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A Straightforward Synthesis of (−)-Phaseolinic Acid

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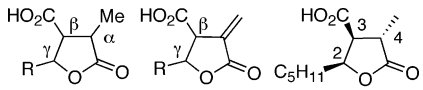
Received July 27, 2004

Abstract: A concise approach to (−)-phaseolinic acid starting from commercially available (*S*)-oct-1-yn-3-ol is disclosed. The key steps are a ring-closing metathesis reaction to prepare a C_2-symmetrical allylic diol and its desymmetrization to a γ-butyrolactone by using an Ireland−Claisen rearrangement. The 2*S*,3*S*,4*S* configuration of the levogyre natural product has been confirmed.

Introduction

Paraconic acids are a class of γ-butyrolactones (**1** or **2**) isolated from various species of lichens, mosses, and fungi (Figure 1). They possess a very similar substitution pattern at the α-position (methyl or methylene group) and β-position (carboxyl group). However, these compounds differ in the residue attached to the γ-position as well as in the stereochemical relationship between these substituents. Since many paraconic acids exhibit important biological activities, such as antifungal, antitumor, and antibacterial,[1] the preparation of these lactones have attracted considerable attention of synthetic chemists. As a result, some efficient methods have been reported for the enantioselective preparation of *trans* β,γ-substituted butyrolactones,[2] but fewer syntheses of *cis* β,γ-substituted products have been described.[3]



1 **2** (2*S*,3*S*,4*S*)-**3**

FIGURE 1. Structure of paraconic acids.

In the course of studies directed toward the synthesis of natural products from unsaturated 1,4-diols,[4] we addressed our attention to the synthesis of (−)-phaseolinic acid (**3**). This compound, isolated from the culture filtrate of the phytotoxic fungus *Macrophomina phaseolina*, constitutes a representative example of the abovementioned *cis* β,γ-substituted paraconic acid. The stereochemistry of **3** was initially assigned to be 2*R*,3*R*,4*R* on the basis of a single-crystal X-ray analysis and its CD spectrum in 1987.[5] Later publications[6,7] on the enantioselective syntheses of (−)-phaseolinic acid seemed to confirm the proposed absolute configuration. However, a more recent report from Valentin et al.[8] based on enzymatic and chemical processes surprisingly concluded that the configuration of natural phaseolinic acid having negative specific rotation is 2*S*,3*S*,4*S* and not 2*R*,3*R*,4*R* as previously described. Prompted by these dissenting reports, we disclose herein a straightforward, stereoselective synthesis of (−)-phaseolinic acid from commercially available (*S*)-oct-1-yn-3-ol, (*S*)-**4**, which concludes that the levogyre phaseolinic acid is the 2*S*,3*S*,4*S* isomer in agreement with Valentin's results.

As depicted in Scheme 1, our synthetic strategy involves two key steps: (i) the preparation of the enantiopure symmetrical diol (*S*,*S*)-**5** from (*S*)-**4** and (ii) the desymmetrization of that allylic diol through an Ireland−Claisen rearrangement to an open-chain compound **6** that possesses the adequate stereoarray.

As far as the first goal is concerned, we envisioned that diol (*S*,*S*)-**5** might be prepared through an olefin metathesis of (*S*)-oct-1-en-3-ol, (*S*)-**8**, which is readily obtained by partial reduction of (*S*)-**4**. Despite the widespread application of homodimerization of terminal olefins via self-metathesis,[9] we were aware that such dimerization could be a difficult task. Expected troubles included low *cis*/*trans* selectivity and also the potential isomerization of secondary allylic alcohols to ketones under metathesis

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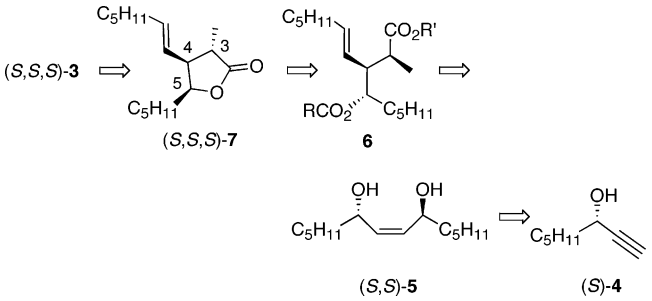
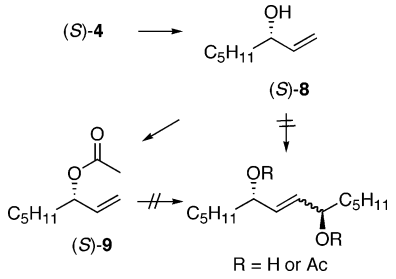
10.1021/jo048705x CCC: $27.50
Published on Web 11/05/2004

SCHEME 1. Retrosynthetic Analysis for (3*S*,4*S*,5*S*)-3



SCHEME 2. Formation of 1,4-Diols by Direct Olefin Metathesis

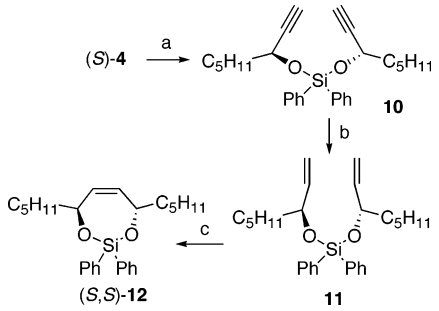


conditions.[10] In practice, when we explored the metathesis of (*S*)-**8** and its acetate derivative (*S*)-**9** in the presence of Grubbs' catalyst [$(P(Cy)_3)_2Cl_2Ru$=CHPh] under different conditions, we did not obtain the expected allylic 1,4-diols in significant amounts (Scheme 2).

This failure was attributed to the presence of a vicinal heteroatom next to the olefin that might decrease the catalyst activity by chelation and/or by sterical congestion.[11] This problem has sometimes been solved by using a temporary protecting group that links the two olefins in a single molecule and favors ring-closing metathesis.[12] This strategy has been particularly successful by using a silicon-tethered protection.[13] Furthermore, the structural requirements to form a cyclic molecule would lead to the exclusive formation of *Z*-isomer (Scheme 3). Accordingly, the protection of (*S*)-**4** as the dimeric silyl ether **10** with Ph_2SiCl_2 followed by partial hydrogenation under Lindlar's conditions afforded diolefin **11**. Ring-closing metathesis of **11** in the presence of Grubbs' catalysts gave protected diol (*S*,*S*)-**12** in good yield. Finally, treatment of the cyclic silyl ether with TBAF in THF afforded the desired diol (*S*,*S*)-**5** in 96% yield.

Then, we turned our attention to the desymmetrization of (*S*,*S*)-**5**. Based on our previous experience on the

SCHEME 3. Formation of (*S*,*S*)-12 by RCM[a]



[a] Reagents and conditions: (a) Ph_2SiCl_2, 2,6-dimethylpyridine, CH_2Cl_2, 85%; (b) H_2, Lindlar's catalyst, EtOAc, 91%; (c) $(PCy_3)_2Cl_2Ru$=CHPh cat., CH_2Cl_2, 76%.

rearrangement of allylic 1,4-diacetates,[4a,d] we envisioned that the key intermediate **6** could be attainable through an Ireland-Claisen rearrangement[14] of the *Z*(O)-*tert*-butyldimethylsilylketene acetal *Z*(O)-**14** arising from the stereoselective enolization of dipropanoate (*S*,*S*)-**13** (Scheme 4). Since both propanoate groups present in (*S*,*S*)-**13** are homotopics, we expected that the *Z*(O) enolization followed by thermal rearrangement of either of the propanoate groups should converge on the same compound **6**, immediate precursor of lactone (3*S*,4*S*,5*S*)-**7**. Alternatively, *E*(O) enolization of (*S*,*S*)-**13** would lead to the 3*R*,4*S*,5*S* isomer (see Scheme 4). Our first attempt was carried out by treatment of (*S*,*S*)-**13** with an excess of *t*-butyldimethylsilyl chloride (TBDMSCl) and potassium bis(trimethylsilyl)amide (KHMDS) in THF at −78 °C and then heating the mixture in refluxing toluene. The resultant crude mixture containing the *tert*-butyldimethylsilyl ester **6a** and the carboxylic acid **6b** was subjected to basic hydrolysis with LiOH. Further lactonization under acidic conditions cleanly afforded the desired lactone (3*S*,4*S*,5*S*)-**7** and its epimer (3*R*,4*S*,5*S*)-**7**, easily separable by flash chromatography, but in a disappointing 1:2 ratio. No other stereoisomer of **7** was detected.[15] Looking for a more extensive *Z*(O) enolization,[16] other experimental conditions of the Ireland−

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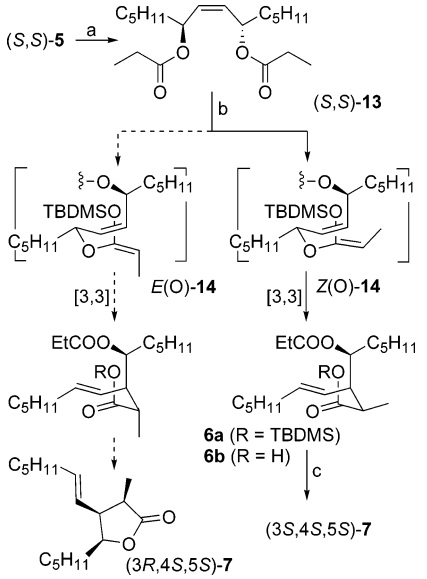
SCHEME 4. Ireland–Claisen Rearrangement[a]



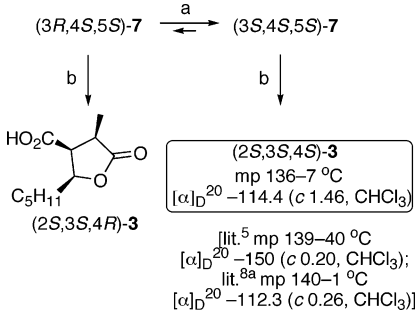
[a] Reagents and conditions: (a) $(EtCO)_2O$, Et_3N, DMAP, CH_2Cl_2, 100%; (b) (i) KHMDS, TBDMSCl, THF/30% DMPU, −78 °C to rt, (ii) toluene, Δ; (c) (i) LiOH, H_2O/THF, Δ, (ii) aq HCl/THF, Δ, 85%.

Claisen rearrangement were explored: changing base (KHMDS, LDA, LHMDS), silylating agent (TMSCl, *tert*-butyldimethylsilyl chloride or triflate), order of addition of the reagents, and the presence of cosolvents as *N*,*N*′-dimethyl-*N*,*N*′-propyleneurea (DMPU).[17] The best tandem of yield/selectivity was obtained when the enolization was performed by slow addition of (*S*,*S*)-**13** to KHMDS (3.03 mmol) and TBDMSCl(4.03 mmol) in 30% DMPU/THF at −78 °C. In such conditions and in a one-pot process without isolation of any intermediate, we obtained a gratifying 85% overall yield of lactones **7** with a 4:1 ratio in favor of the desired stereoisomer (3*S*,4*S*,5*S*)-**7**.

A further improvement in the final yield of that lactone was accomplished by base-catalyzed isomerization of the minor lactone (3*R*,4*S*,5*S*)-**7** to the 3*S*,4*S*,5*S* (DBU/pyridine,[18] ∼70:30 equilibrium mixture in favor of the *S*,*S*,*S* isomer).

Finally, transformation of lactone (3*S*,4*S*,5*S*)-**7** into the carboxylic acid (2*S*,3*S*,4*S*)-**3** was successfully accomplished by ozonolysis followed by oxidation of the crude aldehyde with $NaClO_2$[19] without loss of stereochemical purity (Scheme 5). This two-step process gave better yield (93%) than direct olefin cleavage with $RuCl_3$.[20] As expected, compound **3** showed identical spectral data as

SCHEME 5. Preparation of Phaseolinic Acid and Its Epimer[a]



[a] Reagents and conditions: (a) DBU, pyridine, Δ; (b) (i) O_3, CH_2Cl_2, −78 °C, (ii) Me_2S; (iii) $NaClO_2$, H_2O_2, NaH_2PO_4, H_2O/CH_3CN, 93–98%.

that reported in the literature[5,21] for phaseolinic acid and exhibited a negative optical rotation in agreement with Valentin's results. In analogous fashion, we transformed (3*R*,4*S*,5*S*)-**7** into the carboxylic acid (2*S*,3*S*,4*R*)-**3** in 98% yield.

Conclusion

In this paper, we have reported the synthesis of (−)-phaseolinic acid in eight steps and 40% overall yield from commercially available (*S*)-oct-1-yn-3-ol as the single source of chirality. The key intermediate (6*S*,7*Z*,9*S*)-tetradec-7-ene-6,9-diol, (*S*,*S*)-**5**, was prepared by self-metathesis of an enantioenriched allylic alcohol. This homodimerization has been very effective by using a temporary silicon-protecting group that favored the intramolecular metathesis (RCM) with total control of the stereochemistry of the alkene. Lactone skeleton of (2*S*,3*S*,4*S*)-**3** was achieved by a stereoespecific Ireland-Claisen rearrangement of the dipropanoate of (*S*,*S*)-**5** followed by consecutive basic and acid treatment in a very efficient one-pot process. This synthesis illustrates the value of C_2-symmetrical allylic 1,4-diols in the synthesis of natural products and also corroborates that the (−)-phaseolinic acid is the 2*S*,3*S*,4*S* isomer.

Experimental Section

(*S*,*S*)-4,7-Dipentyl-2,2-diphenyl-4,7-dihydro[1,3,2]dioxasilepine [(*S*,*S*)-12]. Diene **11** (74 mg, 0.17 mmol) was dissolved in CH_2Cl_2 (1 mL) under Ar atmosphere. The solution was sonicated for 20 min. Then, Grubbs' catalyst (15 mg, 0.017 mmol) was dissolved in anhyd CH_2Cl_2 (0.6 mL) and added via cannula. The solution was heated to reflux and the reaction was followed by TLC (95:5 hexane/EtOAc). Additional Grubbs' catalyst (8 mg, 5%mol) was added 7 h later. A last addition of catalyst (4 mg) was added 15 h later. The reaction was quenched after 28 h. The solvent was evaporated in a vacuum. The residue was purified by flash chromatography (95:5 hexane/CH_2Cl_2) to give (52 mg, 76%) as colorless oil: $R_f = 0.56$ (80:20 hexane/CH_2Cl_2); $[\alpha]_D$ −62.5 (*c* 1.01, $CHCl_3$); IR (film) 3072, 1654, 1592, 1090; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.80–0.84 (m, 6H), 1.18–1.40 (m, 12H), 1.40–1.75 (m, 4H), 4.71 (td, $J = 5.8$, 1.6 Hz, 2H), 5.54 (m,

(15) The relative stereochemistry of lactones **7** was confirmed by NOE experiments. It is noteworthy that after isolation, both lactones demostrated to be stereochemical stables under the experimental conditions used to transform **6** into **7**.

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(17) In our hands, the Claisen rearrangement of (*S*,*S*)-**13** mediated by trimethylsilyl triflate and a tertiary amine according to a reported protocol was completely unsuccessful. See: Kobayashi, M.; Masumoto, K.; Nakai, E.; Nakai, T. *Tetrahedron Lett.* **1996**, *37*, 3005–3008.

(18) Similar ratios were obtained when (2*R*,3*S*,4*S*)-**7** was heated with an excess of DBU in toluene, acetonitrile, hexane, or even neat, as the equilibrium balance did not greatly affect the polarity of the solvent.

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(21) ^1H NMR spectra of phaseolinic acid and its C-4 epimer as a racemic mixtures have been described: Pohmakotr, M.; Harnying, W.; Patoomratana, T.; Reutrakul, V. *Helv. Chim. Acta* **2002**, *85*, 3792–3813.

2H), 7.31−7.50 (m, 6H), 7.65−7.75 (m, 4H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.0, 22.6, 24.9, 31.5, 37.9, 70.5, 127.7, 130.3, 132.9, 134.1, 134.8; HRMS (FAB+) calcd for $C_{26}H_{37}O_2Si$ [M + H]$^+$ 409.2563, found 409.2567.

Preparation of Lactone (3*S*,4*S*,5*S*)-7: Optimized Procedure. A toluene solution of KHMDS (0.5 M, 1.74 mL, 0.87 mmol) was added dropwise to a solution of TBDMSCl (176 mg, 1.17 mmol) in anhyd THF (2 mL) and anhyd DMPU (1.35 mL) at −78 °C under argon. Then, a solution of (*S*,*S*)-**13** (100 mg, 0.29 mmol) in anhyd THF (0.5 mL) was added dropwise via cannula, followed by an additional 0.5 mL of THF to wash the flask. After the addition, the mixture was stirred for 45 min and then was allowed warm to rt for 5 h. Then, most of the volatiles were removed under vacuum, anhyd toluene (3 mL) was added, and the mixture was heated (130 °C bath temperature) for 16 h. The progress of the reaction was monitored by TLC (98:2 CH_2Cl_2/MeOH, disappearance of the starting material, R_f = 0.92, and appearance of **6a**, R_f = 0.90, and **6b**, R_f = 0.24). Adding diethyl ether (8 mL) and brine (8 mL) partitioned the reaction mixture. The aqueous layer was washed with additional diethyl ether, and the combined organic layers were dried ($MgSO_4$) and concentrated in a vacuum. The crude mixture was treated with THF (2 mL) and aq LiOH (6 M, 1 mL) at 70 °C for 16 h. Then, the solution was acidified with aq HCl (2 M, 6 mL), additional THF (3 mL) was added, and the mixture was heated at 50 °C for 2 h. The mixture was partitioned by adding CH_2Cl_2 (10 mL), and the aqueous layer was washed with additional CH_2Cl_2 (2 × 5 mL). The organic layers were dried ($MgSO_4$). Evaporation of solvents and purification by flash chromatography on silica gel (9:1 hexane/EtOAc) yielded lactone (3*S*,4*S*,5*S*)-**7** (53 mg, 68%) and lactone (3*R*,4*S*,5*S*)-**7** (13 mg, 17%).

(3*S*,4*S*,5*S*)-4-[(*E*)-Hept-1-enyl]-3-methyl-5-pentyldihydrofuran-2-one [(3*S*,4*S*,5*S*)-7]: colorless oil; R_f = 0.59 (9:1 hexane/EtOAc); $[\alpha]_D$ −75.3 (*c* 1.57, $CHCl_3$); IR (film) 2931, 2860, 1777, 1459, 1171; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87−0.93 (m, 6H), 1.19 (d, *J* = 7.2, 3H), 1.24−1.41 (m, 12H), 1.46−1.56 (m, 2H), 2.05 (m, 2H), 2.43 (dq, *J* = 10.8, 7.2, 1H), 2.74 (m, 1H), 4.45 (m, 1H), 5.32 (ddt, *J* = 15.2, 9.0, 1.2, 1H), 5.58 (dt, *J* = 15.2, 6.8, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 13.4, 13.9, 14.0, 22.4, 22.5, 25.5, 28.9, 30.8, 31.3, 31.6, 32.5, 38.8, 50.5, 81.4, 125.4, 135.5, 179.1; HRMS (EI) calcd for $C_{17}H_{30}O_2$ [M]$^+$ 266.2246, found 266.2241. Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.82; H 11.21.

(3*R*,4*S*,5*S*)-4-[(*E*)-Hept-1-enyl]-3-methyl-5-pentyldihydrofuran-2-one [(3*R*,4*S*,5*S*)-7]: colorless oil; R_f = 0.41 (9:1 hexane/EtOAc); $[\alpha]_D$ −37.7 (*c* 1.03, $CHCl_3$); IR (film) 2958, 2931, 2860, 1777, 1457, 1175; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, *J* = 6.8, 6H), 1.08 (d, *J* = 7.2, 3H), 1.22−1.50 (m, 12H), 1.62−1.68 (m, 2H), 2.06 (m, 2H), 2.79 (dq, *J* = 7.2, 7.2, 1H), 2.90 (m, 1H), 4.32 (dt, *J* = 7.2, 5.2, 1H), 5.13 (dd, *J* = 15.2, 10.8, 1H), 5.54 (dt, *J* = 15.2, 7.2, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 10.7, 13.9, 14.0, 22.4, 22.5, 25.0, 28.9, 30.8, 31.2, 31.6, 32.4, 40.3, 48.5, 82.0, 122.5, 136.4, 179.2; HRMS (EI) calcd for $C_{17}H_{30}O_2$ [M]$^+$ 266.2246, found 266.2247. Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.40; H 11.25.

Isomerization of Lactones 7 under Basic Conditions. An excess of DBU (28 μL, 0.188 mmol) was added to a solution of (3*R*,4*S*,5*S*)-**7** (10 mg, 0.038 mmol) in refluxing toluene (1 mL). The reaction was monitored by TLC. After 56 h, no more changes were observed. The solution was diluted with CH_2Cl_2 (5 mL) and washed with 2 M aq HCl (2 mL), and the organic layer was dried over anhyd $MgSO_4$. Removal of solvent afforded a crude mixture of (3*S*,4*S*,5*S*)-**7** and its 3*R* epimer in a 66:34 ratio (^{1}H NMR). Experiments performed in other solvents gave similar results (CH_3CN or hexane, 42 h, 68:32; pyridine, 43 h, 69:31; neat, 42 h, 70:30).

(2*S*,3*S*,4*S*)-4-Methyl-5-oxo-2-pentyltetrahydrofuran-3-carboxylic Acid [(2*S*,3*S*,4*S*)-3]. Ozone was bubbled through a solution of lactone (3*S*,4*S*,5*S*)-**7** (165 mg, 0.62 mmol) in anhyd CH_2Cl_2 (10 mL) at −78 °C until TLC (CH_2Cl_2) showed complete disappearance of the starting material (∼30 min). Then, nitrogen was bubbled through the blue solution for a few minutes before Me_2S (∼100 μL) was added and stirring continued at rt for 2 h. Then, the solution was diluted with CH_2Cl_2 (10 mL) and a phosphate buffer (pH = 7; 4 mL). The aqueous layer was washed with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried over anhyd $MgSO_4$. Removal of volatiles under vacuum afforded the crude aldehyde (TLC, CH_2Cl_2/MeOH 98:2 R_f = 0.52) that was dissolved in CH_3CN (3.6 mL). An aqueous solution of NaH_2PO_4 (67 mg in 2.5 mL) and H_2O_2 (33% p/v, 0.70 mL) was added, and the mixture was cooled to 0−4 °C. Then, aq $NaClO_2$ (115 mg in 2.5 mL) was added, and the green homogeneous solution was stirred at rt until starting material was consumed (TLC). The reaction mixture was quenched by addition of aq $NaHSO_3$ (150 mg, 2 mL). The mixture was stirred for 30 min and then basified with NaOH 2 M. The aqueous layer was washed with EtOAc (5 mL), acidified with HCl 2 M, and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhyd $MgSO_4$ and filtered, and the solvent was removed to give (2*S*,3*S*,4*S*)-4-methyl-5-oxo-2-pentyltetrahydrofuran-3-carboxylic acid, (2*S*,3*S*,4*S*)-**3**, (124 mg, 93%) as a white solid: mp 136−137 °C (lit.[5] mp 139−140 °C; lit.[8a] mp 140−141 °C); $[\alpha]_D$ −114.4 (*c* 1.46, $CHCl_3$) [lit.[5] $[\alpha]_D$ −150 (*c* 0.20, $CHCl_3$); lit.[8a] $[\alpha]_D$ −112.3 (*c* 0.26, $CHCl_3$)]; IR (KBr) 2958, 1760, 1739, 1260, 1418, 1183; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, *J* = 6.9, 3H), 1.32 (d, *J* = 7.1, 3H), 1.26−1.44 (m, 5H), 1.55−1.60 (m, 3H), 3.04 (dq, *J* = 10.0, 7.1, 1H), 3.22 (dd, *J* = 10.0, 8.2, 1H), 4.69 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.9, 14.4, 22.4, 25.2, 31.0, 31.3, 36.4, 51.6, 77.3, 174.9, 177.4; HRMS (EI) calcd for $C_{11}H_{18}O_4$ [M]$^+$ 214.1205, found 214.1209.

A similar oxidation of (3*R*,4*S*,5*S*)-**7** (80 mg, 0.30 mmol) afforded (2*S*,3*S*,4*S*)-4-methyl-5-oxo-2-pentyltetrahydrofuran-3-carboxylic acid, (2*S*,3*S*,4*R*)-**3** (62 mg, 98%), as a white solid: mp 109−110 °C; $[\alpha]_D$ −60.6 (*c* 1.81, $CHCl_3$); IR (KBr) 2925, 1767, 1700, 1214, 1136. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, *J* = 6.9, 3H), 1.31 (d, *J* = 6.8, 3H), 1.16−1.88 (m, 8H), 2.95 (dq, *J* = 7.2, 7.2, 1H), 3.33 (dd, *J* = 7.2, 5.2, 1H), 4.44 (m, 1H), 9.52 (bs, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.2, 13.9, 22.3, 25.5, 30.7, 31.3, 39.1, 50.3, 78.9, 175.2, 177.1; HRMS (EI) calcd for $C_{11}H_{18}O_4$ [M]$^+$ 214.1205, found 214.1199. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.50; H 8.22.

Acknowledgment. This work has been supported by the Ministerio de Ciencia y Tecnologia (BQU2003-01269) and Direcció General de Recerca, Generalitat de Catalunya (2001SGR00051). We also thank to the Generalitat de Catalunya for a doctorate studentship to J.O. and the Universitat de Barcelona for a doctorate studentship to M.L.

Supporting Information Available: Experimental details for preparation of compounds **10**, **11**, (*S,S*)-**5**, and (*S,S*)-**13**. Rearrangement of (*S,S*)-**13** in THF. ^{1}H and ^{13}C spectra (PDF) of compounds (2*S,*3*S*,4*S*)-**3**, (2*S,*3*S*,4*R*)-**3**, (3*S*,4*S*,5*S*)-**7**, (3*R,*4*S*,5*S*)-**7**, (*S,S*)-**12**, and (*S,S*)-**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048705X