-β-cuparenone (**2a**),[11a] proving in addition the (*S*)-absolute configuration of the succinate **9a**.[20]

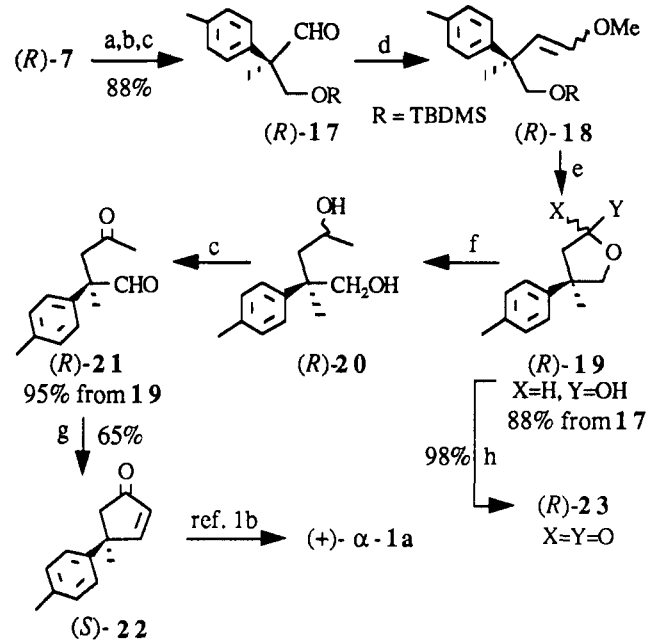
Chiral succinic acids have become important synthetic intermediates. For instance, they have recently been used to prepare several pseudopeptides endowed with antibiotic, anticancer, and enzyme inhibitory properties.[21] We have recently reported efficient and general methods for the asymmetric syntheses of monosubstituted succinic acid derivatives (ternary stereogenic centers) either by enantioselective alkylation of chiral imide enolates[22] or by enzymatic resolution[23] and illustrated their synthetic potential by the syntheses of optically active C_3–C_6-membered-rings and 4-butanolides (e.g., *cis*-Quercus lactone).[22b,24] (For other entries to chiral succinates, see ref 25). Now, transformation of methyl β-hydroxypropionate (*R*)-7 into the dimethyl succinate (*S*)-**9a**, which can be analogously achieved from the readily available enantiomeric hydroxy ester (*S*)-7 to provide (*R*)-**9a**, constitutes an efficient and versatile asymmetric synthesis of α,α-disubstituted succinates and therefore of quaternary stereogenic centers.

(+)-α-Cuparenone (1a) (or (−)-α-Cuparenone (1b))

β-Hydroxy ester (*R*)-7 can also offer a key intermediate for the approach to (+)-α-cuparenone (**1a**) via the γ-keto aldehyde (*R*)-**21** and cyclopentenone (*S*)-**22**.

To this end (*R*)-(+)-7 was successively silylated with *tert*-butyldimethylsilyl chloride and reduced by 2 equiv of diisobutylaluminum hydride (DIBALH)[26] in chloroform

Scheme VI[a]



[a] Reagents: (a) TBDMSCl, imidazole, DMF, 40 °C, 10 min; (b) DIBALH, 2 equiv, CH_2Cl_2, −78 °C; (c) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −60 °C; (d) *n*-BuLi, 2.5 equiv, $(Ph)_3MeOCH_2P^+$ Cl^- 3 equiv, THF, −15 °C, 0.5 h, then 0 °C, 3 h; (e) 2 N HCl, THF, 30 °C, 2 h; (f) MeMgBr, Et_2O, 0 °C, 1 h; (g) cat. KOH/EtOH in THF, 20 °C, 1 h; (h) 2 equiv, PCC, Celite, 1 equiv of NaOAc, CH_2Cl_2, 20 °C, 10 h.

at −78 °C. The resulting alcohol was oxidized by oxalyl chloride activated dimethyl sulfoxide (Swern oxidation)[27] to give the 3-(*tert*-butyldimethylsiloxy)-2-methyl-2-*p*-tolylpropanaldehyde ((*S*)-17) in 88% overall yield from (*R*)-7.

Wittig reaction of the aldehyde (*S*)-17 with (methoxymethylene)triphenylphosphorus ylide[7,28] led to the labile enol ether (*S*)-18 which, upon hydrolysis with 2 N hydrochloric acid, gave a 1:2 epimeric mixture of 2-hydroxy-4-methyl-4-*p*-tolyltetrahydrofuran ((*R*)-**19**) in 88% overall yield from (*S*)-17. Treatment of this lactol with 3 equiv of methylmagnesium bromide provided a 1:1 diastereoisomeric mixture of diol (*R*)-**20**, which, underwent double Swern oxidation[27] to yield 2-methyl-4-oxo-2-*p*-tolylvaleraldehyde ((*R*)-(−)-**21**) in 95% overall yield from the lactol (*R*)-**19**. Aldol cyclization of keto aldehyde (*R*)-**21** with potassium hydroxide (1 M solution in ethanol) gave 4-methyl-4-*p*-tolylcyclopent-2-en-1-one ((*S*)-**22**) in 65% yield (although a 94% yield was reported for the base-induced cyclization of its enantiomer (*S*)-**21** under the same conditions).[1b] Taking into account the optical rotation of (*S*)-**22** ($[\alpha]_D$ = −118°, *c* 0.95, EtOH) compared to its enantiomer (*R*)-**22** ($[\alpha]_D$ = +114°, *c* 1.36, EtOH),[1b] the 96% enantiomeric purity of the starting acid ester (*R*)-(+)-**4**,[14a]

(20) The (*S*) absolute configuration of the ester (+)-**9a** was also assigned comparatively with reported data, (see: des Abbayes, H.; Dadard, R. *Tetrahedron* **1975**, *31*, 2111) therefore confirming the (*R*) absolute configuration of (+)-**4** previously proposed by us (see ref 14a).

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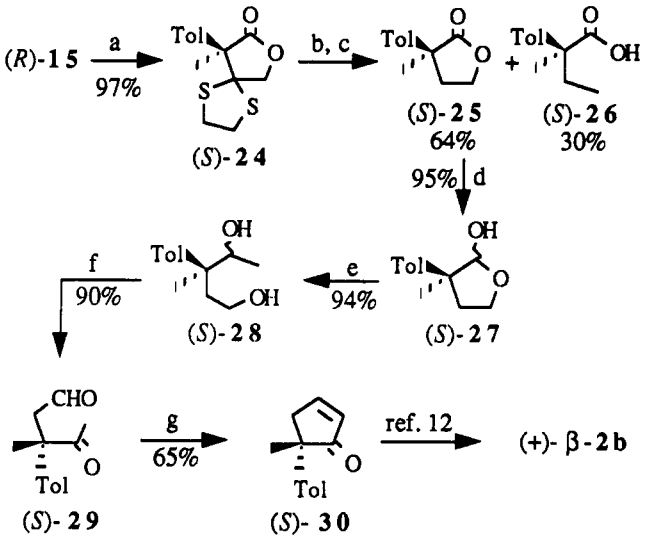
(25) (a) Bashiardes, G.; Davies, S. G. *Tetrahedron Lett.* **1988**, *29*, 6509. (b) Bashiardes, G.; Collingwood, S. P.; Davies, S. G.; Treston, S. C. *J. Organometal. Chem.* **1989**, *364*, C-29–C-32. (c) Larchevêque, M.; Petit, Y. *Synthesis* **1991**, 162.

(26) Use of 1 equiv of DIBALH gave only mixture of alcohol and unreacted ester containing only traces of the expected aldehyde.

(27) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(28) (a) Kametani, T.; Kawamura, K.; Tsubuki, M.; Honda, T. *Chem. Pharm. Bull.* **1985**, *33*, 4821. (b) It is interesting to note that the thermodynamic Wittig reagent prepared in situ from 3 equiv of Ph_3P^+-CH_2OMeCl^- and 2.5 equiv of *n*-BuLi in THF should be treated with ultrasound for 2 h to provide only the corresponding olefin (*S*)-**18**, otherwise when used as described by Kametani (see ref 28a) a byproduct, i.e., 1-(*tert*-butyldimethylsiloxy)-2-methyl-2-*p*-tolylhept-3-ene was formed in 20–50% yields. Likely, it resulted from competing attack of *n*-BuLi at the phosphorus atom forming the corresponding phosphinebutylidene, which in turn reacted with aldehyde **17** to give the byproduct (see ref 28c). (c) For transylidation to the thermodynamically more stable phosphinealkylidene, see: Seyferth, D.; Hughes, W. B.; Heeren, J. K. *J. Am. Chem. Soc.* **1965**, *87*, 2847, 3467.

Scheme VII[a]



[a] Reagents: (a) $(CH_2SH)_2$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 20 °C, 12 h; (b) Raney Ni (W2), EtOH, reflux, 36 h; (c) 6 N HCl; (d) DIBALH, 1 equiv, toluene, −78 °C, 10 min; (e) MeMgBr, 3 equiv, Et_2O, 0 °C; (f) $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C, then NEt_3; (g) cat. KOH/EtOH in THF, 20 °C, 1 h.

and considering that any racemization of the stereogenic quaternary center was highly improbable in each step of the sequence (*R*)-**4** → (*S*)-**22**, it can be assumed that the enantiomeric purity of the cyclopentenone (*S*)-**22** is at least 96%. Finally, introduction of the *gem*-dimethyl group and reduction of the unsaturation as previously reported from the racemic (±)-**22**[29] and from the enantiomer (*R*)-**22**[1b] can lead to the corresponding (*R*)-(+)-α-cuparenone (**1a**).[30]

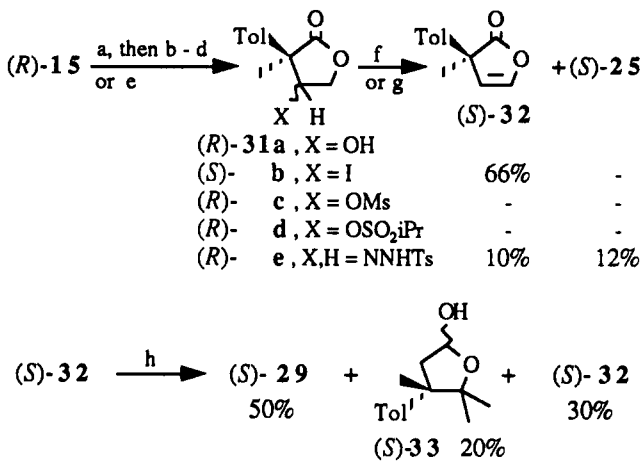
It is noteworthy that simple oxidation of the diastereomeric mixture of lactols (*R*)-**19** with pyridinium chlorochromate[31] dispersed on Celite provided in 98% yield a new γ-lactone, i.e., 4-methyl-2-oxo-4-*p*-tolyl-4-butanolide ((*R*)-(+)-**23**).

Furthermore, it must be also stressed that asymmetric synthesis of (−)-α-cuparenone (**1b**)[1b] is conceivable from the enantiomeric β-hydroxy ester (*S*)-**7**, available in two steps from the acid ester (*R*)-**4**, following a pathway identical to the one proposed herein for (+)-α-**1a**.

(+)-β-Cuparenone (2b)

Thioacetalization of the oxolactone (*R*)-**15**, obtained by simple acidic hydrolysis of the readily available diazo ketone (*R*)-**8** in high yields (vide supra, Scheme IV), with ethanedithiol in the presence of a catalytic amount of trifluoroboron etherate gave the corresponding dithioacetal (*S*)-(−)-**24** in 97% yield. Reduction of (*S*)-**24** with Raney nickel (W2) (ratio 20:1)[32] in refluxing ethanol for 36 h led to the expected 3-methyl-3-*p*-tolyl-4-butanolide ((*S*)-**25**) in 64% yield. The enantiomeric excess of this new γ-lactone (*S*)-**25** determined from its 250-MHz ^{1}H NMR spectra recorded in the presence of $Eu(hfc)_3$, compared to the racemic lactone (±)-**25** (prepared in 80% overall yield by alkylation of **12** with ethylene dioxide in the presence of tetramethylethylenediamine, TMEDA),[33] was 98% ee.

Scheme VIII[a]



[a] Reagents: (a) $NaBH_4$, EtOH, −10 °C; (b) then Ph_3P, imidazole, I_2, toluene, rflx; (c) then NEt_3, MsCl, CH_2Cl_2, 20 °C; (d) then NEt_3, *i*-$PrSO_2Cl$, Et_2O, 20 °C; (e) *p*-toluenesulfonhydrazide, EtOH, reflux, 90%; (f) DBU, THF, reflux; (g) used for **31e** $NaBH_3CN$, H^+, DMF, sulfolane, 110 °C; (h) MeLi, Et_2O, −90 to −78 °C, 1 h.

Moreover, further acid hydrolysis of the nickel-containing solid residue of the reaction gave 2-methyl-2-*p*-tolylbutanoic acid ((*S*)-**26**) in 30% yield. This byproduct likely resulted from ring opening of lactone **24** and reduction.

Reduction of the γ-lactone (*S*)-**25** by 1 equiv of DIBALH led to a 2:1 diastereomeric mixture of 2-hydroxy-3-methyl-3-*p*-tolyltetrahydrofurans ((*S*)-**27**) in 95% yield. This mixture of hemiacetals was treated with an excess of methylmagnesium bromide (3 equiv) to give a 1:1 mixture of 3-methyl-3-*p*-tolylpentan-1,4-diols ((*S*)-**28**) in 94% yield. Double Swern oxidation[27] of the diastereomeric mixture of 1,4-diols (*S*)-**28** afforded in 90% yield 3-methyl-4-oxo-3-*p*-tolylvaleraldehyde ((*S*)-(+)-**29**), *exclusively*. Then aldol cyclization of this keto aldehyde occurred upon treatment with potassium hydroxide (1 M solution in ethanol) at room temperature to provide in 65% yield the expected cyclopentenone (*S*)-(+)-**30**. As determined from its 250-MHz ^{1}H NMR spectrum recorded in the presence of $Eu(hfc)_3$, compared to the racemic cyclopentanone (±)-**30** (prepared analogously from the racemic lactone (±)-**25**), the enantiomeric excess of (*S*)-(+)-**30** was 98%. As recently reported this cyclopentenone now readily available in high yield and with high enantiomeric purity, constitutes an efficient precursor of (+)-β-cuparenone (**2b**) by successive addition of methyllithium, oxidation with pyridinium dichromate and addition of methyl copper.[12]

Alternatively, sodium borohydride[34] reduction of (*R*)-**15** in ethanol led to a 9:1 diastereomeric mixture of 3-hydroxy-2-methyl-2-*p*-tolyl-4-butanolides ((*R*)-(−)-**31a**) in 94% yield.[35] By analogy with reported data for a similar lactone,[34] the chemical shift for the methyl-C(2) of **31a** in ^{13}C NMR allows us to attribute the configuration syn to the major isomer of **31a** ($\Delta\delta_C = \delta_{syn} - \delta_{anti} = 3.8$ ppm). Iodination of the hydroxy lactone (*R*)-**31a** with iodine in

(29) Wenkert, E.; Buckwalter, B. L.; Craviero, A. A.; Sanchez, E. L.; Sathe, S. S. *J. Am. Chem. Soc.* **1978**, *100*, 1267.

(30) The absolute configuration of (+)-α-cuparenone has been earlier established by Ito to be (*R*)-(+) for the natural sesquiterpene: Irie, T.; Suzuki, T.; Ito, S.; Kurosawa, E. *Tetrahedron Lett.* **1967**, 3187.

(31) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2650.

(32) Augustine, R. L. *Catalytic hydrogenation*; Dekker, M., Ed.; M. Dekker: New York, 1965; p 23.

(33) Berkowitz, D. B. *Synth. Commun.* **1990**, *20*, 1819. When the reaction was conducted without TMEDA the yield decreased from 80% to 38%.

(34) For reduction of analogous oxolactone into syn and anti derivatives, see: Wyss, H.; Vögeli, U.; Scheffold, R. *Helv. Chim. Acta* **1981**, *64*, 775 and references cited therein.

(35) When the reduction was conducted at rt the diastereomeric mixture ratio of **31a** was 4:1. To prevent formation of a byproduct (resulting from syn lactone ring opening and ethanol transesterification upon hydrolysis in basic medium) acidic workup is needed. This byproduct, i.e., (2*R*)-(+)-ethyl 3,4-dihydroxy-2-methyl-2-(4-methylphenyl)butanoate ($[\alpha]_D = +18°$, *c* 1.35, $CHCl_3$), was converted into *syn*-**31a** by acidic lactonization (using 6 N HCl).

the presence of triphenylphosphine and imidazole[36] gave the iodo lactone (*S*)-**31b**, which, separable with difficulty from triphenylphosphine and triphenylphosphine oxide, was used crude for the next step. Upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in tetrahydrofuran at reflux, the β-iodo lactone (*S*)-**31b** underwent dehydrohalogenation to provide the expected butenolide (*S*)-**32** in 66% yield.[37] Attempts to improve this yield by elimination reaction from the mesylate (*R*)-**31c** (X = OMs) or isopropylsulfonate (*R*)-**31d**[38] (X = OSO_2iPr) have failed. Otherwise, reaction of the 3-oxo lactone (*R*)-**15** with tosylhydrazide gave the tosylhydrazone (*R*)-**31e** in 90% yield. Unfortunately, reduction of (*R*)-**31e** with sodium cyanoborohydride[39] led to a mixture containing the butenolide (*S*)-**32**, the lactone (*S*)-**25**, and the 3-hydroxybutanolide (*R*)-**31a** in 10, 12, and 20% yields, respectively. Shapiro reactions with various bases have also failed.

Finally, controlled addition of 1 equiv of methyllithium to a solution of the butenolide (*S*)-**32** in ether between −90 and −78 °C gave the expected 4-oxovaleraldehyde (*S*)-(+)-**29** in 50% yield. 5-Hydroxy-3-*p*-tolyl-2,2,3-trimethyltetrahydrofuran ((*S*)-**33**) (20%), resulting from a further methyllithium addition to (*S*)-**29**, and the nonreacted butenolide (*S*)-**32** (30%) were also recovered.

Conclusion

From a single chiron, the monomethyl 2-methyl-2-*p*-tolylmalonic acid ester ((*R*)-**4**), readily available with high enantiomeric purity (96% ee) and high yield (95%) from enzymatic enantioselective hydrolysis of the prochiral dimethyl malonate **3** by pig liver esterase (PLE), it is possible to obtain by simple one carbon homologation reactions (cyanation, Wittig reaction, or diazo ketone synthesis) efficient precursors of the two enantiomers of isomeric α-cuparenones (**1a,b**) and β-cuparenones (**2a,b**), such as the succinate (*S*)-**9a**, γ-lactol (*R*)-**19**, γ-lactone (*S*)-**25**, or but-3-enolide (*S*)-**32**, selectively. It is noteworthy that each enantiomer of these intermediates is also available from the same common precursor. The versatility of these sequences demonstrated herein will allow us to undertake easily the construction of a wide variety of natural or nonnatural compounds containing such chiral quaternary centers; e.g., laurene and epilaurene from (*R*)-**4** and others related compounds, for example, aplysin and trichodiene derivatives, and more generally any framework with chiral quaternary carbon centers.

Experimental Section

General. All solvents were purified and/or dried by standard methods. Melting points were determined on a Mettler FP5 melting point apparatus and are uncorrected. ^1H NMR spectra were recorded at 250 or 200 MHz, and chemical shifts are reported in ppm relative to Me_4Si. ^{13}C NMR spectra were recorded at 62.86 MHz, and chemical shifts are reported in ppm relative to $CDCl_3$. Electron impact mass spectra were obtained at 70 eV. Analytical thin-layer chromatography (TLC) was performed on 250-μm silica gel (Merck). SDS 60ACC silica gel (70–230 mesh) was used for column chromatography. SDS 60ACC silica gel (230–400 mesh) was used for column flash chromatography. Elemental analyses were carried out in the microanalytical laboratory at the CNRS/ICSN Gif-sur-Yvette. Solvents were dried and freshly distilled following usual procedures. All reactions were carried out under argon, unless otherwise reported. Product solutions were dried over $MgSO_4$ prior to evaporation of the solvents under reduced pressure on a rotary evaporator.

Dimethyl 2-Methyl-2-(4-methylphenyl)malonate (3). To a solution of *i*-Pr_2NH (13.6 mL, 0.12 mol, 1.2 equiv) in dry THF (180 mL) at −78 °C was added via syringe *n*-BuLi (1.55 M, 77.4 mL, 0.12 mol, 1.2 equiv) and the resulting solution stirred for 15 min at −78 °C. To this generated LDA solution was added a solution of **12** (17.8 g, 0.1 mol, readily available in two steps from the commercial *p*-tolylacetic acid) in dry THF (150 mL). The resulting mixture was stirred for 1 h at −78 °C. Then CH_3OCOCl (15.4 mL, 0.2 mol, 2 equiv) was added with syringe. The cooling bath was replaced by an ice bath (0 °C) and the solution stirred over a period of 30 min. Then the solution was recooled at −30 °C before addition of saturated aqueous NH_4Cl (50 mL). The malonate was extracted with ether (600 mL). Organic layers were washed with brine, dried, and evaporated, and the yellow residue was subjected to silica gel chromatography (elution with 1:8 ether–hexane). There was isolated 22.42 g (95%) of malonate **3** as a colorless oil: mp 38 °C; IR (neat) 1740, 1260, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (d, *J* = 7.1 Hz, 2 H), 7.15 (d, *J* = 7.1 Hz, 2 H), 3.75 (s, 6 H), 2.35 (s, 3 H), 1.87 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.1 (2s, COO) [6 arom C, 137.3 (s), 135.1 (s), 128.9 (2d), 127.1 (2d)], 58.4 (s, C(2)), 52.7 (2q, OCH_3), 22.2 (q, CH_3-C(2)), 20.9 (q, CH_3, tol.); MS (EI) 236 (M^+, 30), 177 (54), 149 (32), 118 (15), *117* (100), 115 (20), 91 (28). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09: H, 6.83. Found: C, 66.07; H, 6.75.

(*R*)-(+)-2-(Methoxycarbonyl)-2-(4-methylphenyl)-propionic Acid (4). To a stirred solution of malonate **3** (15.32 g, 65 mmol) in water (30 mL) was added at 25 °C pig liver esterase (4 g, acetonic powder purchased from Sigma L 8251). The pH of the reaction was kept at 7.2 by regular addition of 2 N aqueous NaOH via a syringe pump interfaced with a pH controller. After a stirring period of 1 h another portion of PLE (4 g) was added. When 32.2 mL of aqueous 2 N NaOH (48 h) was added, the enzyme was eliminated by filtration (addition of Celite to the mixture facilitates the filtration). The precipitate was washed with water (60 mL) and with ether (70 mL). After separation, the aqueous layer was acidified (2 N aqueous HCl) until pH 2 and the malonate monoester **4** was extracted with ether (6 × 150 mL). The combined organic extracts were washed with brine, dried, and evaporated. Product purification was achieved by chromatography on silica gel (elution with 1:4 ether–hexane). There was isolated 13.70 g (95%) of acid ester (+)-**4**, as a colorless oil: $[\alpha]^{20}_D$ = +11° (*c* 1, $CHCl_3$); ee > 96% from ^1H NMR spectra in presence of (*R*)-(+)-methylbenzylamine; IR (neat) 3250, 1740, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.5 (br s, 1 H), 7.3 (d, *J* = 7 Hz, 2 H), 7.20 (d, *J* = 7 Hz, 2 H), 3.84 (s, 3 H), 2.37 (s, 3 H, CH_3, tol), 1.95 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.4 (s, C(3)), 172.5 (s, C(1)) [6 arom C, 137.5 (s), 134.5 (s), 129.1 (2d), 127.0 (2d)], 58.3 (s, C(2)), 53.0 (q, Me ester), 21.9 (q), 20.9 (q); MS (EI) 222 (M^+, 42), 163 (61), *135* (100), 119 (36), 103 (19), 91 (38). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.79; H, 6.32.

(*S*)-(−)-3-Hydroxy-2-methyl-2-(4-methylphenyl)propionic Acid (6). To a solution of malonate monoester (+)-**4** (8.9 g, 40 mmol) in dry THF (100 mL) was added dropwise at 20 °C Me_2S-BH_3 (4.8 mL of a 10 M solution in THF, 48 mmol, 1.2 equiv); during the addition, the temperature must not exceed 30 °C. The mixture was stirred for 6 h then cooled at 0 °C and quenched with water (30 mL). The hydroxy acid was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine, dried, and concentrated. The resulting product was used without further purification in the next step: mp 103 °C; $[\alpha]^{20}_D$ = −39° (*c* 1, $CHCl_3$); IR (neat) 3220, 1712 cm1−1; ^1H NMR ($CDCl_3$) δ 10.5 (br s, 1 H), 7.15 (m, 4 H), 4.14 (br s, OH), 2.25 (s, 3 H, CH_3 tol), 1.52 (s, 3 H).

(*S*)-(−)-Methyl 3-Hydroxy-2-methyl-2-(4-methylphenyl)-propionate (7). The crude hydroxy acid (−)-**6** (40 mmol) in dry MeOH (40 mL) was added dropwise at 20 °C to a dry MeOH (100 mL) acidified by $SOCl_2$ (4 mL). The mixture was stirred at room temperature for 2 h. Then the solvent was eliminated under reduced pressure and the residue diluted in ether (150 mL). The solution was washed successively with saturated aqueous $NaHCO_3$ and brine and then dried and concentrated. The residue was purified by chromatography on silica gel (using 1:4 ether–hexane

(36) Caregg, P. J.; Samuelson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866.

(37) It was not possible to determine the enantiomeric excess of (*S*)-**32** by ^1H NMR in the presence of a chiral shift reagent ($Eu(hfc)_3$).

(38) Hua, D. H.; Sinai-Zingde, G.; Venkataraman, S. *J. Am. Chem. Soc.* **1985**, *107*, 4088.

(39) For mechanistic studies of reduction of tosylhydrazones see: Miller, V. P.; Yang, D.-Y.; Weigel, Th. M.; Han, O.; Liu, H.-W. *J. Org. Chem.* **1989**, *54*, 4175 and references cited therein.

as eluent) to yield 6.66 g (80% from the malonate monoester (+)-4 of hydroxy ester (−)-7 as a colorless oil: $[\alpha]^{20}_D = -57.2°$ (c 1, $CHCl_3$); IR (neat) 3450, 1735, 1620, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (s, 4 H), 3.83 [AB, $\Delta\nu_{AB}$ = 112.5 Hz, 4.07 (d, J = 11.5 Hz, 1 H), 3.80 (s, 3 H); 3.63 (d, J = 11.5 Hz, 1 H)], 2.35 (s, 3 H), 2.10 (br s, OH), 1.67 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.7 (s, C(1)) [6 arom C, 137.3 (s), 135.0 (s), 129.3 (2d), 126.0 (2d)], 69.7 (t, C(3)), 52.2 (q, C(2)), 20.9 (q), 19.94 (q); MS (EI) 208 (M^+, 0.5), 178 (79), 149 (32), 146 (49), *119* (100), 118 (29), 117 (76), 91 (52), 77 (19). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.19; H, 7.75. Found: C, 69.43; H, 7.70.

(*R*)-(+)-Methyl 3-Hydroxy-2-methyl-2-(4-methylphenyl)propionate (7). To a cold (−15 °C) stirred solution of malonate monoester 4 (8.88 g, 40 mmol) in dry THF (100 mL) was added Et_3N (6.8 mL, 44 mmol, 1.1 equiv) and MeOCOCl (3.04 mL, 40 mmol, 1 equiv). The cold bath was removed and the solution stirred for 1 h at room temperature. The mixture was then filtered, and the white precipitate obtained was washed with THF (2 × 50 mL) and ether (50 mL). The combined filtrate was concentrated and the residue diluted in MeOH (100 mL). Then $NaBH_4$[15b] (3.2 g, 88 mmol, 2.2 equiv) was added by small amounts at −15 °C and the solution allowed to warm to room temperature. The mixture was stirred for 1 h then cooled at 0 °C before addition of 6 N aqueous HCl (16 mL dropwise). The MeOH was evaporated, and the residue was diluted in water (50 mL). The hydroxy ester was extracted with CH_2Cl_2 (4 × 100 mL). The combined organic extracts were washed with brine, dried, and concentrated. Product separation was achieved by chromatography on silica gel (elution with 2:3 ether–hexane). There was isolated 6.8 g (81%) of the hydroxy ester (+)-7 as a colorless oil: $[\alpha]^{20}_D = +60°$ (c 1, $CHCl_3$). Spectral data were identical with those reported for the (*S*)-(−) material 7.

Reduction of Acid Ester (*R*)-4 with Disiamylborane. To a stirred solution of malonate monoester (*R*)-4 (222 mg, 1 mmol) in dry THF (5 mL) was added dropwise a solution of freshly prepared Me_2S·HB(Sia)$_2$ (from THF·BH_3, 0.6 M, 5.07 mL, 3 mmol and 2-methylbut-2-ene, 0.635 mL, 6 mmol, 0 °C). The resulting solution was stirred at room temperature for 1 h. Then Me_2S·BH_3 (0.12 mL of a 10 M solution in THF) was added. The mixture was stirred at room temperature for 6 h, and then the reaction was quenched at 0 °C with water (3 mL). The reaction mixture was extracted with ethyl acetate (3 × 20 mL). The organic layer was dried and concentrated, and the residue was subjected to silica gel chromatography (elution with 2:3 ether–hexane). Only 210 mg of starting material (*R*)-4 was isolated.

(*R*)-(+)-Methyl 4-Diazo-2-methyl-2-(4-methylphenyl)-3-oxobutanoate (8). To a stirred solution of malonate monoester (+)-4 (5.50 g, 25 mmol) in dry benzene (50 mL) was added dropwise at room temperature $(COCl)_2$ (2.41 mL, 7.5 mmol, 1.1 equiv). The mixture was stirred at 45 °C for 12 h. Then after the solution was cooled at room temperature, saturated aqueous $NaHCO_3$ (30 mL) was added. The organic layer was dried and evaporated. The residue was distilled (150 °C (0.6 mmHg)) to furnish 5.65 g (95%) of (*S*)-(+)-methyl 2-(chloroformyl)-2-(4-methylphenyl)propionate as a colorless liquid: $[\alpha]^{20}_D = +1.8°$ (c 1, $CHCl_3$); IR (neat) 1805, 1750, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (m, 4 H), 3.84 (s, 3 H), 2.37 (s, 3 H), 2.01 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.2 (s), 169.6 (s) [6 arom C, 138.5 (s), 132.8 (s), 129.2 (2d), 127.4 (2d)], 67.3 (s), 53.2 (q), 22.4 (q), 20.9 (q); MS (EI) 242 (M^+, ^{37}Cl, 5), 240 (M^+ ^{35}Cl, 15), *177* (100), 153 (18), 149 (33), 117 (60), 91 (19).

To a stirred solution of acyl chloride (4.81 g, 20 mmol) in dry ether was added dropwise an excess of CH_2N_2 (4 equiv ethereal solution). After being stirred at 0 °C for a further 15 min, the solvent was evaporated and the residue was purified by flash chromatography on a silica gel column (using 1:4 ethyl acetate–hexane as eluent) to give the diazo ketone (+)-8 (3.94 g, 80% yield) as a yellow oil which, instable, was directly treated: $[\alpha]^{20}_D = +72.3°$ (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.18 (m, 4 H), 5.14 (s, 1 H, CH=N_2), 3.78 (s, 3 H), 2.36 (s, 3 H), 1.80 (s, 3 H).

Arndt Eistert Reaction, General Procedure. To a freshly prepared solution of diazo ketone (+)-8 (1.23 g, 5 mmol) in absolute alcohol (25 mL) was added at room temperature Et_3N (catalytic quantity), and the solution was heated at reflux. Then freshly prepared catalyst solution (made by dissolving 1 g of PhCOOAg in 10 mL of Et_3N) was added by injection through a septum. Evolution of nitrogen occurred, and the mixture turned black. A second quantity of catalyst solution was added when the evolution of nitrogen almost stopped. This procedure was continued until further additions of catalyst caused no further evolution of nitrogen. Then the reaction mixture was refluxed for 3 h, cooled, and filtered through Celite. The solvents were removed on a rotary evaporator under reduced pressure. The residue was taken up in ether (25 mL), and the solution washed twice with aqueous 10% Na_2CO_3 with water and brine successively. Each aqueous layer was extracted with ether (25 mL). The combined ethereal extract was dried and evaporated, and the residue was purified by chromatography on silica gel (elution with 1:9 ethyl acetate–hexane).

Arndt Eistert Reaction in Absolute Methanol. Following the general procedure, 1.23 g (5 mmol) of diazo ketone 8 gave 1.1 g of a crude oil which after chromatography furnished the following: 310 mg (25%) of **9a**, 175 mg (14%) of **10a**, 125 mg (14%) of **12**.

(*S*)-(+)-Dimethyl 2-methyl-2-(4-methylphenyl)succinate (9a): $[\alpha]^{20}_D = +17.8°$ (c 1, EtOH) (lit.[11] $[\alpha]_D = +18°$, c 1, EtOH); 98% ee from ^1H NMR spectra in presence of Eu(hfc)$_3$; ^1H NMR ($CDCl_3$) δ 7.23 (d, J = 7.5 Hz, 2 H), 7.14 (d, J = 7.5 Hz, 2 H), 3.71 (s, 3 H), 3.67 (s, 3 H), 3.05 [AB, $\Delta\nu_{AB}$ = 99.3 Hz, 3.28 (d, J = 16.3 Hz, 1 H), 2.79 (d, J = 16.3 Hz, 1 H)], 2.33 (s, 3 H), 1.69 (s, 3 H). All spectral data were identical with those reported.[11]

(±)-Methyl 2-[2-[(methoxycarbonyl)methyl]-4-methylphenyl]propionate (10a): ^1H NMR ($CDCl_3$) δ 7.35–7.05 (m, 3 H), 4.02 (q, J = 7.4 Hz, H-C(2), 3.77 [AB, $\Delta\nu_{AB}$ = 42 Hz, 3.88 (d, J = 15.5 Hz, 1 H), 3.66 (d, J = 15.5 Hz, 1 H)], 3.77 (s, 3 H), 3.69 (s, 3 H), 2.37 (s, 3 H), 1.53 (d, J = 7.4 Hz, 3 H); MS (EI) 250 (M^+, 6), 218 (31), 191 (17), 190 (29), 175 (18), 159 (29), 158 (52), 132 (18), *131* (100), 115 (17), 91 (19).

(±)-Methyl 2-(4-methylphenyl)propionate (12): IR (neat) 1740, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (m, 4 H), 3.72 (q, J = 7.2 Hz, 1 H), 2.34 (s, 3 H), 1.5 (d, J = 7.2 Hz, 3 H); MS (EI) 178 (M^+, 21), *119* (100), 91 (16), 77 (8).

Arndt Eistert Reaction in Absolute Ethanol. Following the general procedure, 1.23 g (5 mmol) of racemic diazo ketone 8 gave 1.05 g of a crude oil which after chromatography furnished the following: 356 mg (27%) of **9b**, 265 mg (20%) of **10b**, 63 mg (7%) of **12**.

(±)-4-Ethyl 1-methyl 2-methyl-2-(4-methylphenyl)-succinate (9b): ^1H NMR ($CDCl_3$) δ 7.23–7.15 (m, 4 H), 4.13 (q, J = 7.1 Hz, 2 H, ethyl ester), 3.70 (s, 3 H), 3.04 [AB, $\Delta\nu_{AB}$ = 96.6 Hz, 3.28 (d, J = 16.6 Hz, 1 H), 2.80 (d, J = 16.6 Hz, 1 H)], 2.33 (s, 3 H), 1.70 (s, 3 H), 0.74 (t, J = 7.1 Hz, 3 H).

(±)-Methyl 2-[2-[(ethoxycarbonyl)methyl]-4-methylphenyl]propionate (10b): ^1H NMR ($CDCl_3$) δ 7.30–7.01 (m, 3 H), 4.16 (q, J = 7.2 Hz, 2 H, ethyl ester), 3.99 (q, J = 7.2 Hz, 1 H), 3.72 [AB, $\Delta\nu_{AB}$ = 44.8 Hz, 3.83 (d, J = 15.7 Hz, 1 H), 3.60 (d, J = 15.7 Hz, 1 H)], 3.64 (s, 3 H), 2.32 (s, 3 H, CH_3 tol), 1.48 (d, J = 7.2 Hz, 3 H), 1.25 (t, J = 7.2 Hz, 3 H); MS (EI) 265 (M^+ + 1, 2), 264 (M^+, 7), 232 (19), 205 (16), 204 (37), 191 (21), 175 (64), 159 (50), 158 (72), 147 (12), 132 (27), *131* (100), 117 (20), 91 (27).

Arndt Eistert Reaction in Absolute *n*-Propanol. Following the general procedure, 1.23 g (5 mmol) of diazo ketone 8 gave 850 mg of a crude oil which after chromatography furnished the following: 312 mg (25%) of **9c**, 170 mg (12%) of **10c**, 125 mg (14%) of **12**:

(*S*)-(+)-1-Methyl 4-propyl 2-methyl-2-(4-methylphenyl)-succinate (9c): $[\alpha]^{20}_D = +24.3°$ (c 1, $CHCl_3$); IR (neat) 1740, 1515, 1170, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26–7.10 (m, 4 H), 4.04 (t, J = 6.8 Hz, 2 H, OCH_2 ester), 3.70 (s, 3 H), 3.05 [AB, $\Delta\nu_{AB}$ = 120 Hz, 3.30 (d, J = 16.2 Hz, 1 H), 2.82 (d, J = 16.2 Hz, 1 H)], 2.34 (s, 3 H, CH_3, tol), 1.70 (s, 3 H), 1.63 (m, 2 H, CH_2CH_3 ester), 0.93 (t, J = 7.3 Hz, 3 H, CH_3CH_2, ester); MS (EI) 279 (M^+ + 1, 5), 278 (M^+, 27), 220 (15), *219* (100), 177 (23), 159 (34), 135 (40), 133 (14), 132 (17), 131 (50), 117 (27), 115 (18), 91 (17), 43 (49), 41 (27).

(±)-Methyl 2-[2-[(propoxycarbonyl)methyl]-4-methylphenyl]propionate (10c): IR (neat) 1740, 1515, 1260, 1111 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30–7.04 (m, 3 H), 4.06 (t, J = 6.8 Hz, 2 H, OCH_2 ester), 3.99 (q, J = 7.4 Hz, 1 H), 3.72 [AB, $\Delta\nu_{AB}$ = 55 Hz, 3.82 (d, J = 16.3 Hz, 1 H), 3.62 (d, J = 16.3 Hz, 1 H)], 3.65 (s, 3 H), 2.32 (s, 3 H), 1.75–1.54 (m, 2 H, CH_2CH_3), 1.47 (d, J = 7.4 Hz, 3 H), 0.93 (t, J = 7.1 Hz, 3 H, CH_3CH_2); MS (EI) 279 (M^+

+ 1, 2), 278 (M^+, 12), 219 (28), 218 (64), 191 (20), 177 (15), 176 (16), 175 (86), 159 (47), 158 (87), 132 (25), *131* (100), 129 (14), 117 (20), 116 (24), 115 (24), 91 (28), 43 (21).

(*R*)-Methyl 2-Methyl-2-(4-methylphenyl)-3-oxo-4-propoxypentanoate (11c). Data of **11c** from the ^1H NMR of crude **10c/11c**: ^1H NMR ($CDCl_3$) δ 7.35–7.00 (m, 4 H), 4.14 [AB syst, $\Delta\nu_{AB}$ = 26.6 Hz, 4.21 (A part, J_{AB} = 17 Hz, 1 H, H-C(4)), 4.06 (B part, J_{AB} = 17 Hz, 1 H, H-C(4))], 3.33 (t, J = 6.7 Hz, CH_2 ether), 2.35 (s, 3 H, CH_3 tol), 1.80 (s, CH_3), 1.56 (m, CH_2CH_3), 0.88 (t, J = 7.3 Hz, CH_3CH_2); MS (EI) 279 (M^+ + 1, 7), 278 (M^+, 29), 177 (27), 159 (25), *135* (100), 132 (23), 131 (42), 117 (23), 115 (15), 91 (24), 43 (38).

Arndt Eistert Reaction in Absolute Methanol, in the Presence of Silver Oxide. Following the general procedure, 1.23 g (5 mmol) of diazo ketone 8 and 200 mg of silver oxide[17a] gave a crude mixture (850 mg) which showed from the ^1H NMR spectrum the presence of oxo lactone **15** (5%), traces of succinate **9a** (1%), and methyl 4-hydroxy-2-methyl-3-oxo-2-(4-methylphenyl)butanoate (10%).

Arndt Eistert Reaction in Absolute Methanol, by Photolysis. A solution of diazo ketone (+)-8 (250 mg, 2 mmol) in 10 mL of MeOH, was irradiated in a quartz vessel with low-pressure Hg lamps (300 nm)[18] at 20 °C. After 6 h of irradiation the reaction did not take place as shown from the gas chromatography. Then the reaction mixture was concentrated, diluted with ether (100 mL), and washed with brine (4 mL). The ethereal layer was dried and evaporated to provide only 235 mg of the starting material 8.

(*R*)-(+)-2-Methyl-2-(4-methylphenyl)-3-oxo-4-butanolide (15). To a cold (0 °C) stirred solution of crude diazo ketone (+)-8 (4.92 g, 20 mmol) in THF (60 mL) was added dropwise a 6 N aqueous HCl solution (30 mL). After the solution was stirred for 12 h at 20 °C, the THF was evaporated and the residue diluted in ether (100 mL). The organic layer was washed with $NaHCO_3$ then brine, dried, and evaporated. The residue was subjected to silica gel chromatography (elution with 1:9 ethyl acetate–hexane) to furnish 3.67 g (90% overall yield from acyl chloride) of the butanolide (+)-15 as a white solid (recrystallized from ether hexane): mp = 66.3 °C; $[\alpha]^{20}_D$ = +11.3° (*c* 1, $CHCl_3$); IR (KBr) 1795, 1755, 1270, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.14 (m, 4 H), 4.69 [AB, $\Delta\nu_{AB}$ = 20 Hz, 4.74 (d, J = 16.8 Hz, 1 H), 4.63 (d, J = 16.8 Hz, 1 H)], 2.35 (s, 3 H, CH_3 tol), 1.66 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 206.6 (s, C(3)); 175.3 (s, C(1)) [6 arom C, 138.5 (s), 131.8 (s), 130.0 (2d), 125.9 (2d)], 71.9 (t, C(4)), 52.5 (s, C(2)), 20.8 (q), 20.4 (q); MS (EI) 206 (M^+ + 2, 1), 205 (M^+ + 1, 13), *204* (M^+, 100), 146 (81), 132 (14), 118 (50), 117 (61), 115 (25), 91 (24), 58 (13). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.56; H, 5.93. Found: C, 70.78; H, 5.96.

In smooth acidic conditions (0.5 N HCl), the diazo ketone 8 led to an unstable acyloin, i.e., the methyl 4-hydroxy-2-methyl-2-(4-methylphenyl)-3-oxobutanoate: ^1H NMR ($CDCl_3$) δ 7.14 (m, 4 H), 4.23 [AB, $\Delta\nu_{AB}$ = 49.1 Hz, 4.36 (A part d, J = 19 Hz, 1 H), 4.12 (B part d, J = 19 Hz, 1 H)], 3.80 (s, 3 H), 2.36 (s, 3 H), 1.82 (s, 3 H); which was readily transformed into oxolactone (+)-15 in the NMR tube solution ($CDCl_3$).

(*S*)-(+)-Dimethyl 2-Methyl-2-(4-methylphenyl)succinate (9a). To a stirred solution of hydroxy ester (+)-7 (1.84 g, 8.85 mmol) in $CHCl_3$ (30 mL),[40] was added at 0 °C pyridine (1.44 mL, 17.7 mmol, 2 equiv). Then TsCl (2.52 g, 13.3 mmol, 1.5 equiv) was added by small amounts. The mixture was held at 4 °C without stirring for 48 h. The solution was then diluted with ether (90 mL) and water (15 mL). The organic layer, washed successively with 2 N aqueous HCl, saturated aqueous $NaHCO_3$, and brine, was dried and evaporated. The crude product was purified on silica gel chromatography (using 15:85 ethyl acetate–hexane as eluent) to give 2.84 g (90%) of (*R*)-(+)-methyl 2-methyl-2-(4-methylphenyl)-3-(tosyloxy)propionate as a colorless solid (recrystallized from ether–hexane): mp = 65.9 °C: $[\alpha]^{20}_D$ = +6.8° (*c* 1, $CHCl_3$); IR (neat) 2960, 1740, 1365, 1180, 975 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (d, J = 8.4 Hz, 2 H, tosyl), 7.30 (d, J = 8.4 Hz, 2 H, tosyl), 7.09 (s, 4 H, tolyl), 4.30 [AB, $\Delta\nu_{AB}$ = 68 Hz, 4.47 (d, J = 9.2 Hz, 1 H), 4.13 (d, J = 9.2 Hz, 1 H)], 3.64 (s, 3 H, CH_3, ester), 2.45 (s, 3 H, CH_3, tosyl), 2.33 (s, 3 H, CH_3, tolyl), 1.65 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.3 (s, C(1)) [12 arom C, 144.6 (s), 137.5 (s), 135.5 (s), 132.4 (s), 129.6 (2d), 129.3 (2d), 127.8 (2d), 125.6 (2d)], 74.4 (t, C(3)), 52.3 (q, Me ester), 49.9 (s, C(2)), 21.5 (q), 20.8 (q), 19.9 (q). Anal. Calcd for $C_{19}H_{22}O_5S$: C, 62.96; H, 6.12; S, 8.85. Found: C, 63.00; H, 6.13; S, 9.07.

To a stirred solution of this tosylate (2.61 g, 8 mmol) in DMSO (20 mL) was added KCN (1.35 g, 20.71 mmol, 2.5 equiv) and water (12 drops). The mixture was heated at 100 °C and stirred for 12 h. After being cooled to room temperature, the solution of the cyanide (*S*)-(+)-16 was diluted with water (10 mL) then extracted with $CHCl_3$ (3 × 60 mL). Evaporation of solvent gave the crude nitrile **16**: a sample was purified by chromatography on silica gel (using 15:85 ether–hexane as eluent) to give (*S*)-(+)-methyl 3-cyano-2-methyl-2-(4-methylphenyl)propionate **16**: $[\alpha]^{20}_D$ = +65.5° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.21 (s, 4 H), 3.73 (s, 3 H), 2.97 [AB, $\Delta\nu_{AB}$ = 41.8 Hz, 3.05 (d, J = 16.0 Hz, 1 H), 2.87 (d, J = 16.0 Hz, 1 H)], 2.35 (s, 3 H, CH_3, tolyl), 1.82 (s, 3 H); MS (EI) 219 (M^+ + 2, 1), 218 (M^+ + 1, 7), 217 (M^+, 33), 177 (22), *158* (100), 118 (12), 117 (27), 115 (19), 91 (23).

The crude nitrile was heated with a 10 N aqueous HCl solution (15 mL) at 100 °C for 14 h. After being cooled, the mixture was extracted with $CHCl_3$ (3 × 80 mL) and concentrated under vacuum. The residue was diluted with ethylene glycol (25 mL) and treated with KOH (5.4 g, 96 mmol, 12 equiv) on heating at reflux for 14 h. After the mixture was cooled at room temperature, organic impurities were removed with ether (35 mL) and the aqueous layer acidified with 6 N aqueous HCl until pH 2. The diacid was extracted with $CHCl_3$ (3 × 10 mL). After removal of solvent under vacuum the residue was diluted with ether (35 mL). To this solution was added an excess of CH_2N_2 (ethereal solution). The esterification was complete after a stirring period of 5 min at 20 °C. The organic layer was dried and evaporated, and the crude residue was purified by chromatography on silica gel (elution with 15:85 ether–hexane). There was isolated 1.28 g (64% overall yield from tosylate) of pure succinate (+)-9a as a colorless liquid. All spectral data were identified with those reported above.

(*R*)-(−)-3-(*tert*-Butyldimethylsiloxy)-2-methyl-2-(4-methylphenyl)propanal (17). To a stirred solution of TBDMSCl (1.8 g, 12 mmol, 1.2 equiv) and imidazole (1.7 g, 25 mmol, 2.5 equiv) in dry DMF (20 mL) was added, dropwise at 40 °C, a solution of hydroxy ester (+)-7 (2.08 g, 10 mmol) in DMF (10 mL). The mixture was stirred for 10 min at 40 °C. After being cooled at room temperature, the solution was diluted with ether (50 mL) and water (10 mL). The organic layer was washed with brine, dried, and evaporated. The residue was purified on silica gel column (using 1:9 ether–hexane as eluent) to furnish 2.96 g (92%) of (*R*)-(+)-methyl 3-(*tert*-butyldimethylsiloxy)-2-methyl-2-(4-methylphenyl)propionate as a colorless liquid: $[\alpha]^{20}_D$ = +6.0° (*c* 1, $CHCl_3$); IR (neat) 1740, 1465, 1250, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18 (d, J = 8.4 Hz), 7.13 (d, J = 8.4 Hz, 2 H), 3.95 [AB, $\Delta\nu_{AB}$ = 115 Hz, 4.20 (d, J = 9.5 Hz, 1 H), 3.73 (d, J = 9.5 Hz, 1 H)], 3.68 (s, 3 H), 2.34 (s, 3 H, CH_3, tolyl), 1.60 (s, 3 H), 0.87 (s, 9 H), 0.03 (s, 3 H), 0.00 (s, 3 H).

To a stirred solution of silylated ester (3.22 g, 10 mmol) in dry CH_2Cl_2 (10 mL) was added slowly via cannula at −78 °C, a solution of DIBALH (20 mL of a 1 M solution in CH_2Cl_2, 20 mmol, 2 equiv). The mixture was stirred for 30 min at −78 °C before quenching with MeOH (3 mL) then allowed to warm to room temperature. The solution was poured in a 6:1 mixture of ethyl acetate–potassium sodium tartrate (140 mL). The organic layer was dried and concentrated and the residue purified by chromatography on silica gel (using 1:4 ether–hexane as eluent) to yield 2.82 g (96%) of pure (*S*)-(+)-3-(*tert*-butyldimethylsiloxy)-2-methyl-2-(4-methylphenyl)propanol as a colorless oil: $[\alpha]^{20}_D$ = +3.2° (*c* 1, $CHCl_3$); IR (neat) 3430, 1470, 1210, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31 (d, J = 8 Hz, 2 H), 7.18 (d, J = 8 Hz, 2 H), 3.84 [AB, $\Delta\nu_{AB}$ = 80 Hz, 4.00 (d, J = 10 Hz, 1 H), 3.68 (d, J = 10 Hz, 1 H)], [ABM syst, 3.88 (AB part of ABM syst, $\Delta\nu_{AB}$ = 54 Hz), 3.99 (A part, J_{AB} = 10.5 Hz, J_{AM} = 6.0 Hz, 1 H), 3.77 (B part, J_{AB} = 10.5 Hz, J_{BM} = 6.0 Hz, 1 H), 2.63 (M part, J_{AM} = 6.6 Hz, J_{BM} = 6.6 Hz, 1 H)], 2.33 (s, 3 H), 1.35 (s, 3 H), 0.91 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H).

A solution of this alcohol (2.37 g, 8 mmol) in dry CH_2Cl_2 (20 mL) was added to a cold (−60 °C) stirred solution of $(COCl)_2$ (0.75 mL, 8.8 mmol, 1.1 equiv) and DMSO[27] (1.24 mL, 17.6 mmol, 2.2

(40) Kabalka, G. W.; Varma, M.; Varma, R. S. *J. Org. Chem.* **1986**, *51*, 2386.

equiv) in dry CH_2Cl_2 (30 mL). The solution was stirred for 15 min at −60 °C, and then NEt_3 (5.22 mL, 40 mmol, 5 equiv) was added. After being stirred at −60 °C for a period of 15 min, the reaction mixture was quenched with water (15 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with brine, dried, and evaporated, and the residue was purified by chromatography on silica gel (elution with 1:9 ethyl acetate–hexane). There was isolated 2.29 g (98%) of pure aldehyde (−)-**17** as a colorless liquid: $[\alpha]^{20}_D = -22°$ (*c* 1, $CHCl_3$); IR (neat) 2705, 1735, 1255, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.65 (s, 1 H), 7.17 (m, 4 H), 4.01 [AB, $\Delta\nu_{AB}$ = 98 Hz, 1 H), 4.20 (d, *J* = 9.9 Hz, 1 H), 3.82 (d, *J* = 9.9 Hz, 1 H)], 2.36 (s, 3 H), 1.49 (s, 3 H), 0.87 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 202.2 (d, CHO) [6 arom C, 137.0 (s), 135.4 (s), 129.3 (2d), 126.9 (2d)], 67.2 (t, C(3)), 55.4 (s, C(2)), 25.7 (3q), 20.8 (q), 18.1 (s, $C(Me)_3$), 17.5 (q), −5.7 (2q, Me-Si).

(4*R*)-2-Hydroxy-4-methyl-4-(4-methylphenyl)tetrahydrofuran (19). To a cold (−15 °C) stirred suspension of (methoxymethyl)triphenylphosphonium chloride[28a] (5.13 g, 15 mmol, 3 equiv) in dry THF (65 mL) was added *n*-BuLi (1.6 M, 7.8 mL, 12.5 mmol, 2.5 equiv). The mixture was irradiated by sonication in a cleaning bath (Bransonic 60 kHz) for 2 h.[28b,c] Then a solution of aldehyde **17** (1.46 g, 5 mmol) in THF (20 mL) was added and the resulting mixture stirred for 3 h at 0 °C. The solution was allowed to warm to room temperature and diluted with ether (100 mL), washed with brine, dried, and concentrated. The crude enol ether, i.e., 4-(*tert*-butyldimethylsiloxy)-1-methoxy-3-methyl-3-(4-methylphenyl)but-1-ene (**18**), was obtained as a 1:1 unseparable mixture of *Z*,*E* isomers: ^1H NMR ($CDCl_3$) δ 7.22 (m, 2 H), 7.12 (m, 2 H), 6.30 (d, *J* = 13.4 Hz, 0.5 H, *E*), 5.86 (d, *J* = 7.2 Hz, 0.5 H, *Z*), 5.03 (d, *J* = 13.4 Hz, 0.5 H, *E*), 4.58 (d, *J* = 7.2 Hz, 0.5 H, *Z*), 3.78–3.50 (m, 2 H, *ZE*), 3.54 (s, 1.5 H, *Z*), 3.46 (s, 1.5 H, *E*), 2.33 (s, 1.5 H, *Z*), 2.32 (s, 1.5 H, *E*), 1.52 (s, 1.5 H, *E*), 1.38 (s, 1.5 H, *Z*), 0.87 (s, 9 H, *EZ*), −0.04 (s, 3 H, *Z*), −0.06 (s, 1.5 H, *E*), −0.08 (s, 1.5 H, *E*).

This enol ether **18** was diluted with THF (20 mL) containing 10% aqueous HCl (20 mL), and the resulting mixture was stirred for 12 h at room temperature. Then the solution was extracted with ether (3 × 40 mL). The combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ and brine, dried, and evaporated. The residue was purified on a silica gel column (using 1:4 ethyl acetate–hexane as eluent) to give 0.844 g (88%) of an inseparable 2:1 mixture of diastereoisomers **19a,b** as a colorless oil: IR (neat) 3400, 1020 cm^{-1}; ^1H NMR (mixture of diastereoisomers ***a***,**b**, 2:1) ($CDCl_3$) δ 7.16 (m, 4 H,), *5.75*/5.66 (X, part of ABX, m, 1 H), 4.07 [AB, $\Delta\nu_{AB}$ = 71.5 Hz, *4.22* (d, *J* = 8.0 Hz, 0.66 H), *3.92* (d, *J* = 8.0 Hz, 0.66 H)], 4.14 [AB, $\Delta\nu_{AB}$ = 12.0 Hz, 4.16 (d, *J* = 8.5 Hz, 0.33 H), 4.12 (d, *J* = 8.5 Hz, 0.33 H)], 2.89 (d, *J* = 3.3 Hz, 0.33 H, OH), *2.74* (d, *J* = 4.4 Hz, 0.66 H, OH), 2.31 [AB, part of ABX, $\Delta\nu_{AB}$ = 89 Hz, 2.54 (A part, J_{AB} = 10.8 Hz, J_{AX} = 4.7 Hz, 0.33 H), 2.08 (B part, J_{AB} = 10.8 Hz, J_{BX} = 2.5 Hz, 0.33 H)], 2.30 [AB part of ABX, $\Delta\nu_{AB}$ = 42.3 Hz, *2.41* (A part, J_{AB} = 11 Hz, J_{AX} = 4.7 Hz, 0.66 H), *2.20* (B part, J_{AB} = 11 Hz, J_{BX} = 3.1 Hz, 0.66 H)], 2.36 (s, 3 H), 1.60 (s, 3 × 0.33 H), *1.43* (s, 3 × 0.66 H); MS (EI) 192 (M^+, 4), 146 (14), 132 (12), *131* (100), 11 (20), 117 (12), 115 (18), 105 (12), 91 (26), 77 (9), 65 (9). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.71; H, 8.41.

Mild acidic hydrolysis of the enol ether gave the isolated (*R*)-4-(*tert*-butyldimethylsiloxy)-2-methyl-2-(4-methylphenyl)-butanal: ^1H NMR ($CDCl_3$) δ 9.61 (X part of ABX system, dd, $J_{AX} = J_{BX}$ = 2.7 Hz, CHO), 7.28 (d, *J* = 8.5 Hz, 2 H), 7.15 (d, *J* = 8.5 Hz, 2 H), 3.64 [AB system, $\Delta\nu_{AB}$ = 41.7 Hz, 3.75 (A part, J_{AB} = 9.7 Hz, 1 H-C(4)), 3.54 (B part, J_{AB} = 9.7 Hz, 1 H-C(4)), 2.75 (AB part of ABX system, like m, 2 H-C(2)), 2.35 (s, 3 H), 1.48 (s, 3 H), 0.90 (s, 9 H, *t*-Bu), 0.00 (s, 6 H, $2CH_3Si$); MS (EI) 250 (M^+ − 56, 7), 249 (M^+ − *t*-Bu, 15), 205 (27), 158 (17), *157* (100), 131 (12), 115 (10), 101 (38), 91 (11), 89 (27), 75 (52), 73 (48), 59 (24).

(2*R*)-2-Methyl-2-(4-methylphenyl)pentane-1,4-diol (20). To a cold (0 °C) stirred solution of the diastereomeric mixture of lactol **19** (768 mg, 4 mmol) in dry ether (16 mL) was added dropwise MeMgBr (4 mL of a 3 M solution in ether, 12 mmol, 3 equiv). The reaction was quenched with saturated aqueous NH_4Cl (4 mL) after 30 min of stirring at 0 °C. The reaction mixture was extracted with ether (3 × 40 mL). The combined organic extracts were washed with brine, dried, and evaporated. The 1:1 diastereoisomeric mixture of diol **20** was separated by chromatography on silica gel (elution with 1:1 ethyl acetate–CH_2Cl_2) to yield, as colorless oils, diastereomers A and B.

Diastereomer A (400 mg, 48%): R_f = 0.30 (TLC, Et_2O); $[\alpha]^{20}_D = +22.1°$ (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.25 (d, *J* = 8.5 Hz, 2 H), 7.16 (d, *J* = 8.5 Hz, 2 H), 3.83 [AB, $\Delta\nu_{AB}$ = 56.4 Hz, 3.96 (d, *J* = 11.3 Hz, 1 H), 3.68 (d, *J* = 11.3 Hz, 1 H)], 3.82 (m, 1 H-C(4)), 3.03 (s, 2 OH), 2.34 (s, 3 H), 1.87 (m, 2 H), 1.25 (s, 3 H), 1.17 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ [6 arom C, 142.1 (s), 135.6 (s), 129.3 (2d), 126.4 (2d)], 70.0 (t, C(1)), 65.0 (d, C(4)), 48.3 (t, C(3)), 42.4 (s, C(2)), 27.2 (q), 25.0 (q), 20.8 (q).

Diastereomer B (400 mg, 48%): R_f = 0.23 (TLC, Et_2O); $[\alpha]^{20}_D = -28.2°$ (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.30 (d, *J* = 8.4 Hz, 2 C, 7.15 (d, *J* = 8.4 Hz, 2 H), 4.04 (X part of ABX, m, 1 H), 3.73 [AB, $\Delta\nu_{AB}$ = 32.0 Hz, 3.79 (d, *J* = 11.4 Hz, 1 H), 3.66 (d, *J* = 11.4 Hz, 1 H)], 2.37 (s, 2 OH), 2.33 (s, 3 H), 1.86 [AB part of ABX, $\Delta\nu_{AB}$ = 64.3 Hz, 1.98 (A part, J_{AB} = 14.4 Hz, J_{AX} = 9.0 Hz, 1 H), 1.73 (B part, J_{AB} = 14.4 Hz, J_{BX} = 1.5 Hz, 1 H], 1.41 (s, 3 H), 1.20 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ [6 arom C, 144.1 (s), 135.6 (s), 129.3 (2d), 125.7 (2d)], 71.1 (t, C(1)), 64.7 (d, C(4)), 49.2 (t, C(3)), 42.1 (s, C(2)), 25.3 (q), 21.3 (q), 20.8 (q). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.90; H, 9.73.

(*R*)-(−)-2-Methyl-2-(4-methylphenyl)-4-oxopentanal (21). This aldehyde was prepared following the procedure described above for **17** from diol **20** (208 mg, 1 mmol), $(COCl)_2$ (0.186 mL, 2.2 mmol, 2.2 equiv), DMSO (0.31 mL, 4.4 mmol, 4.4 equiv), and Et_3N (1.3 mL, 10 mmol, 10 equiv). Chromatography on silica gel (elution with 1:9 ethyl acetate–hexane) furnished 196 mg (97%) of pure keto aldehyde (−)-**21** as a colorless liquid: $[\alpha]^{20}_D = -114°$ (*c* 1, $CHCl_3$); IR (neat) 2710, 1725, 1360 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.53 (s, 1 H), 7.18 (m, 4 H), 3.10 [AB, $\Delta\nu_{AB}$ = 24.1 Hz, 3.17 (d, *J* = 17.3 Hz, 1 H), 3.04 (d, *J* = 17.3 Hz, 1 H)], 2.35 (s, 3 H), 2.10 (s, 3 H), 1.61 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 206.1 (s, C(4)), 200.9 (d, C(1)) [6 arom C, 137.1 (s), 136.0 (s), 129.5 (2d), 126.6 (2d)], 51.4 (s, C(2)), 50.2 (t, C(3)), 30.9 (q, C(5)), 20.8 (q), 19.7 (q).

(*S*)-(−)-4-Methyl-4-(4-methylphenyl)cyclopent-2-enone (22). To a stirred solution of keto aldehyde (−)-**21** (204 mg, 1 mmol) in dry THF (25 mL) was added at room temperature KOH (100 μL of a 1 M solution in ethanol).[1b] The solution was stirred at room temperature for 1 h and concentrated under vacuum. The residue was dissolved in ether (25 mL), washed with water and brine, and then dried and concentrated. The crude product purified on a silica gel column (using 1:9 ethyl acetate–hexane as eluent) yielded 122 mg (65%) of cyclopentenone (−)-**22** as a colorless liquid: $[\alpha]^{20}_D = -118°$ (*c* 0.95, EtOH) (lit.[1b] $[\alpha]^{20}_D = +114°$ (*c* 1.36, EtOH) for the enantiomer); ^1H NMR ($CDCl_3$) δ 7.68 (d, *J* = 5.5 Hz, 1 H), 7.18 (s, 4 H), 6.22 (d, *J* = 5.5 Hz, 1 H), 2.61 [AB, $\Delta\nu_{AB}$ = 28.5 Hz, 2.66 (d, *J* = 19.0 Hz, 1 H), 2.55 (d, *J* = 19.0 Hz, 1 H)], 2.36 (s, 3 H), 1.64 (s, 3 H). Spectral data were identical with those reported.[1b]

(*R*)-(+)-3-Methyl-3-(4-methylphenyl)-4-butanolide (23). To a stirred suspension of pyridinium chlorochromate[31] (380 mg, 1.76 mmol, 2 equiv), AcONa (120 mg, 0.88 mmol, 1 equiv), and Celite (2v/v, Celite/PCC) in CH_2Cl_2 (8 mL) was added at room temperature a solution of diastereomeric mixture of lactols (*R*)-**19** (168 mg, 0.88 mmol) in CH_2Cl_2 (4 mL). The resulting suspension was stirred for 12 h at 20 °C and then filtered on Florisil. The solid residue was washed with ether (5 × 20 mL). Evaporation of the solvents followed by chromatography on silica gel (elution with 1:4 ethyl acetate–hexane) gave 164 mg (97%) of pure lactone (+)-**23** as a colorless oil: $[\alpha]^{20}_D = +11.3°$ (*c* 1, $CHCl_3$); IR (neat) 1780, 1520, 1170, 1020, 815 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.21 (d, *J* = 8.5 Hz, 2 H), 7.10 (d, *J* = 8.5 Hz, 2 H), 4.43 (AB syst like, s, 2 H), 2.79 [AB, $\Delta\nu_{AB}$ = 63.5 Hz, 2.93 (d, *J* = 16.3 Hz, 1 H), 2.66 (d, *J* = 16.3 Hz, 1 H)], 2.36 (s, 3 H), 1.54 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.1 (s, C(1)) [6 arom C, 141.3 (s), 139.9 (s), 129.6 (2d), 125.0 (2d)], 78.5 (t, C(4)), 43.7 (s, C(3)), 42.1 (t, C(2)), 27.9 (q), 20.8 (q); MS (EI) 192 (M^+ + 2, 1), 191 (M^+ + 1, 6), 190 (M^+, 36), 133 (17), *132* (100), 117 (31), 115 (16), 91 (20), 65 (15). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.82; H, 7.41.

(*S*)-(−)-3,3-(Ethylenedithio)-2-methyl-2-(4-methylphenyl)-4-butanolide (24). To a stirred solution of keto lactone (+)-**15** (1.02 g, 5 mmol) in dry CH_2Cl_2 (15 mL) was added successively at room temperature ethanedithiol (576 μL, 5.5 mmol, 1.1 equiv) and $Et_2O{\cdot}BF_3$[41] (1.35 mL of a 10% solution in CH_2Cl_2).

The resulting mixture was stirred at room temperature for 24 h, and then the reaction was quenched with 2 N aqueous NaOH (4 mL). The organic layer was diluted with CH_2Cl_2 (25 mL), washed with brine, dried, and evaporated, and the residue was subjected to silica gel chromatography (eluent 1:9 ethyl acetate–hexane). There was isolated 1.12 g (80%) of dithiolane (–)-**24** as a white solid: mp = 142.1 °C; $[\alpha]^{20}_D$ = –3.1° (*c* 1, $CHCl_3$); IR ($CHCl_3$) 1780, 1512, 1375, 1060, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34 (d, J = 8.5 Hz, 2 H), 7.16 (d, J = 8.5 Hz, 2 H), 4.46 [AB $\Delta\nu_{AB}$ = 16.5 Hz, 4.51 (d, J = 9.5 Hz, 1 H), 4.42 (d, J = 9.5 Hz, 1 H)] [like AA'BC syst, 3.30–3.20 (m, 2 H), 3.15–3.00 (m, 1 H), 3.00–2.80 (m, 1 H)], 2.36 (s, 3 H), 1.76 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 177.5 (s, C(1)) [6 arom C, 137.8 (s), 134.5 (s), 128.6 (2d), 127.5 (2d)], 77.9 (t, C(4)), 75.8 (s, C(3)), 54.1 (s, C(2)), 39.1 (t), 38.6 (t), 21.6 (q), 21.0 (q). Anal. Calcd for $C_{14}H_{16}O_2S_2$: C, 59.97; H, 5.75; S, 22.87. Found: C, 60.09; H, 5.74; S, 22.85.

(*S*)-(–)-2-Methyl-2-(4-methylphenyl)-4-butanolide (25). To a stirred solution of dithioacetal (–)-**24** (560 mg, 2 mmol) in dry EtOH (50 mL) was added Raney nickel (W2, 2 g)[32] and the resulting suspension heated under reflux. After 1 h, another portion of Raney nickel (1 g) was added. This operation was repeated four times, and the solution was stirred under reflux for 24 h. Then the solution was allowed to cool to room temperature before elimination of Raney nickel by filtration through a silica gel column. The filtrate was concentrated under vacuum and the crude product purified by chromatography on silica gel (using 15:85 ethyl acetate–hexane as eluent) to yield 243 mg (64%) of pure lactone (–)-**25** as a colorless liquid: $[\alpha]^{20}_D$ = –11.3° (*c* 1, $CHCl_3$); 99% ee from ^1H NMR spectra in presence of Eu(hfc)$_3$; IR (neat) 1770, 1515, 1200, 1170, 1078, 1026 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32 (d, J = 8.4 Hz, 2 H), 7.17 (d, J = 8.4 Hz, 2 H) [like ABMN syst, 4.41–4.26 (m, 1 H), 4.24–4.05 (m, 1 H), 2.68–2.58 (m, 1 H), 2.52–2.30 (m, 1 H)], 2.35 (s, 3 H), 1.62 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 180.0 (s, C(1)) [6 arom C, 138.0 (s), 137.0 (s), 129.4 (2d), 125.7 (2d)], 64.9 (t, C(4)), 41.7 (s, C(2)), 38.0 (t, C(3)), 25.4 (q), 20.8 (q); MS (EI) 190 (M^+, 33), *131* (100), 115 (16), 91 (21), 39 (11). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.95; H, 7.18.

The Raney nickel residue obtained above by filtration was collected and slowly dissolved at 0 °C in concentrated aqueous HCl (50 mL). The product was then extracted with ethyl acetate (6 × 50 mL). The combined organic extracts were washed with brine, dried, and evaporated, and the residue was purified by chromatography on silica gel (elution with 3:7 ethyl acetate–hexane). There was isolated 119 mg (31%) of (*S*)-(+)-2-methyl-2-(4-methylphenyl)butanoic acid (**26**) as a colorless oil: $[\alpha]^{20}_D$ = +9.2° (*c* 1, $CHCl_3$); IR (neat) 3100, 1705, 1518, 1460, 1270 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.23 (s, 2 H), 7.29 (d, J = 7.8 Hz, 2 H), 7.17 (d, J = 7.8 Hz, 2 H), 2.37 (s, 3 H), 2.20–1.90 (m, 2 H), 1.57 (s, 3 H), 0.85 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 183.2 (s, C(1)) [6 arom C, 139.9 (s), 136.4 (s), 129.1 (2d), 126.1 (2d)], 50.0 (s, C(2)), 31.5 (t, C(3)), 21.6 (q), 20.9 (q), 9.0 (q); MS (EI) 192 (M^+, 15), *147* (100), 117 (23), 115 (15), 105 (46), 91 (10), 55 (16), 43 (29). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.05; H, 8.55.

(±)-2-Methyl-2-(4-methylphenyl)-4-butanolide (25) (from 12). To a solution of *i*-Pr_2NH (0.97 mL, 6.72 mmol, 1.2 equiv) and tetramethylethylenediamine (TMEDA)[33] (1.68 mL, 11.2 mmol, 2 equiv) in THF (25 mL), at –78 °C, was added via cannula *n*-BuLi (1.55 M, 4.32 mL, 6.72 mmol, 1.2 equiv), and the resulting solution was stirred for 20 min at 0 °C. The LDA solution generated was recooled to –78 °C, and a solution of **12** (1 g, 5.6 mmol) in dry THF (10 mL) was added via cannula. The resulting orange solution was stirred for 1 h at –60 °C. Then the cooling bath was removed and an excess of ethylene oxide (6 g) bubbled into the stirred solution over a period of 1 h. The reaction was quenched by pouring into ether (50 mL) containing methanol (0.28 mL, 7 mmol, 1.25 equiv) and vigourously stirred for 10 min. After concentration of the solvents, the residue was poured into 20 mL of a 1:1 mixture of THF/4 N HCl, heated at 50 °C for 3 h. The residue was diluted in ether (100 mL), and the resulting organic layer was washed with brine, dried, and concentrated. Chromatography on silica gel (using 15:85 ethyl acetate–hexane as eluent) yielded 850 mg (80%) of pure lactone (±)-**25** as a colorless oil. Spectral data were identical with those reported for optically active material (see above).

(3*S*)-2-Hydroxy-3-methyl-3-(4-methylphenyl)tetrahydrofuran (27). This alcohol was prepared following the procedure described above for **17**, from lactone (–)-**25** (475 mg, 2.5 mmol) and DIBALH (2.5 mL of a 1 M solution in toluene, 2.5 mmol, 1 equiv). Chromatography on silica gel (15:85 ethyl acetate–hexane) furnished 470 mg (98%) of a 1:2 unseparable mixture of diastereoisomers of lactol **27** as a colorless oil: IR (neat) 3400, 1515, 1460, 1065, 1035 cm^{-1}; ^1H NMR (mixture of diastereoisomers a and b) ($CDCl_3$) δ 7.35–7.12 (m, 4 H, a and b), 5.47–5.35 (m, 1 H, a and b), 4.34–4.22 (m, 0.66 H, a), 4.2–4.04 (m, 1 H, a and b), 3.95–3.83 (m, 0.33 H, b), 3.22 (br s, OH, a and b), 2.72–2.54 (m, 0.66 H, a), 2.44–2.14 (m, 0.66 H, b), 2.36 (s, 3 H and b), 2.10–1.95 (m, 0.66 H, a), 1.42 (s, 3 × 0.33 H, b), 1.31 (s, 3 × 0.66 H, a); MS (EI) 193 (M^+ + 1, 1), 192 (M^+, 6), 146 (22), 145 (15), 132 (14), *131* (100), 130 (34), 129 (10), 119 (25), 117 (14), 116 (14), 115 (22), 105 (17), 91 (32), 77 (12), 65 (12). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.55; H, 8.53.

(3*S*)-3-Methyl-3-(4-methylphenyl)pentane-1,4-diol (28). This diol was prepared following the procedure described above for **20**, from a diastereomeric mixture of lactol **27** (384 mg, 2 mmol) and MeMgBr (3 M, 2 mL, 6 mmol, 3 equiv). Chromatography on silica gel (1:1 ethyl acetate–CH_2Cl_2 as eluent) yielded the 1:1 mixture of diastereoisomeric diols **28** as colorless oils.

Diastereomer A (200 mg, 48%): R_f = 0.30 (TLC, Et_2O); $[\alpha]^{20}_D$ = –6.5° (*c* 1, $CHCl_3$); IR (neat) 3350, 1515, 1450, 1380, 1075, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.31 (d, J = 7.9 Hz, 2 H), 7.16 (d, J = 7.9 Hz, 2 H), 3.89 (q, J = 6.2 Hz, 1 H-C(4)), 3.73–3.38 (m, 2 H, –C(1)), 2.34 (s, 3 H), 2.17–1.87 (m, 2 H), 1.63 (br s, 2 OH), 1.34 (s, 3 H), 1.10 (d, J = 6.2 Hz, 3 H); MS (EI) 190 ($M^+ - H_2O$, 1), 164 (38), 163 (15), 146 (23), 145 (22), 133 (30), 132 (18), 131 (71), 120 (17), *119* (100), 118 (21), 117 (30), 105 (43), 93 (17), 91 (35), 77 (15), 43 (21), 41 (20). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.71; H, 9.73.

Diastereomer B (200 mg, 48%): R_f = 0.23 (TLC, Et_2O); $[\alpha]^{20}_D$ = +3.3° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.23 (d, J = 7.8 Hz, 2 H), 7.14 (d, J = 7.8 Hz, 2 H), 4.05 (q, J = 6.7 Hz, 1 H-C(4)), 3.75–3.46 (m, 2 H, –C(1)), 2.33 (s, 3 H), 2.26 (br s, 2 OH), 2.19–1.93 (m, 2 H), 1.33 (s, 3 H), 0.97 (d, J = 6.7 Hz, 3 H). IR, MS, and elemental analysis data were identical with those reported for isomer A.

(*S*)-(+)-3-Methyl-3-(4-methylphenyl)-4-oxopentanal (29). This aldehyde was prepared following the procedure described above for **17**, from a diastereomeric mixture of diols **28** (312 mg, 1.5 mmol), $(COCl)_2$ (0.252 mL, 3.3 mmol, 2.2 equiv), DMSO[27] (0.465 mL, 6.6 mmol, 4.4 equiv), and Et_3N (1.95 mL, 15 mmol, 10 equiv). Chromatography on silica gel (1:9 ethyl acetate–hexane as eluent) furnished 294 mg (97%) of pure keto aldehyde (+)-**29** as a colorless liquid: $[\alpha]^{20}_D$ = +244° (*c* 1, $CHCl_3$); IR (neat) 2745, 1728, 1715, 1515, 1355, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.62 (X part of ABX syst, J_{AX} = 2.5, J_{BX} = 1.9 Hz, 1 H), 7.26–7.10 (m, 4 H), 2.86 [AB part of ABX, $\Delta\nu_{AB}$ = 48.2 Hz, 2.96 (A part, J_{AB} = 16.0 Hz, J_{AX} = 2.5 Hz, 1 H), 2.77 (B part, J_{AB} = 16.0 Hz, J_{BX} = 1.9 Hz, 1 H)], 2.36 (s, 3 H, CH_3 tol), 1.97 (s, 3 H, CH_3CO), 1.70 (s, 3 H); MS (EI) 205 (M^+ + 1, 1), 204 (M^+, 1), 161 (27), 145 (10), 144 (68), 143 (14), 133 (88), 117 (24), 116 (10), 115 (40), *105* (100), 93 (65), 91 (55), 77 (23), 65 (13), 43 (84), 41 (69).

(*S*)-(+)-5-Methyl-5-(4-methylphenyl)cyclopent-2-en-1-one (30). This ketone was prepared following the procedure described above for **21**, from keto aldehyde (+)-**29** (280 mg, 1.4 mmol) and KOH (120 μL of a 1 M solution in EtOH).[1b] Chromatography on silica gel (1:9 ethyl acetate–hexane as eluent) yielded 170 mg (65%) of cyclopentenone (+)-**30** as a colorless liquid: $[\alpha]^{20}_D$ = +5.3° (*c* 0.6, $CHCl_3$); IR (neat) 1715, 1592, 1515, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ [like ABXY system, 7.78 (Y part, J_{XY} = 6 Hz, $J_{AY} = J_{BY}$ = 2.7 Hz, 1 H), 6.27 (X part, J_{XY} = 6 Hz, $J_{AX} = J_{BX}$ = 2.3 Hz, 1 H)], 3.00 [AB part of ABXY, $\Delta\nu_{AB}$ = 65.3 Hz, 3.13 (B part, J_{AB} = 19.5 Hz, J_{BX} = 2.3 Hz, J_{BY} = 2.7 Hz, 1 H), 2.87 (A part, J_{AB} = 19.5 Hz, J_{AX} = 2.3 Hz, J_{AY} = 2.7 Hz, 1 H)], 2.33 (s, 3 H), 154 (s, 3 H); MS (EI) 187 (M^+ + 1, 13), 186 (M^+, 90), 172 (13), *171* (100), 157 (16), 143 (56), 142 (21), 141 (19), 129 (14), 128 (44), 127 (19), 117 (21), 116 (12), 115 (45), 92 (11), 91 (31), 77 (20), 65 (14), 39 (25).

(41) Hatch, R. P.; Shringarpure, J.; Weinreb, S. M. *J. Org. Chem.* **1978**, *43*, 4172 and references cited therein.

(2*R*)-3-Hydroxy-2-methyl-2-(4-methylphenyl)-4-butanolide (31a). To a cold (−10 °C) stirred solution of keto lactone (+)-15 (408 mg, 2 mmol) in dry EtOH (20 mL), was added $NaBH_4$ (92 mg, 2.4 mmol, 1.2 equiv) by small amounts[34] and the resulting mixture stirred for 30 min at −10 °C. Then the solution was acidified with 2 N aqueous HCl at −5 °C to pH 2. After concentration of the EtOH under reduced pressure, the product was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with water and brine, dried and evaporated. The 1:9 mixture of diastereoisomeric hydroxy lactone (2*R*)-**31a** purified by chromatography on silica gel (1:9 ethyl acetate–hexane) furnished the following as colorless oils.

syn-(2*R*,3*S*)-**31a** (333 mg, 81%): R_f = 0.44 (TLC, ethyl acetate/hexane = 3/7); $[\alpha]^{20}_D$ = −159° (*c* 2.1, $CHCl_3$); IR (Et_2O) 3680, 3580, 1780, 1520, 1390, 1180, 1125, 1070, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40–7.15 (m, 4 H) [like ABCX system, 4.37 (AB part of ABCX, $\Delta\nu_{AB}$ = 66 Hz), 4.53 (A part, ddd, J_{AB} = 9.6 Hz, J_{AC} = 4.3 Hz, J_{AX} = 1.7 Hz, 1 H), 4.31 (C part, m, J_{AC} = 4.3 Hz, J_{BC} = 2.8 Hz, J_{CX} = 4.1 Hz, 1 H), 4.20 (B part, dd, J_{AB} = 9.6 Hz, J_{BC} = 2.8 Hz)], 2.37 (s, 3 H), 1.57 (s, 3 H), 1.43 (X part, dd, J_{AX} = 1.7 Hz, J_{BX} = 4.1 Hz, 1 OH); ^{13}C NMR ($CDCl_3$) δ 178.4 (s, C(1)) [6 arom C, 138.0 (s), 132.1 (s), 129.7 (2d), 127.7 (2d)], 76.0 (d, C(3)), 71.2 (t, C(4)), 52.6 (s, C(2)), 22.2 (q), 20.9 (q); MS (EI) 208 (M^+ + 2, 1), 207 (M^+ + 1, 9), 206 (M^+, 73), 147 (27), 146 (68), 145 (17), 129 (12), 119 (65), 118 (62), *117* (100), 116 (22), 115 (33), 105 (21), 103 (15), 102 (12), 92 (10), 91 (50), 90 (11), 77 (16), 65 (15), 51 (16), 43 (56).

anti-(2*R*,3*R*)-**31a** (37 mg, 9%): R_f = 0.51 (TLC, ethyl acetate/hexane = 3/7); $[\alpha]^{20}_D$ = −70.7° (*c* 1.35, $CHCl_3$); IR (Et_2O) 3460, 1775, 1515, 1180, 1080, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18 (s, 4 H), 4.59 (m, 1 H, –C(3)), 4.28–4.11 (m, 2 H), 2.94 (br s, 1 OH), 2.34 (s, 3 H), 1.57 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 179.3 (s, C(1)) [6 arom C, 137.5 (s), 136.7 (s), 129.7 (2d), 126.0 (2d)], 76.5 (d, C(3)), 72.0 (t, C(4)), 53.5 (s, C(2)), 20.9 (q), 18.4 (q); MS (EI) 208 (M^+ + 2, 1), 207 (M^+ + 1, 10), 206 (M^+, 78), 147 (50), 146 (70), 129 (17), 120 (15), 119 (93), 118 (69), *117* (100), 116 (24), 115 (36), 105 (31), 103 (17), 92 (18), 91 (65), 90 (22), 77 (19), 65 (15), 55 (17), 43 (50).

(2*S*,3*R*)-3-Iodo-2-methyl-2-(4-methylphenyl)-4-butanolide (31b). To a stirred solution of hydroxy lactone (2*R*,3*S*)-(−)-**31a** (412 mg, 2 mmol) in dry toluene (40 mL) was added at room temperature Ph_3P (790 mg, 3 mmol, 1.5 equiv), imidazole (268 mg, 4 mmol, 2 equiv), and iodine (1.26 g, 5 mmol, 2.5 equiv).[36] The resulting mixture was stirred at reflux during 12 h and then cooled. An equal volume of aqueous $NaHCO_3$ was added and the mixture stirred for 5 min. Iodine was added in small portions, until the toluene layer remained iodine-colored, and then stirred for an additional 10 min. Excess of iodine was removed by the addition of aqueous $Na_2S_2O_3$. The organic layer was diluted with toluene (60 mL), washed with water, and dried. Filtration on silica gel column followed by concentration gave the crude (2*S*,3*R*)-iodobutanolide **31b** selectively which, unstable, was used directly in the next step without further purification: ^1H NMR ($CDCl_3$) δ 7.32–7.15 (m, 4 H), [ABC system, 4.79 (C part, dd, J_{AC} = 5.7 Hz, J_{BC} = 5.3 Hz, 1 H), 4.51 (AB part of ABC system, $\Delta\nu_{AB}$ = 17.3 Hz, 4.58 (B part, J_{AB} = 7.7 Hz, J_{BC} = 5.3 Hz, 1 H), 4.48 (A part, J_{AB} = 7.7 Hz, J_{AC} = 5.7 Hz, 1 H))], 2.37 (s, 3 H), 1.72 (s, 3 H).

(*S*)-(−)-2-Methyl-2-(4-methylphenyl)-4-but-3-enolide (32). To a stirred solution of crude iodobutenolide **31b** (316 mg, 1 mmol), in THF (15 mL), was added diazabicycloundecene (DBU) (1.5 mL, 10 mmol, 10 equiv), and the resulting mixture was stirred at reflux for 12 h. The solution was then cooled and diluted with CH_2Cl_2 (20 mL), washed with brine, dried, and evaporated. Chromatography on silica gel (1:9 ethyl acetate–hexane as eluent) yielded 118 mg (63% overall yield from alcohol (2*R*)-**31a**) of pure butenolide (−)-**32** as a colorless liquid: $[\alpha]^{20}_D$ = −56.7° (*c* 1, $CHCl_3$); IR (neat) 3120, 1800, 1620, 1515, 1120, 1070, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (d, *J* = 8.0 Hz, 2 H), 7.18 (d, *J* = 8.0 Hz, 2 H), 6.94 (d, *J* = 4.2 Hz, 1 H), 5.87 (d, *J* = 4.2 Hz, 1 H-C(4)), 2.35 (s, 3 H), 1.72 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 179.8 (s, C(1)), 141.3 (d, C(4)) [6 arom C, 137.5 (s), 136.1 (s), 129.4 (2d), 125.9 (2d)], 116.3 (d, C(3)), 49.7 (s, C(2)), 24.7 (q), 20.9 (q); MS (EI) 190 (M^+ + 2, 1), 189 (M^+ + 1, 12), 188 (M^+, 95), 173 (10), 159 (45), 145 (100), 119 (10), 117 (21), 116 (13), 115 (35), 91 (34), 77 (11), 65 (15), 63 (11), 39 (15). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.56; H, 6.18.

(2*R*,3*S*)-(+)-2-Methyl-2-(4-methylphenyl)-3-(mesyloxy)-4-butanolide (31c). To a stirred solution of (2*R*,3*S*)-(−)-**31a** (206 mg, 1 mmol) in dry CH_2Cl_2 (5 mL) was added at 20 °C Et_3N (0.43 mL, 3 mmol, 3 equiv). The mixture was cooled (0 °C) before addition of freshly distilled MsCl (120 μL, 1.5 mmol, 1.5 equiv).[42] The resulting solution was stirred for 12 h at 20 °C and then washed with saturated aqueous $NaHCO_3$ and brine, dried, and evaporated. The crude mesylate **31c** (290 mg) obtained was used directly in the next step without further purification: ^1H NMR ($CDCl_3$) δ 7.36–7.13 (m, 4 H), 5.25 (C part of ABC, J_{AC} = 2.1 Hz, J_{BC} = 4.2 Hz, 1 H), 4.59 [AB part of ABC, $\Delta\nu_{AB}$ = 33.7 Hz, 4.68 (B part, J_{AB} = 11.6 Hz, J_{BC} = 4.2 Hz, 1 H), 4.50 (A part, J_{AB} = 11.6 Hz, J_{AC} = 2.1 Hz, 1 H)], 2.42 (s, 3 H, CH_3, mesyl), 2.36 (s, 3 H, CH_3, tol), 1.75 (s, 3 H).

(2*R*,3*S*)-2-Methyl-2-(4-methylphenyl)-3-[(isopropylsulfonyl)oxy]-4-butanolide (31d). To a stirred solution of hydroxybutanolide (2*R*,3*S*)-**31a** (206 mg, 1 mmol) in dry ether (5 mL) was added at 20 °C Et_3N (0.43 mL, 3 mmol, 3 equiv). The mixture was cooled (0 °C) before addition dropwise of *i*-$PrSO_2Cl$ (168 μL, 3 mmol, 3 equiv).[38] The solution was stirred for 24 h at 20 °C and then diluted with ether (10 mL). The organic layer was washed successively with aqueous 2 N HCl and saturated aqueous $NaHCO_3$, dried, and evaporated. The product was purified by chromatography on silica gel (3:7 ethyl acetate–hexane as eluent) to furnish 280 mg (90%) of the isopropylsulfonate **31d** as a white solid: mp = 121 °C; $[\alpha]^{20}_D$ = −125.6° (*c* 0.5, $CHCl_3$); IR (KBr) 1790, 1350, 965 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (d, *J* = 7.9 Hz, 2 H), 7.20 (d, *J* = 7.9 Hz, 2 H), 5.23 (M part of ABM syst, m, 1 H), 4.60 [AB part of ABM, $\Delta\nu_{AB}$ = 28.0 Hz, 4.65 (A part, dd, J_{AB} = 11.7 Hz, J_{AM} = 4.7 Hz, 1 H), 4.54 (B part, dd, J_{AB} = 11.7 Hz, J_{BM} = 2.3 Hz, 1 H)], 3.35 (m, 1 H), 2.35 (s, 3 H), 1.74 (s, 3 H), 1.07 (d, *J* = 7.0 Hz, 3 H), 0.99 (d, *J* = 7.0 Hz, 3 H). Anal. Calcd for $C_{15}H_{20}O_5S$: C, 57.67; H, 6.45; S, 10.26. Found: C, 57.78; H, 6.55; S, 10.14.

(*R*)-(+)-2-Methyl-2-(4-methylphenyl)-3-[[(4-methylphenyl)sulfonyl]hydrazono]-4-butanolide (31e). To a stirred solution of keto lactone (+)-**15** (204 mg, 1 mmol) in dry EtOH (5 mL) was added by small amounts *p*-toluenesulfonhydrazide (223 mg, 1.2 mmol, 1.2 equiv).[39] The resulting mixture was stirred and heated under gentle reflux until complete precipitation of the tosylhydrazone (2.5 h). After cooling, the product was collected by filtration, washed with ether, and recrystallized from ether to furnish 333 mg (90%) of butanolide (+)-**31e** as a white solid: mp = 158 °C; $[\alpha]^{20}_D$ = +139.6° (*c* 1.25, acetone); IR (KBr) 3220, 1790, 1170 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.87 (s, 1 H), 7.73 (d, *J* = 7.9 Hz, 2 H), 7.40 (d, *J* = 7.9 Hz, 2 H), 6.96 (m, 4 H), 4.91 [AB, $\Delta\nu_{AB}$ = 45 Hz, 5.00 (d, *J* = 15.8 Hz, 1 H), 4.81 (d, *J* = 15.8 Hz, 1 H)], 2.40 (s, 3 H), 2.23 (s, 3 H), 1.49 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 176.5 (s, C(1)), 157.6 (s, C(3)), [12 arom C, 143.7 (s), 137.1 (s), 135.9 (2s), 129.6 (2d), 129.3 (2d), 127.6 (2d), 125.7 (2d)], 67.0 (t, C(4)), 49.0 (s, C(2)), 23.0 (q), 21.1 (q), 20.5 (q).

Reduction of the Tosylhydrazone (*R*)-31e. To a stirred solution of **31e** (370 mg, 1 mmol) in a 1:1 mixture of DMF–sulfolane (5 mL) was added $NaBH_3CN$[39] (251 mg, 4 mmol, 4 equiv) and TsOH (50 mg). The resulting solution was stirred at 110 °C for 18 h, cooled to room temperature, and then diluted with brine. The layers were separated, and the organic extract was dried and concentrated. Chromatography on silica gel (elution with 15:85 ethyl acetate–hexane) furnished 41 mg (20%) of hydroxy lactone (*R*)-**31a** (diastereomeric mixture), 19 mg (10%) of butenolide (*S*)-**32**, and 23 mg (12%) of butyrolactone (*S*)-**25**. All spectral data of **25**, **31a**, and **32** were identical with those reported above.

(*S*)-(+)-3-Methyl-3-(4-methylphenyl)-4-oxopentanal (29) (from (*S*)-32). To a cold (−90 °C) and stirred solution of butenolide (−)-**32** (94 mg, 0.5 mmol) in dry ether (3 mL) was added, dropwise, MeLi (1 M, 0.5 mL, 0.5 mmol, 1 equiv). The resulting mixture was stirred for 1 h at −90 °C then 1 h at −78 °C. The solution cooled at −90 °C was hydrolyzed with saturated aqueous NH_4Cl (1 mL). The reaction mixture was allowed to warm slowly to room temperature. After separation, the aqueous layer was

(42) Yadav, J. S.; Mysorekar, S. V. *Synth. Commun.* **1989**, *19*, 1057.

extracted with ether (10 mL). The combined organic extract was washed with brine, dried, and evaporated. The residue purified by chromatography on silica gel (1:9 ethyl acetate–hexane) yielded keto aldehyde (+)-**29** (52 mg, 50%) as a colorless liquid, a by-product, i.e., 2-hydroxy-4-methyl-4-(4-methylphenyl)-5,5-dimethyltetrahydrofuran (**33**) (22 mg, 20%) as an unseparable mixture of diastereoisomers, and starting material (−)-**32** (28 mg, 30%). Spectral data of (+)-**29** were identical with those reported above.

Data of **33**: ^{1}H NMR ($CDCl_3$) δ in 2:1 *a*/b mixture, 7.35–7.05 (m, 4 H), *5.70*/5.67 (X part of ABX system, 1 H, *a*/b), 3.80–3.55 (br s, OH, a/b), 2.54 [AB part of ABX system of b isomer, $\Delta\nu_{AB}$ = 165.6 Hz, 2.95 (A part, J_{AB} = 13.8 Hz, J_{AX} = 6.5 Hz, 0.33 H), 2.12 (B part, J_{AB} = 13.8 Hz, J_{BX} = 2.3 Hz, 0.33 H)], 2.54 [AB part of ABX system of a isomer, $\Delta\nu_{AB}$ = 100 Hz, 2.78 (A part, J_{AB} = 13.1 Hz, J_{AX} = 6.2 Hz, 0.66 H), 2.29 (B part, J_{AB} = 13.1 Hz, J_{BX} = 6.0 Hz, 0.66 H)], 2.35 (s, 6 H, 2 Me, tolyl a/b), 1.56 (s, 3 × 0.33 H, Me, b), 1.52 (s, 3 × 0.33 H, Me, b), 1.43 (s, 3 × 0.66 H, Me, a), 1.37 (s, 3 × 0.66 H, Me, a), 1.03 (s, 3 × 0.66 H, Me, a), 0.79 (s, 3 × 0.33 H, Me, b).

Supplementary Material Available: ^{1}H NMR spectra for obtained compounds (26 pages). Ordering information is given on any current masthead page.

Syntheses of the Anti-AIDS Drug 2′,3′-Dideoxycytidine from Cytidine

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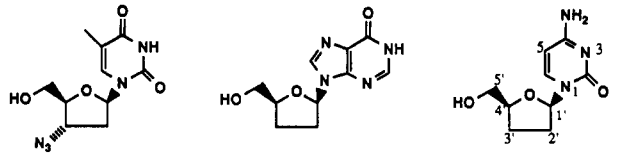
Two efficient syntheses of the anti-AIDS drug 2′,3′-dideoxycytidine (**3**) from N^4-acetylcytidine (**4**) are described. In one, silylation of the C-5′ hydroxyl group of **4** with *tert*-butyldimethylsilyl chloride followed by treatment with 1′,1′-(thiocarbonyl)diimidazole gave the cyclic thionocarbonate **7**, which on reaction with 1,3-dimethyl-2-phenyl-1,3-diazaphospholidine gave the crystalline alkene **8**. Hydrogenation of **8**, followed by desilylation with tetrabutylammonium fluoride and hydrolysis, gave **3** in 27% overall yield from **4**. In the other synthesis, **4** was converted into a regioisomeric mixture of bromo acetates **11** with 2-acetoxy-2-methylpropanoyl bromide. Reductive elimination of **11** with zinc–copper couple in acetic acid or electrochemically gave the crystalline alkene **15**, whose stereostructure was established by a single-crystal X-ray analysis. Hydrogenation of **15**, followed by hydrolysis, gave ddC (**3**). In a through process, which is suitable for large-scale work, this second synthesis gave **3** in over 40% overall yield from **4**. The use of (*S*)-(−)-2-acetoxypropanoyl bromide, of 2-acetoxybenzoyl bromide, and of hydrogen bromide/acetic acid in the bromoacetylation of **4** is also described.

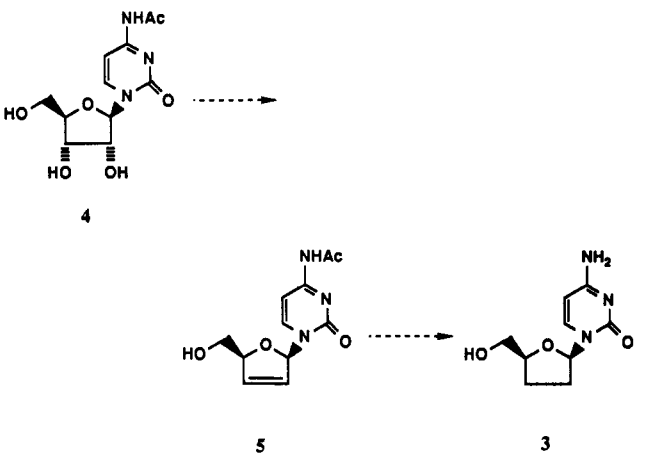
The recognition that the human immunodeficiency virus (HIV) is responsible for the etiology of acquired immune deficiency syndrome (AIDS) has prompted an enormous effort to find agents that would combat this disease.[1] For its early phase of replication, HIV, a retrovirus, requires the viral specific reverse transcriptase to transcribe its RNA into viral DNA. Of the various compounds tested to inhibit this process, 2′,3′-dideoxynucleosides have been the most successful.[2] Two of these, 3′-azido-3′-deoxythymidine (**1**, AZT) and 2′,3′-dideoxyinosine (**2**, ddI), have



1 (AZT) 2 (ddI) 3 (ddC)

been approved by the Food and Drug Administration for the treatment of AIDS, while 2′,3′-dideoxycytidine (**3**, ddC) is in the late stages of clinical trials.[1,2] These 2′,3′-dideoxynucleotides, after cytoplasmic phosphorylation to their 5′-triphosphates, have a higher affinity for HIV reverse transcriptase than for cellular DNA polymerases and are therefore incorporated into the growing viral DNA chain; however, since they lack a hydroxyl group at the C-3′ position, formation of the 5′,3′-phosphodiester linkage is not possible, resulting in termination of viral DNA synthesis.

Scheme I



4 5 3

Previous syntheses of ddC followed two principal routes. In one, the starting material is a nucleoside that is subjected to a number of transformations giving **3**, usually in low overall yields.[3] In the other, a protected form of 2′,3′-dideoxyribose is coupled to a cytosine derivative in

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