Concise Syntheses of Natural γ-Butyrolactones, (+)-*trans*-Whisky Lactone, (+)-*trans*-Cognac Lactone, (−)-Methylenolactocin, (+)-Nephrosteranic Acid, and (+)-Roccellaric Acid Using Novel Chiral Butenolide Synthons

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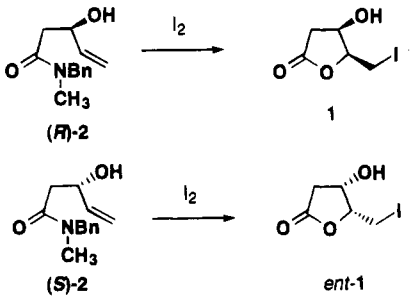
cis-4-Hydroxy-5-(iodomethyl)-4,5−dihydro-2(3*H*)-furanones (**1** and *ent*-**1**) were converted by cross-coupling with several Grignard-derived cuprates followed by benzoylation and base-induced elimination into new chiral butenolides **12**, **14**, *ent*-**14**, **20**, and **27**. The sequential conjugate addition−quenching of these butenolides under complete stereocontrol provided several polysubstituted γ-butyrolactones including flavor components [(+)-*trans*-whisky lactone (**3**) and (+)-*trans*-cognac lactone (**4**)], the antitumor antibiotic lactone (−)-methylenolactocin (**5**), and lichen components [(+)-nephrosteranic acid (**7**) and (+)-roccellaric acid (**8**)].

Introduction

γ-Butyrolactones with various ring appendages are ubiquitous in nature and many of them are biologically significant.[1] Chiral γ-butyrolactones functionalized at the ring carbons are useful as building blocks in natural product syntheses, and, as a consequence, their asymmetric synthesis has drawn much attention.[2,3] The goal of our investigations has been to establish a method for the construction of the carbon−oxygen bond of the ring system in conjunction with the generation of several stereogenic centers on the newly formed heterocycle. To this end, we have focused on the application of an electrophile-mediated heterocyclization to the synthesis of this class of compounds.[4,5] Recently we described the stereoselective synthesis of both enantiomers of *cis*-4-hydroxy-5-(iodomethyl)-4,5-dihydro-2(3*H*)-furanones (**1** and *ent*-**1**) based on the iodine-induced lactonization of the enatiomerically pure *N,N*-dialkyl-3-hydroxy-4-pentenylamide **2** (Scheme 1).[6] We set out to develop a short and divergent route from a readily available chiral synthon to various γ-substituted-γ-butyrolactones found as flavor components [(+)-*trans*-whisky lactone (**3**)[7] and (+)-*trans*-cognac lactone (**4**)[8]], antitumor antibiotic lactones [(−)-methylenolactocin (**5**)[9] and (−)-protolichesterinic acid (**6**)[10]], and lichen components [(+)-nephrosteranic acid (**7**),[11] (+)-roccellaric acid (**8**),[12] and (+)-neodihydromuroic acid (**9**)[13]] (Chart 1). This paper presents full details of concise syntheses of these polysubstituted γ-butyrolactones. The approach is based on a sequential conjugate addition−quenching or −alkylation sequence on the chiral butenolide **ii**, derived from **1** by a cross-coupling followed by formal dehydration (Scheme 2).[14]

Scheme 1



Results and Discussion

The functionalized γ-butyrolactone **1** could be regarded as an equivalent of chiral butenolide synthon **10** on the

[⊗] Abstract published in *Advance ACS Abstracts,* July 15, 1995.

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(2) For examples as syntheses of chiral γ-butyrolactones, see: Koch, S. S.; Chamberlin, A. R. *J. Org. Chem.* **1993**, *58*, 2725 and refs cited therein.

(3) For examples as syntheses of chiral γ-butenolides, see: Nagao, Y.; Dai, W.-N.; Ochiai, M.; Shiro, M, *J. Org. Chem.* **1989**, *54*, 5211 and references cited therein.

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(7) (a) Masuda, M.; Nishimura, K. *Phytochemistry* **1971**, *10*, 1401. (b) Masuda, M.; Nishimura, K. *Chem. Lett.* **1981**, 1333. For chiral synthesis: (c) Pai, Y.-C.; Fang, J.-M.; Wu, S.-H. *J. Org. Chem.* **1994**, *59*, 6018. (d) Ebata, T.; Matsumoto, K.; Yoshikoshi, H.; Koseki, K.; Kawakami, H.; Okano, K.; Matsushita, H. *Heterocycles* **1993**, *36*, 1017 and references have been cited therein.

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(10) (a) Zopf, W. *Liebigs Ann. Chem.* **1902**, *324*, 39. (b) Asahina, Y.; Asano, M. *J. Pharm. Sci. Jpn.* **1927**, *539*, 1. (c) Asahina, Y.; Yanagita, M. *Chem. Ber.* **1936**, *69B*, 120. Chiral synthesis: Murta, M. M.; de Azevedo, M. B. M.; Greene, A. E. *J. Org. Chem.* **1993**, *58*, 7537.

(11) Asahina, Y.; Yanagita, M. *Ber. Dtsch. Chem. Ges.* **1937**, *70*, 227.

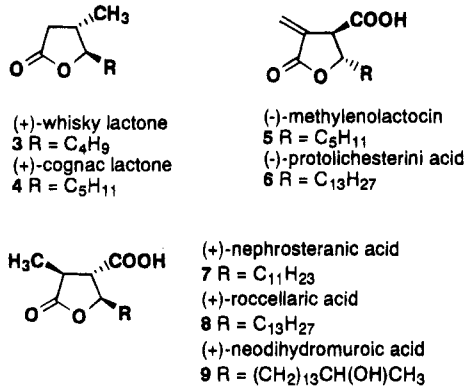
(12) (a) Hesse, O. *J. Prakt. Chem.* **1898**, *57*, 232. (b) Huneck, S.; Follmann, G. Z. *Naturforsch. B* **1967**, *22*, 666. (c) Mulzer, J.; Salimi, N.; Hartl, H. *Tetrahedron: Asymmetry* **1993**, *4*, 457.

(13) (a) Huneck, S. Schreiber, K.; Hofle, G.; Snatzke, G. *J. Hattori Bot. Lab.* **1979**, *45*, 1. (b) Reference 11.

(14) For a preliminary account, see: Takahata, H.; Uchida, Y.; Momose, T. *Tetrahedron Lett.* **1994**, *35*, 4123.

0022-3263/95/1960-5628$09.00/0

Chart 1



Scheme 2

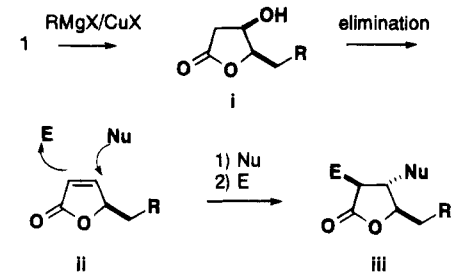
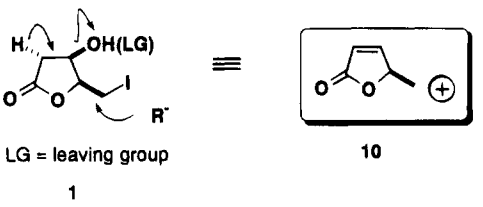
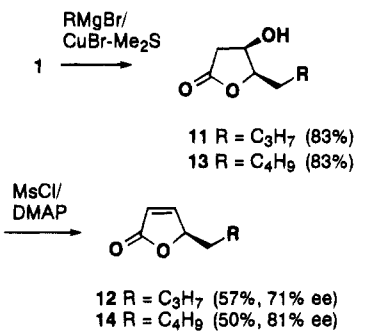


Chart 2



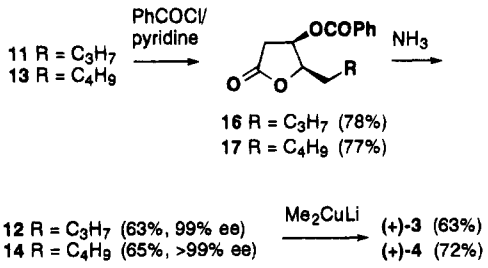
Scheme 3



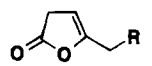
basis of the following considerations: (1) cross-coupling of the iodomethyl appendage at C_5 with a Grignard-derived cuprate should function as a homologation sequence and (2) modification of the hydroxyl at C_4 into a leaving group followed by elimination with a base should be facile (Chart 2). Accordingly, our approach to intermediate **12** for the synthesis of **3** began with the homologation of **1** with propylmagnesium bromide in combination with a cuprous bromide–dimethyl sulfide complex, yielding lactone **11** in 82% yield. The mesylation of **11** with methanesulfonyl chloride using DMAP as a base gave the desired butenolide **12** in 57% yield (Scheme 3).[15] Unfortunately, the optical purity of **12** was found to be only 71%.[16] The application of a similar two-step sequence (1. *n*-butylmagnesium bromide/CuBr–Me_2S (83%);

(15) Wender, P. A.; Mckinney, J. A.; Mukai, C. *J. Am. Chem. Soc.* **1990**, *112*, 5369.

Scheme 4



2. MsCl/DMAP) provided the butenolide **14** in 50% yield, but the enantiomeric excess was again somewhat low (81% ee).[16] This observed decrease in optical purity was probably the result of the formation of enol lactone **15** followed by isomerization of the double bond. In an effort



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to circumvent this problem, hydroxy lactone **11** was instead treated with benzoyl chloride in the presence of pyridine in benzene to give benzoate **16** in 78% yield.[17] The elimination reaction of **16** was accomplished with ammonia in methanol to yield butenolide **12** in 63% yield (Scheme 4). The enantiomeric excess of **12** thus prepared was determined to be 99% by an HPLC analysis with a chiral column (Daicel AS).[16] In a similar manner, lactone **13** was transformed into butenolide **14** in 50% yield with no loss of optical purity (>99% ee). Thus, iodolactone **1** was successfully employed as a butenolide synthon.

With the requisite chiral butenolides **12** and **14** in hand, we carried out the synthesis of whisky and cognac lactones **3** and **4**. Chiral butenolides have been shown to be excellent asymmetric Michael acceptors.[18] The conjugate addition of dimethylcopper lithium to **12** provided (+)-**3** in 64% yield with complete diastereoselectivity.[19] As expected, the alkyl substituent at the C_5-position in **12** directs the introducing methyl unit to an anti attack with respect to the γ-appendage. Analogously, **14** was converted into (+)-**4** in 72% yield. Spectral data and specific rotations for **3** and **4** were identical with those reported.[7c]

Next we turned our attention to the synthesis of (−)-methylenolactocin (**5**), an antitumor antibiotic isolated from the culture filtrate of *Penicillium* sp.[9a] and a highly functionalized dihydrofuranone prone to isomerization. Three enantioselective syntheses of **4** have been reported to date. The first, by Green,[9d] was achieved by the methylenation of a 3,4-disubstituted 2-furanone (**18**) *via* an asymmetric [2 + 2] cycloaddition as the key step. The other two methods involve formal syntheses of **18** using as crucial reactions an enantioselective deprotonation and an intramolecular carbozinication, by Honda[9c] and Knochel,[9b] respectively. Our access to intermediate **18**

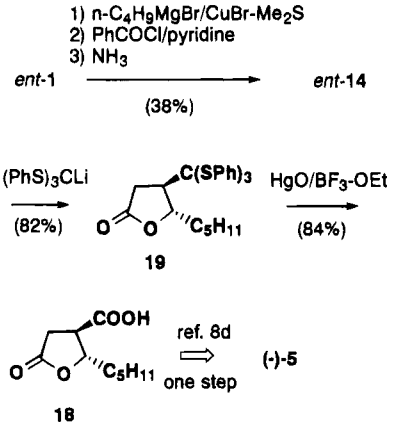
(16) Analysis by HPLC with a chiral column (Daisel AS) established the enantiomeric ratio: see Experimental Section.

(17) Afonso, C. A. M.; Barros, M. T.; Godinho, L. S.; Maycock, C. D. *Tetrahedron* **1993**, *49*, 4283.

(18) (a) Perkmutter, P. In *Conjugate Addition Reactions in Organic Synthesis*; Baldwin, J. E., Ed.; Pergamon: Oxford, 1992; p 283. (b) Stork, G.; Rychnovsky, S. D . *J. Am. Chem. Soc.* **1987**, *109*, 1564. (c) Vigneron, J. P. *Tetrahedron* **1984**, *40*, 3521. (d) van Oeveren, A.; Jansen, J. F. G. A.; Feringa, B. L. *J. Org. Chem.* **1994**, *59*, 5999 and references cited therein.

(19) Bloch, R.; Gilbert, L. *J. Org. Chem.* **1987**, *52*, 4603.

Scheme 5

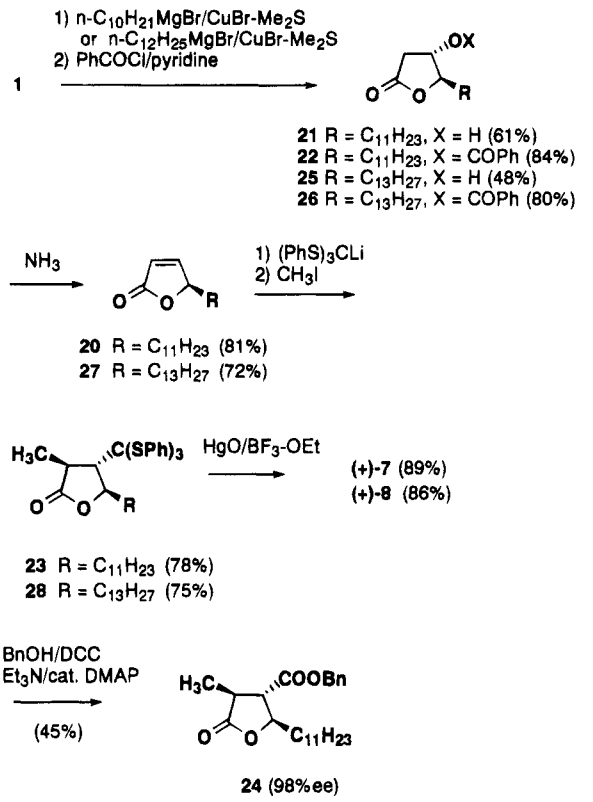


for the synthesis of **4** began with a synthesis of *ent*-**14** from *ent*-**1** by the method used for the synthesis of **12**. Thus, butenolide *ent*-**14** was obtained in 38% overall yield from *ent*-**1**. The conjugate addition of lithiated tris(phenylthio)methane,[20] a carboxyl equivalent, to *ent*-**14** at −78 °C gave the adduct **19** stereoselectively in 82% yield. Subsequently, **19** was converted by treatment with mercuric oxide in the presence of boron trifluoride–ether complex[21] to the paraconic acid **18** (84%), whose spectral data and specific rotation were identical with those reported.[9c] This completed the formal synthesis of (−)-methylenolactocin (**5**) (Scheme 5).

Two *trans,trans*-5-alkyl-4-carboxy-3-methyl-4,5-dihydro-2(3*H*)-furanones have been isolated from lichen: (+)-nephrosteranic acid (**7**) from *Nephromopsis endocrocea*[10a] and (+)-roccellaric acid (**8**) from *Roccellaria mollis* (HAMPE) ZAHLBR.[11a] The synthesis of **8** has recently been reported,[11b] and **7** has never been synthesized in a scalemic form. Additionally, the absolute configuration of **7** remains undetermined. We carried out the first asymmetric synthesis of **7** *via* sequential Michael addition–enolate alkylation to butenolide **20**. By means of the procedure used for the synthesis of **12**, a three-step sequence from **1** yielded **20** in 41% overall yield. The conjugate addition of lithiated tris(phenylthio)methane to **20** at −78 °C was followed by quenching of the resulting lactone enolate with methyl iodide to yield the all-*trans*-trisubstituted γ-butyrolactone **23** in 84% yield. Hydrolysis ($HgO/BF_3-Et_2O/THF/H_2O$)[21] of the tris(phenylthio)methyl moiety of **23** gave the desired (+)-**7** in 89% yield (Scheme 6). The synthetically derived product provided spectroscopic data in excellent agreement with the literature values.[13] Thus, the dextro-enantiomer **7** of natural origin was unequivocally assigned to be of 3*S*,4*S*,5*R*. However, the optical rotation $\{[\alpha]^{25}_D$ +27.2 ($CHCl_3$)} was found to be considerably lower than that reported for the natural product $\{[\alpha]^{21}_D$ +38.4 ($CHCl_3$)}.[13] The optical purity of the benzyl ester **24** derived from **7** was determined by HPLC to be 98%. As described in the experimental section, (+)-roccellaric acid (**8**), a homolog with a two-methylene unit at the C_5-appendage of **7**, has a specific rotation $\{[\alpha]^{21}_D$ +27 ($CHCl_3$)}[12c] similar to that of our synthesized **7**. Therefore, it is quite likely that our optical rotation of **7** may be more representative of the actual value.

Finally, the synthesis of (+)-roccellaric acid (**8**) was accomplished in 18% overall yield by the method mentioned above for the synthesis of **7**, keeping all-*trans* stereoselectivity in the sequential conjugate addition–alkylation step from **1** (Scheme 6). Its spectral data and specific rotation were in complete agreement with those reported.[12c]

Scheme 6



Conclusion

We have demonstrated that the readily available iodolactones **1** and *ent*-**1** serve as versatile chiral butenolide synthons which can be applied to the preparation of natural polysubstituted γ-butyrolactones **3**, **4**, **5**, **7**, and **8** by a short and completely diastereoselective reaction sequence. The flexibility offered by this sequential conjugate addition–quenching methodology involving the homologation of the C_5-iodomethyl appendage should permit the construction of a large array of optically active *trans*-4,5-disubstituted and *trans,trans* 3,4,5-trisubstituted 4,5-dihydro-2(3*H*)-furanones (γ-butyrolactones).

Experimental Section

All NMR spectra were measured in $CDCl_3$, and chemical shifts are expressed in ppm relative to internal $CHCl_3$ (7.26 ppm). Column chromatography was performed on silica gel (Fuji-Division BW-200 or Merck 60 (No 9385) with a medium pressure apparatus and a mixture of ethyl acetate/hexane was used as eluant unless otherwise specified. The extracts were dried over Na_2SO_4 unless otherwise specified.

(4*R*,5*R*)-5-Butyl-4-hydroxy-4,5-dihydro-2(3*H*)-furanone (11). To a slurry of CuBr–Me_2S (3.04 g, 14.8 mmol) in THF (17.2 mL) was added a 1 M *n*-propylmagnesium bromide–THF solution (15.1 mmol) at −78 °C with stirring. After the mixture was stirred for 30 min, a solution of **1** (600 mg, 2.48 mmol) in THF (3.9 mL) was slowly added. The mixture was gradually warmed to rt, stirred for 6 h, and quenched with saturated NH_4Cl. The insoluble materials were filtered off through Celite, and the filtrate was washed with an ammonia solution and extracted with ethyl acetate three times. The extract was dried and evaporated. The residue was chromato-

(20) Stork, G.; Rychnovsky, S. D. *Pure Appl. Chem.* **1987**, *59*, 345.
(21) Vedejs, E.; Fuchs, P. L. *J. Org. Chem.* **1971**, *36*, 366.

graphed to give **11** (326 mg, 83%) as an oil: bp 115−118 °C (3 mmHg); $[\alpha]^{25}_D$ +60.1 (*c* 1.43, $CHCl_3$); IR (neat) 3445, 2958, 2872, 1766 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.94 (3 H, t, *J* = 6.8 Hz), 1.33−1.94 (6 H, m), 2.50−2.53 (1 H, m), 2.60 (1 H, s), 2.81 (1 H, dd, *J* = 17.8, 5.4 Hz), 4.35−4.42 (1 H, m), 4.47−4.50 (1 H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.02, 22.66, 27.76, 28.03, 39.70, 68.94, 85.67, 176.97; HRMS calcd for $C_8H_{14}O_3$ 158.0942, found 158.0935.

(4*R*,5*R*)-4-(Benzoyloxy)-5-butyl-4,5-dihydro-2(3*H*)-furanone (16). Benzoyl chloride (356 μL, 3.06 mmol) and pyridine (485 μL, 6.12 mmol) were successively added to a solution of **11** (322 mg, 2.04 mmol) in benzene (1.94 mL), and the reaction mixture was stirred for 12 h at rt. After the addition of Et_2O (10 mL) and 10% HCl (7 mL) to the mixture, the organic phase was separated. The aqueous layer was extracted with Et_2O (5 mL) three times, and the combined organic extracts were washed with 10% HCl, dried, and evaporated. The residue was chromatographed to yield **16** (417 mg, 78%) as a solid: mp 69−70 °C (hexane−CH_2Cl_2); $[\alpha]^{25}_D$ +22.7 (*c* 1.495, $CHCl_3$); IR (KBr) 2958, 1778, 1716, 1272, 1171, 1111, 1071, 988, 914, 711 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, *J* = 7.1 Hz), 1.31−1.92 (6 H, m), 2.72 (1 H, d, *J* = 18.7 Hz), 3.00 (1H, dd, *J* = 18.1, 6.0 Hz), 4.59−4.69 (1 H, m), 5.70−5.73 (1 H, m), 7.47 (2 H, t, *J* = 7.7 Hz), 7.61 (1 H, t, *J* = 7.7 Hz), 8.02 (2 H, d, *J* = 7.7 Hz). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.41; H, 6.78.

(*R*)-5-Butyl-2(5*H*)-furanone (12). (a) A solution of **16** (927 mg, 3.53 mmol) in saturated ammonia methanol (17.5 mL) was stirred for 10 min at rt. After evaporation of the solvent, ethyl acetate was added to the residue. The solvent was filtered through Celite, and the filtrate was evaporated. The residue thus obtained was chromatographed to yield **12** (312 mg, 63%) as an oil: bp 90−95 °C (12 mmHg); $[\alpha]^{25}_D$ −112.0 (*c* 1.57, $CHCl_3$); (99% ee by HPLC using DAICEL CHIRALPAC AS (25 cm × 0.46 cm); 40 °C; hexane−2-propanol = 9:1; flow 0.7 mL/min); IR (neat) 2958, 1752, 1163, 1025, 820 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.91 (3 H, t, *J* = 7.1 Hz), 1.36−1.79 (6 H, m), 5.04−5.06 (1 H, m), 6.12 (1H, dd, *J* = 5.6, 1.9 Hz), 7.47 (1 H, dd, *J* = 5.6, 1.9 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.01, 22.60, 27.23, 33.05, 83.60, 121.73, 156.46, 173.35; HRMS calcd for $C_8H_{12}O_2$ 140.0836, found 140.0831. (b) MsCl (157 μL, 2.05 mmol) was added to a solution of **11** (215 mg, 1.36 mmol) in CH_2Cl_2 (3.54 mL) at 0 °C and the reaction mixture was stirred for 5 h. After the addition of Et_2O (20 mL) to the mixture, the organic layer was washed with water (5 mL) twice and dried, and the solvent was removed by rotary evaporation. The residue thus obtained was purified by chromatography to yield **12** (85 mg, 57%) as an oil: $[\alpha]^{25}_D$ −79.84 (*c* 1.02, $CHCl_3$); (71% ee by HPLC using DAICEL CHIRALPAC AS (25 cm × 0.46 cm); 40 °C; hexane−2-propanol = 9:1; flow 0.7 mL/min).

(4*R*,5*R*)-4-Hydroxy-5-pentyl-4,5-dihydro-2(3*H*)-furanone (13). By means of a procedure analogous to that described for **11**, the reaction of the Grignard reagent with **1** (496 mg, 2.05 mmol) in THF (3.29 mL) gave **13** (294 mg, 83%) as an oil: bp 115−120 °C (4 mmHg); $[\alpha]^{25}_D$ +49.42 (*c* 1.175, $CHCl_3$); IR (neat) 3440, 2930, 2860, 1766 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.91 (3 H, t, *J* = 6.8 Hz), 1.34−1.94 (6 H, m), 2.22 (1 H, d, *J* = 4.4 Hz), 2.55 (1 H, d, *J* = 17.6 Hz), 2.80 (1 H, dd *J* = 17.6, 5.4 Hz), 4.34−4.39 (1 H, m), 4.40−4.50 (1 H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.15, 22.64, 25.41, 28.40, 31.79, 39.67, 69.23, 85.06, 175.95; HRMS calcd for $C_9H_{16}O_3$ 172.110, found 172.1136.

(4*R*,5*R*)-4-(Benzoyloxy)-5-pentyl-4,5-dihydro-2(3*H*)-furanone (17). By means of a procedure analogous to that described for **16**, a mixture of **13** (175 mg, 1.00 mmol), benzoyl chloride (175 μL, 1.50 mmol), and pyridine (238 μL, 3.00 mmol) in benzene (1.00 mL) yielded **17** (213 mg, 77%) as an oil: bp 155 °C (2 mmHg); $[\alpha]^{25}_D$ +18.82 (*c* 1.46, $CHCl_3$); IR (neat) 2956, 1790, 1723, 1271, 1199, 1163, 1109, 1071, 918, 712 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.89 (3 H, t, *J* = 7.2 Hz), 1.24−1.96 (8 H, m), 2.71 (1 H, d, *J* = 18.5 Hz), 3.01 (1H, dd, *J* = 18.0, 6.0 Hz), 4.59−4.67 (1 H, m), 5.69−5.74 (1 H, m), 7.46 (2 H, t, *J* = 7.8 Hz), 7.60 (1 H, t, *J* = 7.8 Hz), 8.03 (2 H, d, *J* = 7.8 Hz). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.40; H, 7.30.

(*R*)-5-Pentyl-2(5*H*)-furanone (14). (a) By means of a procedure similar to that described for **12** (a), a mixture of **17** (124 mg, 0.45 mmol) in saturated ammonia methanol (2.22 mL) gave **14** (45 mg, 65%) as an oil: bp 85−87 °C (15 mmHg); $[\alpha]^{25}_D$ −85.53 (*c* 1.36, $CHCl_3$); (>99% ee by HPLC using DAICEL CHIRALPAC AS (25 cm × 0.46 cm); 40 °C; hexane−2-propanol = 9:1; flow 0.7 mL/min); IR (neat) 2932, 1752, 1163, 1032, 816 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.90 (3 H, t, *J* = 6.8 Hz), 1.30−1.81 (8 H, m), 5.02−5.07 (1 H, m), 6.11 (1H, dd, *J* = 5.6, 2.0 Hz), 7.45 (1 H, dd, *J* = 5.9, 1.2 Hz). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.90; H, 9.07.

(b) By means of a procedure similar to that described for **12** (b), a mixture of **13** (123 mg, 0.714 mmol), DMAP (262 mg, 2.14 mmol), and MsCl (82.9 μL, 1.08 mmol) in CH_2Cl_2 (1.85 mL) gave **14** (55 mg, 50%) as an oil; $[\alpha]^{25}_D$ −84.05 (*c* 0.71, $CHCl_3$); (81% ee using DAICEL CHIRALPAC AS (25 cm × 0.46 cm); 40 °C; hexane−2-propanol = 9:1; flow 0.7 mL/min).

(4*S*,5*R*)-5-Butyl-4-methyl-4,5-dihydro-2(3*H*)-furanone [(+)-*trans*-whisky lactone] (3). A solution of **12** (82 mg, 0.585 mmol) in Et_2O (6.03 mL) was dropwise added to a stirred solution of lithium dimethylcuprate [2.92 mmol: prepared from addition of a solution of methyllithium (1.4 M) in ether (5.13 mL, 5.84 mmol) to a suspension of CuI (556 mg, 2.92 mmol) in Et_2O (7.52 mL) at −20 °C] at −60 °C, and the reaction mixture was stirred for 2 h at the same temperature. After the addition of 10% HCl (6.03 mL) to the mixture, the resulting mixture was stirred for 30 min. The mixture was filtered through Celite, and the organic solvent was separated. The aqueous solution was extracted with Et_2O (5 mL) three times. The combined organic solvents were washed with an ammonia solution and dried, and the solvent was removed by rotary evaporation. The residue was purified by chromatography using hexane−Et_2O (3:1) as eluant to yield **3** (58 mg, 63%) as an oil: bp 67−68 °C (6 mmHg); $[\alpha]^{25}_D$ +84.52 (*c* 2.125, MeOH), lit.[7c] $[\alpha]^{23}_D$ +79.5 (*c* 1.0, MeOH); IR (neat) 2959, 2933, 1774, 1112, 985 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.91 (3 H, t, *J* = 7.1 Hz), 1.13 (3 H, d, *J* = 6.0 Hz), 1.33−1.67 (6 H, m), 2.13−2.23 (2 H, m), 2.65−2.68 (1 H, m), 4.01 (1 H, dt, *J* = 7.6, 4.2 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.05, 17.68, 22.66, 28.02, 33.87, 36.24, 37.30, 87.64, 176.77; HRMS calcd for $C_9H_{16}O_2$ 156.1149, found 156.1142.

(4*S*,5*R*)-Methyl-5-pentyl-4,5-dihydro-2(3*H*)-furanone [(+)-*trans*-cognac lactone] (4). By means of a procedure similar to that described for **3**, the reaction of **14** (54 mg, 0.35 mmol) in Et_2O (3.61 mL) with lithium dimethylcuprate (1.75 mmol) in Et_2O (7.0 mL) gave **4** (43 mg, 72%) as an oil: bp 80 °C (6 mmHg); $[\alpha]^{25}_D$ +82.20 (*c* 0.71, MeOH), lit.[7c] $[\alpha]^{23}_D$ +83.2 (*c* 0.69, MeOH); IR (neat) 2933, 2872, 1779, 1208, 1172 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.89 (3 H, t, *J* = 7.0 Hz), 1.13 (3 H, d, *J* = 6.5 Hz), 1.26−1.70 (8 H, m), 2.15−2.24 (2 H, m), 2.63−2.70 (1 H, m), 4.01 (1 H, dt, *J* = 7.9, 4.1 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.15, 17.62, 22.58, 22.64, 31.73, 34.12, 36.24, 37.30, 87.67, 176.90; HRMS calcd for $C_{10}H_{18}O_2$ 1170.1303, found 170.1305.

(4*S*,5*S*)-4-Hydroxy-5-pentyl-4,5-dihydro-2(3*H*)-furanone (*ent*-13). By means of a procedure similar to that described for **13**, the reaction of the Grignard (n-C_4H_9MgBr)-derived cupurate reagent (23.48 mmol) with *ent*-**1** (1.80 g, 7.45 mmol) in THF (7.0 mL) gave *ent*-**13** (795 mg, 78%) as an oil: $[\alpha]^{25}_D$ −49.2 (*c* 2.23, $CHCl_3$).

(4*S*,5*S*)-4-(Benzoyloxy)-5-pentyl-4,5-dihydro-2(3*H*)-furanone (*ent*-17). By means of a procedure analogous to that described for **17**, a mixture of *ent*-**13** (795 mg, 4.54 mmol), benzoyl chloride (792 μL, 6.81 mmol), and pyridine (1.08 mL, 13.62 mmol) in benzene (4.54 mL) yielded **17** (1.012 g, 81%) as an oil: $[\alpha]^{25}_D$ −18.6 (*c* 2.56, $CHCl_3$).

(*S*)-5-Pentyl-2(5*H*)-furanone (*ent*-14). By means of a procedure similar to that described for **14** (a), a mixture of *ent*-**17** (492 mg, 1.78 mmol) in saturated ammonia methanol (8.82 mL) gave *ent*-**14** (164 mg, 60%) as an oil: $[\alpha]^{25}_D$ +85.3 (*c* 1.85, $CHCl_3$).

(4*R*,5*S*)-4-[Tris(phenylthio)methyl]-5-pentyl-4,5-dihydro-2(3*H*)-furanone (19). To a stirred solution of $(PhS)_3CH$ (198 mg, 0.584 mmol) in THF (2.35 mL) was added 0.36 mL of n-BuLi in hexane (1.6 N, 0.584 mmol) at −78 °C. After being stirred for 2 h, a solution of *ent*-**14** (90 mg, 0.584 mmol) in

THF (0.7 mL) was added to the mixture at −78 °C. The reaction mixture was stirred for 2 h and water was added to the mixture. The organic solvent was separated and the aqueous solution was extracted with ethyl acetate (5 mL) three times. The combined solvents were washed with brine, dried, and evaporated. The residue thus obtained was chromatographed to yield **19** (237 mg, 82%) as an oil: $[\alpha]^{25}_D$ +123.05 (*c* 1.835, $CHCl_3$); IR (neat) 2926, 2859, 1773, 1472,1439, 1190, 1024, 747, 689 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.85 (3 H, t, *J* = 6.6 Hz), 1.14−1.43 (8 H, m), 2.42−2.59 (2 H, m), 2.96 (1 H, dd, *J* = 17.6, 2.7 Hz), 4.90−4.95 (1 H, m), 7.32−7.45 (9 H, m), 7.64−7.71 (6 H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.11, 22.54, 24.95, 31.34, 32.87, 37.09, 50.64, 79.31, 81.94, 128.97, 130.03, 130.77, 136.72, 176.31; HRMS calcd for $C_{28}H_{30}O_2S_3$ (M^+ − SPh) 385.1306, found 385.1305.

(4*R*,5*S*)-4-Carboxy-5-pentyl-4,5-dihydro-2(3*H*)-furanone (18). A mixture of **19** (103 mg, 0.208 mmol), HgO (227 mg, 1.05 mmol), and BF_3−Et_2O (0.385 mL, 3.12 mmol) in THF−H_2O (4:1) (0.78 mL) was stirred for 3 h at rt. After the addition of water to the mixture, the organic solvent was separated. The aqueous solution was extracted with ethyl acetate (3 mL) three times. The combined organic solvents were washed with brine and dried, and the solvent was removed by rotary evaporation. The residue thus obtained was chromatographed to yield **18** (35 mg, 84%) as a solid: mp 103−105 °C dec, lit.[9d] mp 105−107 °C; $[\alpha]^{25}_D$ −52.0 (*c* 0.52, $CHCl_3$), lit.[9d] $[\alpha]^{21}_D$ −54 (*c* 0.5, $CHCl_3$); IR (neat) 2956, 2930, 1748, 1722, 1260, 1240 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.89 (3 H, t, *J* = 6.6 Hz), 1.25−1.83 (8 H, m), 2.82 (1 H, dd, *J* = 17.6, 9.9 Hz), 2.94 (1 H, dd, *J* = 17.6, 8.2 Hz), 3.06−3.14 (1 H, m), 4.56−4.65 (1H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.14, 22.62, 25.03, 31.50, 32.10, 35.51, 45.51, 81.96, 174.48; HRMS calcd for $C_{10}H_{16}O_4$ (M^+ + 1) 201.1126, found 201.1111.

(4*R*,5*R*)-4-Hydroxy-5-undecyl-4,5-dihydro-2(3*H*)-furanone (21). By means of a procedure similar to that described for **11**, the reaction of the Grignard (n-$C_{10}H_{21}$MgBr)-derived cupurate reagent (34.4 mmol) with **1** (2.782 g, 11.5 mmol) in THF (13.6 mL) gave **21** (1.786 g, 61%) as a solid: mp 79−81 °C (CCl_4); $[\alpha]^{25}_D$ +44.9 (*c* 1.495, $CHCl_3$); IR (KBr) 3484, 2924, 2851, 1740, 1238, 1022, 970 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, *J* = 6.6 Hz), 1.21−1.91 (20 H, m), 1.78 (1 H, d, *J* = 4.4 Hz), 2.55 (1 H, dd, *J* = 17.6, 1.1 Hz), 2.80 (1 H, dd, *J* = 17.6, 5.5 Hz), 4.34−4.39 (1 H, m), 4.45−4.50 (1 H, m). Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.29; H, 10.93.

(4*R*,5*R*)-4-(Benzoyloxy)-5-undecyl-4,5-dihydro-2(3*H*)-furanone (22). By means of a procedure analogous to that described for **16**, a mixture of **21** (1.167 g, 4.55 mmol), benzoyl chloride (0.79 mL, 6.63 mmol), and pyridine (1.08 mL, 13.62 mmol) in benzene (6 mL) yielded **22** (1.385 g, 84%) as a solid: mp 50−52 °C (CCl_4); $[\alpha]^{25}_D$ +13.75 (*c* 2.175, $CHCl_3$); IR (KBr) 2918, 2851, 1775, 1724, 1278, 1165, 1102, 718 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.87 (3 H, t, *J* = 6.6 Hz), 1.22−1.92 (20 H, m), 2.72 (1 H, dd, *J* = 18.1, 1.1 Hz), 3.00 (1H, dd, *J* = 18.1, 6.0 Hz), 4.59−4.65 (1H, m), 5.70−5.74 (1 H, m), 7.47 (2 H, t, *J* = 7.7 Hz), 7.62 (1 H, t, *J* = 7.7 Hz), 8.03 (2 H, d, *J* = 7.7 Hz). Anal. Calcd for $C_{21}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.67; H, 8.94.

(*R*)-5-Undecyl-2(5*H*)-furanone (20). By means of a procedure similar to that described for **14** (a), a mixture of **22** (104 mg, 0.288 mmol) in saturated ammonia methanol (1.43 mL) gave **20** (58 mg, 81%) as a solid: mp 32−34 °C (CCl_4); $[\alpha]^{25}_D$ −66.6 (*c* 1.945, $CHCl_3$); IR (KBr) 2922, 2853, 1742, 1178 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.87 (3 H, t, *J* = 7.1 Hz), 1.25−1.77 (20 H, m), 5.00−5.05 (1 H, m), 6.10 (1 H, dd, *J* = 6.0, 2.2 Hz), 7.45 (1 H, dd, *J* = 6.0, 1.6 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.27, 22.83, 25.12, 29.47, 29.52, 29.62, 29.73, 32.05, 33.34, 83.60, 121.64, 156.49, 173.32. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 78.53; H, 10.97.

(3*S*,4*S*,5*R*)-3-Methyl-4-[tris(phenylthio)methyl]-5-undecyl-4,5-dihydro-2(3*H*)-furanone (23). To a stirred solution of $(PhS)_3CH$ (253 mg, 0.74 mmol) in THF (2.98 mL) was added 0.47 mL of n-BuLi in hexane (1.6 N, 0.74 mmol) at −78 °C. After being stirred for 2 h, a solution of **20** (186 mg, 0.74 mmol) in THF (0.8 mL) was added to the mixture at −78 °C. The reaction mixture was stirred for 2 h, and a solution of MeI (0.46 mL, 7.4 mmol) in a mixture of HMPA (1.34 mL) and THF (3.1 mL) was added to the mixture. The reaction mixture was slowly warmed up to rt, stirred for 24 h, and quenched with water. The organic solvent was separated, and the aqueous solution was extracted with ethyl acetate (5 mL) three times. The combined solvents were washed with brine and dried, and the solvent was removed by rotary evaporation. The residue thus obtained was chromatographed to yield **7** (343 mg, 78%) as an oil: $[\alpha]^{25}_D$ −2.75 (*c* 2.085, $CHCl_3$); IR (neat) 2924, 2853, 1773, 1466, 1438, 1191, 1024, 746, 689 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, *J* = 7.1 Hz), 1.15 (3 H, d, *J* = 7.7 Hz), 1.19−1.60 (20 H, m), 2.65 (1 H, t, *J* = 3.3 Hz), 3.15−3.18 (1 H, m), 4.74−4.77 (1 H, m), 7.30−7.42 (9 H, m), 7.66−7.69 (6 H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.31, 19.11, 22.87, 25.89, 29.03, 29.53, 29.70, 29.79, 32.10, 37.93, 39.75, 58.03, 78.99, 80.69, 128.90, 129.69, 131.29, 135.95, 179.82; HRMS calcd for $C_{35}H_{45}O_2S_3$ 593.2580, found 593.2574.

(3*S*,4*S*,5*R*)-4-Carboxy-3-methyl-5-undecyl-4,5-dihydro-2(3*H*)-furanone [(+)-nephrosteranic acid] (7). By means of a procedure similar to that described for **18**, a mixture of **23** (613 mg, 1.03 mmol), HgO (1.119 g, 5.17 mmol), and BF_3−Et_2O (1.90 mL, 15.52 mmol) in THF−H_2O (4:1) (5 mL) gave **7** (273 mg, 89%) as a solid: mp 96−98 °C (CCl_4); $[\alpha]^{25}_D$ +27.2 (*c* 1.45, $CHCl_3$); IR (KBr) 2852, 1747, 1716, 1260, 1201, 1173, 698 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.89 (3 H, t, *J* = 6.8 Hz), 1.39 (3 H, d, *J* = 7.1 Hz), 1.27−1.85 (20 H, m), 2.70−2.74 (1 H, m), 2.98−3.02 (1 H, m), 4.47−4.52 (1 H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.31, 14.72, 22.87, 25.50, 29.41, 29.52, 29.58, 29.69, 29.79, 32.10, 35.12, 40.02, 54.06, 79.52, 176.04, 176.78. Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 67.92; H, 9.99.

(3*S*,4*S*,5*R*)-4-(Benzyloxycarbonyl)-3-methyl-5-undecyl-4,5-dihydro-2(3*H*)-furanone (24). DCC (42.5 mg, 0.187 mmol) was added to a solution of **7** (34 mg, 0.114 mmol), benzyl alcohol (17.7 μL, 0.17 mmol), Et_3N (30.9 μL, 0.238 mmol), and DMAP (1.4 mg, 0.01 mmol) in CH_2Cl_2 (0.44 mL) at 0 °C, and the reaction mixture was stirred for 17 h at rt. After the addition of ethyl acetate to the mixture, the insoluble materials were filtered off through Celite. The filtrate was evaporated to give the residue, which was chromatographed to yield **24** (20 mg, 45%) as an oil: bp 156−160 °C (0.4 mmHg); $[\alpha]^{25}_D$ +14.1 (*c* 0.865, $CHCl_3$); (98% ee by HPLC using DAICEL CHIRALPAC AS (25 cm × 0.46 cm); 40 °C; hexane−2-propanol = 95:5; flow 0.7 mL/min); IR (neat) 2925, 2854, 1781, 1735 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, *J* = 6.0 Hz), 1.31 (3 H, d, *J* = 6.6 Hz), 1.24−1.85 (20 H, m), 2.64−2.71 (1 H, m), 2.93−3.01 (1 H, m), 4.41−4.48 (1 H, m), 5.20 (2 H, s), 7.34−7.40 (5 H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.30, 14.66, 22.87, 25.38, 29.37, 29.53, 29.67, 29.79, 32.10, 35.06, 40.14, 54.54, 67.53, 79.72, 128.92, 135.28, 170.76, 176.92. Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.11; H, 9.47.

(4*R*,5*R*)-4-Hydroxy-5-tridecyl-4,5-dihydro-2(3*H*)-furanone (25). By means of a procedure similar to that described for **11**, the reaction of the Grignard (n-$C_{12}H_{25}$MgBr)-derived cuprate reagent (64.88 mmol) with **1** (5.234 g, 21.63 mmol) in THF (30 mL) gave **25** (2.90 g, 48%) as a solid: mp 87−88 °C (CCl_4); $[\alpha]^{25}_D$ +40.05 (*c* 1.89, $CHCl_3$); IR (KBr) 3479, 2954, 2850, 1743, 1237, 1015, 971 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, *J* = 6.6 Hz), 1.25−1.91 (24 H, m), 2.02 (1 H, d, *J* = 4.9 Hz), 2.55 (1 H, dd, *J* = 17.6, 1.1 Hz), 2.80 (1 H, dd, *J* = 17.6, 5.5 Hz), 4.33−4.39 (1 H, m), 4.46−4.50 (1 H, m). Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.78; H, 11.34. Found: C, 71.73; H, 11.34.

(4*R*,5*R*)-4-(Benzoyloxy)-5-tridecyl-4,5-dihydro-2(3*H*)-furanone (26). By means of a procedure analogous to that described for **16**, a mixture of **25** (1.258 g, 4.42 mmol), benzoyl chloride (0.87 mL, 7.52 mmol), and pyridine (1.19 mL, 13.62 mmol) in benzene (6.6 mL) yielded **26** (1.371 g, 80%) as a solid: mp 58−59 °C (CCl_4); $[\alpha]^{25}_D$ +12.74 (*c* 0.12, $CHCl_3$); IR (KBr) 2922, 2851, 1776, 1728, 1268, 1164, 1102, 720 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, *J* = 6.6 Hz), 1.22−1.97 (24 H, m), 2.73 (1 H, d, *J* = 18.1 Hz), 3.01 (1H, dd, *J* = 18.1, 6.0 Hz), 4.60−4.66 (1H, m), 5.71−5.74 (1 H, m), 7.48 (2 H, t, *J* = 7.7 Hz), 7.62 (1 H, t, *J* = 7.7 Hz), 8.02 (2 H, d, *J* = 7.7

Hz). Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 73.95; H, 9.42.

(*R*)-5-Tridecyl-2(5*H*)-furanone (27). By means of a procedure similar to that described for **14** (a), a mixture of **26** (1.271 g, 3.27 mmol) in saturated ammonia methanol (16 mL) gave **27** (627 mg, 72%) as a solid: mp 44–46 °C (CCl_4); $[\alpha]^{25}_D$ −56.6 (*c* 2.285, $CHCl_3$); IR (KBr) 2925, 2851, 1740, 1178 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, *J* = 6.6 Hz), 1.26–1.83 (24 H, m), 5.01–5.07 (1 H, m), 6.11 (1 H, dd, *J* = 6.0, 2.2 Hz), 7.46 (1 H, dd, *J* = 5.5, 1.6 Hz). Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.37; H, 10.90.

(3*S*,4*S*,5*R*)-3-Methyl-4-[tris(phenylthio)methyl]-5-tridecyl-4,5-dihydro-2(3*H*)-furanone (28). By means of a procedure similar to that described for **23**, the reaction of a solution of $(PhS)_3CLi$ (0.323 mmol) in THF (1.3 mL) with **27** (86 mg, 0.323 mmol) in THF (0.4 mL) followed by a solution of MeI (0.2 mL, 3.24 mmol) in a mixture of HMPA (0.58 mL) and THF (1.35 mL) gave **28** (149 mg, 75%) as an oil: $[\alpha]^{25}_D$ −2.13 (*c* 1.05, $CHCl_3$); IR (neat) 2924, 2853, 1772, 1472,1438, 1192, 1025, 746, 689 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, *J* = 6.6 Hz), 1.15 (3 H, d, *J* = 7.7 Hz), 1.18–1.60 (24 H, m), 2.65 (1 H, t, *J* = 3.3 Hz), 3.14–3.18 (1 H, m), 4.73–4.78 (1 H, m), 7.30–7.42 (9 H, m), 7.65–7.70 (6 H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.33, 19.12, 22.89, 25.91, 29.05, 29.55, 29.73, 29.82, 29.85, 29.88, 32.11, 37.94, 39.76, 58.05, 79.01, 80.71, 128.92, 129.71, 131.30, 135.96, 179.82; HRMS calcd for $C_{31}H_{43}O_2S_2$ (M^+ − SPh) 511.2703, found 511.2668.

(3*S*,4*S*,5*R*)-4-Carboxy-3-methyl-5-tridecyl-4,5-dihydro-2(3*H*)-furanone [(+)-roccellaric acid] (8). By means of a procedure similar to that described for **18**, a mixture of **28** (91 mg, 0.147 mmol), HgO (160 mg, 0.74 mmol), and BF_3–Et_2O (0.27 mL, 2.21 mmol) in THF–H_2O (4:1) (0.55 mL) gave **8** (41 mg, 86%) a solid: mp 107–108 °C (petroleum ether), lit.[12c] mp 109 °C; $[\alpha]^{25}_D$ +27.0 (*c* 0.87, $CHCl_3$), lit.[12c] $[\alpha]^{20}_D$ +27 (*c* 1.73, $CHCl_3$); IR (KBr) 2851, 1748, 1717, 1257, 1206, 1172, 698 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, *J* = 6.6 Hz), 1.37 (3 H, d, *J* = 7.1 Hz), 1.25–1.87 (24 H, m), 2.66–2.73 (1 H, m), 2.93–3.04 (1 H, m), 4.44–4.51 (1 H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.31, 14.72, 22.89, 25.50, 29.43, 29.55, 29.58, 29.70, 29.81, 29.84, 29.87, 32.11, 35.12, 40.04, 53.95, 79.52, 174.72, 176.72; HRMS calcd for $C_{19}H_{34}O_4$ 326.2457, found 326.2484.

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Supporting Information Available: Various ^{1}H and ^{13}C NMR spectra (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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