# Synthesis and Absolute Stereochemistry of (−)-Protolichesterinic Acid, Antitumor Antibiotic Lactone from *Cetraria islandica*

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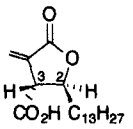
The first synthesis of (−)-protolichesterinic acid is described. The approach, based on a facially selective 2 + 2 cycloaddition reaction of dichloroketene with an enantiopure O-alkyl enol ether, permits the assignment of the absolute stereochemistry of the natural product to be made (2*S*,3*R*).

Protolichesterinic acid (1), first isolated at the beginning of this century by Zopf from various species of the moss *Cetraria*,[1] was structurally elucidated some 25 years later by Asahina and Asano.[2] Interestingly, both the dextro- and levorotatory forms of 1 have been secured from different sources of *Cetraria*.[1-3] Dextrorotatory 1 has,



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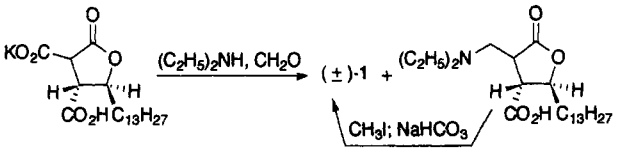
Protolichesterinic acid

additionally, been found by several groups to be present in *Parmelia* species,[4] lichens indigenous to India. Protolichesterinic acid is today probably the best known member of the class of lactone fatty acids that also includes lichesterinic acid,[1,2b] alloprotolichesterinic acid,[3a] nephromopsinic acid,[5a] and nephrosterinic acid.[5b]

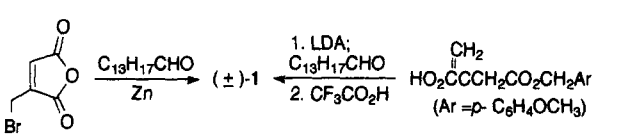
The first synthesis of racemic protolichesterinic acid, a deceptively simple compound, was elegantly achieved by van Tamelen and Bach in 1958.[6] The key intermediate in their approach was the monopotassium salt of α,β-dicarboxy-γ-tridecyl-γ-butyrolactone, which was converted directly, albeit in modest yield, to protolichesterinic acid through decarboxylative methylenation (eq 1). This then novel transformation was effected by a Mannich reaction with formaldehyde and diethylamine in methanol for 2 days, which gave in addition to protolichesterinic acid the α-decarboxylated α-(*N*,*N*-diethylamino)methyl



(eq 1)

derivative. The latter, on treatment with methyl iodide and then sodium bicarbonate, provided additional protolichesterinic acid. The total yield of the pure racemic material was approximately 20%. These workers correctly concluded from their studies that the relative stereochemistry of the natural product was trans. In addition, ancillary studies that were carried out confirmed the predictable ease of both ring-opening in the normethylene derivative and double-bond isomerization in the final product.

In 1969, Gelbard and co-workers[7] realized a short synthesis of an equimolar mixture of methyl protolichesterinate and its cis isomer in 57% yield by a Reformatsky reaction with methyl bromomesaconate and tetradecanal. Unfortunately, but not surprisingly, attempts to saponify the mixture produced double-bond migration to give methyl lichesterinate. Racemic protolichesterinic acid could, however, be obtained in 12% yield by using bromocitraconic anhydride in lieu of methyl bromomesaconate. Carlson and Oyler[8] a few years later, also unable to effect clean hydrolysis of methyl protolesterinate formed through reaction of methyl itaconate dianion with tetradecanal, resorted to the dianion of *p*-methoxybenzyl itaconate. Racemic protolichesterinic acid could thus be obtained in 20% yield (eq 2).



(eq 2)

Johnson and co-workers[9] in 1974 found that *trans*-β-carboxy-γ-tridecyl-γ-butyrolactone could be efficiently α-carboxylated with methyl methoxymagnesium carbonate (Stiles' reagent) without suffering appreciable ring cleavage

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(1) Zopf, W. *Liebigs Ann. Chem.* **1902**, *324*, 39–78; **1904**, *336*, 46–85.

(2) (a) Asahina, Y.; Asano, M. *J. Pharm. Soc. Jpn.* **1927**, *539*, 1–17; *Chem. Abstr.* **1928**, *22*, 4470. (b) Asano, M.; Kanematsu, T. *Chem. Ber.* **1932**, *65B*, 1175–1178.

(3) (a) Asahina, Y.; Yanagita, M. *Chem. Ber.* **1936**, *69B*, 120–125. (b) Asahina, Y.; Yasue, M. *Chem. Ber.* **1937**, *70B*, 1053–1059. (c) Gertig, H. *Diss. Pharm.* **1963**, *15*, 235–240; *Chem. Abstr.* **1964**, *60*, 2041f. See also ref 11a.

(4) (a) Shah, L. G. *J. Ind. Chem. Soc.* **1954**, *31*, 253–256. (b) Aghoramurty, K.; Neelakantan, S.; Seshadri, T. R. *J. Sci. Ind. Res. (India)* **1954**, *13B*, 326–328; *Chem. Abstr.* **1955**, *49*, 8900c. (c) Rangaswami, S.; Subba Rao, V. *Ind. J. Pharm.* **1955**, *17*, 50–53.

(5) (a) Asano, M.; Azumi, T. *Chem. Ber.* **1935**, *68B*, 995–997. (b) Asahina, Y.; Yanagita, M.; Sakurai, Y. *Chem. Ber.* **1937**, *70B*, 227–235. See also: (c) Brookes, D.; Tidd, B. K.; Turner, W. B. *J. Chem. Soc.* **1963**, 5385–5391. (d) McCorkindale, N. J.; Wright, J. L. C.; Brian, P. W.; Clarke, S. M.; Hutchinson, S. A. *Tetrahedron Lett.* **1968**, 727–730. (e) Bérdy, J. *Handbook of Antibiotic Compounds*; CRC Press: Boca Raton, FL, 1982; Vol. IX, and references cited therein.

(6) van Tamelen, E. E.; Bach, S. R. *J. Am. Chem. Soc.* **1958**, *80*, 3079–3086.

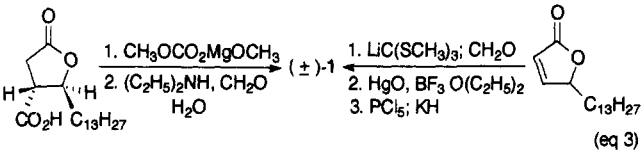
(7) Löffler, A.; Pratt, R. D.; Pucknat, J.; Gelbard, G.; Dreiding, A. S. *Chimica* **1969**, *23*, 413–416.

(8) Carlson, R. M.; Oyler, A. R. *J. Org. Chem.* **1976**, *41*, 4065–4069.

(9) Martin, J.; Watts, P. C.; Johnson, F. *J. Org. Chem.* **1974**, *39*, 1676–1681.

0022-3263/93/1958-7537$04.00/0 

and that the product could be converted with diethylamine in formalin, as shown earlier by van Tamelen and Bach, to racemic protolichesterinic acid in ca. 30% yield. Finally, Damon and Schlessinger[10] in 1976 published an efficient, stereoselective synthesis of racemic protolichesterinic acid that was based on the conjugate addition of [tris(methylthio)methyl]lithium to γ-tridecylbutenolide and in situ trapping with formaldehyde, followed by hydrolysis and methylene formation. Methylene formation, however, could only be achieved under carefully worked out conditions; other conditions led through double-bond isomerization to lichesterinic acid "in good to excellent yield" (eq 3).

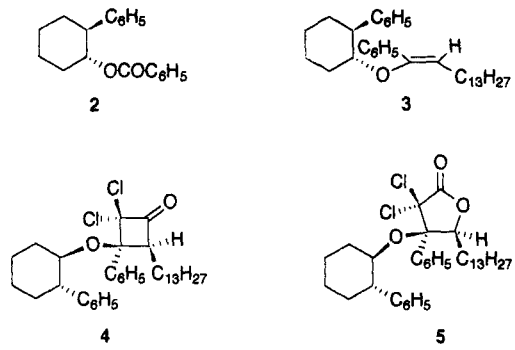



(eq 3)

The considerable interest over the years in this α-methylene-γ-butyrolactone has in large measure been due to its antibacterial,[5e,11a-f] antifungal,[11a] antitumoral,[11g] and growth-regulating[11h] effects. Surprisingly, in light of this interest and the time that has elapsed since its initial isolation and structural elucidation, the absolute stereochemistry of protolichesterinic acid until now has remained largely conjectural.[12] In this paper we detail the first synthesis of (−)-protolichesterinic acid, which serves to establish the absolute stereochemistry of this well-known natural product.

The approach, based to a large extent on our recently achieved synthesis of methylenolactocin,[13] was designed to delay until the final stage the problematical introduction of the methylene group (see above). The synthesis of this deceptively simple molecule began with the conversion of (1*R*,2*S*)-(−)-2-phenylcyclohexyl benzoate[13] (**2**, Chart I) to enol ether **3** through use of Takai and co-workers' *Z*-selective alkylidenation procedure[14] with 1,1-dibromotetradecane, Zn, $TiCl_4$, and TMEDA in THF–$CH_2Cl_2$ (86% yield). Although ca. 6% of the corresponding *E*-enol ether was also produced in this reaction, it could be readily removed by dry-column chromatography on $SiO_2$ pretreated with $(C_2H_5)_3N$.

**Chart I**



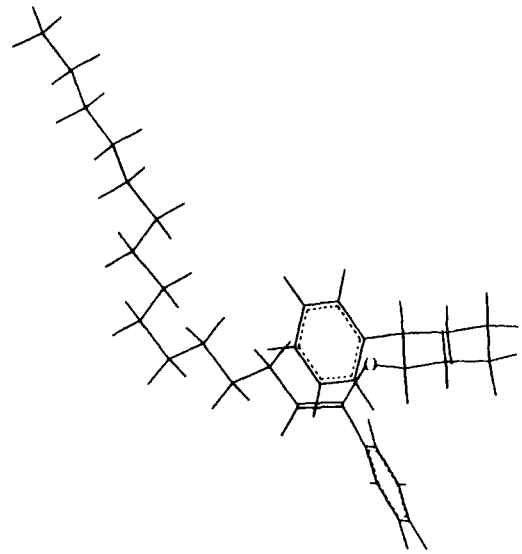



**Figure 1.** Global minimum-energy conformation of enol ether **3** (Insight II Discover, version 2.1.2).

The pure *Z*-enol ether in the presence of dichloroketene, generated under the usual conditions ($Cl_3CCOCl$,Zn, ether),[15] underwent cycloaddition with substantial diastereofacial differentiation (9:1 by $^1H$ NMR). The major product in the crude mixture, which unfortunately was chromatographically unstable and resisted all attempts at crystallization, was tentatively assigned the stereochemistry depicted in **4** on the basis of what was considered from molecular mechanics calculations to be the probable reactive conformation of the enol ether. As can be seen in Figure 1, the $C_\alpha$-*re* olefinic face of the enol ether in its lowest energy ground-state conformation appears to be clearly more accessible than the $C_\alpha$-*si* to the incoming dichloroketene reagent. This stereochemical assignment proved to be correct (see below).

*m*-Chloroperbenzoic acid treatment of the crude cycloaddition mixture smoothly effected the desired Baeyer–Villiger reaction to provide the corresponding lactone diastereomers (also 9:1 by $^1H$ NMR); unfortunately, the major isomer (**5**) once again proved to be both chromatographically unstable and unwilling to crystallize. Faced with this untoward situation, we elected to continue the synthesis with the expectation that protolichesterinic acid, if not a prior crystalline intermediate, would probably offer a reasonable opportunity to upgrade the enantiomeric purity.

Addition of aqueous chromous perchlorate[16] to the lactones in acetone solution at 0 °C rapidly gave the

(10) Damon, R. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1976**, 1561–1564.

(11) (a) Cavallito, C. J.; Fruehauf, McK. D.; Bailey, J. N. *J. Am. Chem. Soc.* **1948**, *70*, 3724–3726. (b) Shibata, S.; Miura, Y.; Sugimura, H.; Toyoizumi, Y. *J. Pharm. Soc. Jpn.* **1948**, *68*, 300–303; *Chem. Abstr.* **1951**, *45*, 6691i. (c) Fujikawa, F.; Hitosa, Y.; Yamaoka, M.; Fujiwara, Y.; Nakazawa, S.; Omatsu, T.; Toyoda, T. *Ibid.* **1953**, *73*, 135–138; *Chem. Abstr.* **1954**, *48*, 230a. (d) Borkowski, B.; Wozniak, W.; Gertig, H.; Werakso, B. *Diss. Pharm.* **1964**, *16*, 189–194; *Chem. Abstr.* **1965**, *62*, 1995b. (e) Sticher, O. *Pharm. Acta Helv.* **1965**, *40*, 183–195; *Chem. Abstr.* **1965**, *63*, 8778d. (f) Sticher, O. *Pharm. Acta Helv.* **1965**, *40*, 385–394; *Chem. Abstr.* **1965**, *63*, 12026c. (g) Hirayama, T.; Fujikawa, F.; Kasahara, T.; Otsuka, M.; Nishida, N.; Mizuno, D. *Yakugaku Zasshi* **1980**, *100*, 755–759; *Chem. Abstr.* **1980**, *93*, 179563f. (h) Huneck, S.; Schreiber, K. *Phytochemistry* **1972**, *11*, 2429–2434.

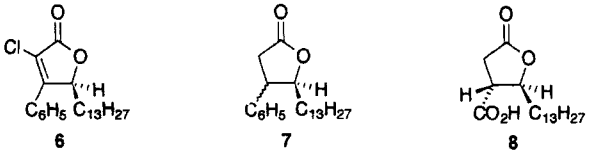
(12) Boll, P. M.; *Acta Chem. Scand.* **1968**, *22*, 3245–3250. See also: Huneck, S.; Follmann, G. *Z. Naturforsch.* **1967**, *B22*, 666–670; *Chem. Abstr.* **1968**, *68*, 49000t. **Note added in proof**: A recently disclosed preparation from chiral pool material of the dihydro derivatives indirectly allows assignment of absolute stereochemistry: Mulzer, J.; Salimi, N.; Hartl, H. *Tetrahedron: Asymmetry* **1993**, *4*, 457–471.

(13) B. M. de Azevedo, M.; Murta, M. M.; Greene, A. E. *J. Org. Chem.* **1992**, *57*, 4567–4569.

(14) Okazoe, T.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 4410–4412. 1,1-Dibromotetradecane was prepared by a procedure analogous to that described in Hoffmann, R. W.; Bovicelli, P. *Synthesis* **1990**, 657–659.

(15) Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 3173–3179.

**Chart II**



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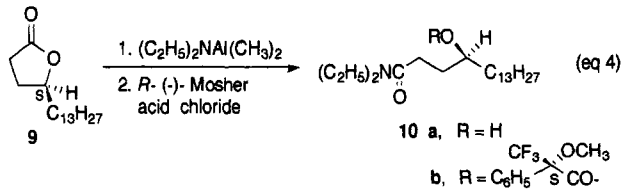
expected α-chlorobutenolide **6** (Chart II) in 73% overall yield from the enol ether (90%/step). Importantly, the inductor could be recovered in 78% yield. Hydrogenation over 10% palladium on carbon served to saturate the double bond and also to remove the chloro substituent and gave a mixture of cis and trans lactones (**7**).[17] Although the exact cis–trans composition tended to vary, the former was in all cases preponderant.

In that electron-withdrawing groups seriously deactivate ketenophiles,[18] the phenyl substituent was selected at the start as a latent carboxyl (carbalkoxyl) group. An added benefit that resulted from this choice was that the reductive elimination of the chiral auxiliary was decidedly more facile with a phenyl substituent (vs H) in the β position. The unmasking of the carboxyl group could be cleanly accomplished under Sharpless conditions ($RuCl_3$(cat.)–$NaIO_4$)[19] to give the expected mixture of β-carboxy-γ-butyrolactones. In spite of the documented propensity of this type of molecule to suffer ring opening with base,[6,9] DBU treatment of the methyl esters ($CH_2N_2$) effected without incident smooth equilibration and provided, following hydrolysis, the crystalline acid **8** in 63% overall yield.

For the dual purpose of confirming the enantiomeric series and establishing the enantiomeric excess, lactone acid **8**, $[\alpha]^{21}_D$ −33°, was decarboxylated by irradiation (high-pressure Hg arc, Pyrex filter) in the presence of acridine and *tert*-butyl mercaptan in benzene solution.[20] This simple, direct, and under-used method provided the known γ-heptadecanolactone (**9**) with $[\alpha]^{21}_D$ −25° (lit.[21] $[\alpha]^{21}_D$ −28.2°), corresponding to the *S* configuration,[21] which was that expected on the basis of the predicted transition-state conformation of enol ether **3**. In that optical rotation values are open to various sources of error and thus a poor measure of enantiomeric purity,[22] the optically active lactone **9** was converted (as was the racemic lactone) in two steps[23] to the Mosher ester of *N*,*N*-diethyl-4-hydroxyheptadecanamide (**10b**, eq 4). Fluorine-19 NMR showed well-separated signals that reflected an 88:12 ratio of diastereomers, in harmony with the earlier 9:1 ratio of cyclobutanone diastereomers.

Pleasingly, simple recrystallization of the enantiomerically enriched lactone acid from ethyl acetate–cyclohexane



9 10 a, R = H b, R = $C_6H_5C(CF_3)(OCH_3)CO$- (eq 4)

was efficient and raised the specific rotation to −41°. This value indicated a very high degree of enantiopurity, which was confirmed through photodecarboxylation[20] to give (−)-γ-heptadecanolactone with $[\alpha]^{21}_D$ −28.5° (lit.[21] $[\alpha]^{21}_D$ −28.2°) and by conversion of this latter product to the Mosher ester of its hydroxy amide derivative, which now displayed a single resonance in its $^{19}F$ NMR spectrum.

Completion of the synthesis required methylenation of **8**. For this problematic transformation (see above), our recently reported[24] improvement of Johnson's two-step procedure[9] once again proved highly useful. Thus, prolonged reaction of **8** with methyl methoxymagnesium carbonate in DMF at 135–140 °C produced the expected lactone diacid, which without purification was treated with *N*-methylaniline in the presence of formalin and sodium acetate in acetic acid to give (−)-protolichesterinic acid in a pleasingly high 68% yield after rapid passage over silica gel. The synthetically derived natural product, mp 103–105 °C (lit.[1,4c] mp 104–105 °C), $[\alpha]^{21}_D$ −15° (lit.[11a] $[\alpha]^{22}_D$ −15°), provided spectroscopic data in excellent agreement with the literature values.[7-9] Levorotatory protolichesterinic acid is thus the 2*S*,3*R* stereoisomer.

In conclusion, enantiopure (−)-protolichesterinic acid has been synthesized for the first time in approximately 11 steps and with an overall yield of 17%.[25] The approach, which for stereoselection relies on π-face differentiation in a chiral enol ether–ketene cycloaddition reaction, should find further application in natural product synthesis.

## Experimental Section[26]

**(−)-((1*S*,2*R*)-2-(((1*Z*)-1-Phenyl-1-pentadecenyl)oxy)cyclohexyl)benzene (3).** A solution of $TiCl_4$ in $CH_2Cl_2$ (19.4 mL, 19.4 mmol) was added to 49 mL of THF at 0 °C. To this solution at 20 °C was added 6.25 mL (4.81 g, 41.4 mmol) of tetramethylethylenediamine, and the mixture was stirred for 10 min. Zinc dust (2.85 g, 43.6 mmol) was added, and the resulting mixture was sonicated for 5 min and then stirred for 25 min, whereupon a solution of 1.36 g (4.86 mmol) of (1*R*,2*S*)-(−)-2-phenylcyclohexyl benzoate[13] (**2**) and 3.80 g (10.68 mmol) of 1,1-dibromotetradecane[14] in 8.0 mL of THF was added with a syringe pump over 4 h. After

(16) Kochi, J. K.; Singleton, D. M. *J. Am. Chem. Soc.* **1968**, *90*, 1582–1589. Wade, R. S.; Castro, C. E. *Org. Synth.* **1972**, *52*, 62–66.

(17) While hydrogenation of the dichloro lactone diastereomers afforded directly and in good yield the lactones **7**, by carrying out the transformation in two stages the chromatographic removal of the chiral auxiliary was greatly simplified.

(18) Brady, W. T. *Synthesis* **1971**, 415–422; *Tetrahedron* **1981**, *37*, 2949–2966 and references cited therein.

(19) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938. See also: Nunez, M. T.; Martin, V. S. *Ibid.* **1990**, *55*, 1928–1932.

(20) Okada, K.; Okubo, K.; Oda, M. *Tetrahedron Lett.* **1989**, *40*, 6733–6736.

(21) Thijs, L.; Waanders, P. P.; Stokkingreef, E. H. M.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 332–337.

(22) See, for example: Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1993**, *58*, 36–42.

(23) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171–4174. (b) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.

(24) Murta, M. M.; B. M. de Azevedo, M.; Greene, A. E. *Synth. Commun.* **1993**, *23*, 495–503.

(25) The first synthesis of (+)-protolichesterinic acid has also been realized through a completely analogous approach starting from (1*S*,2*R*)-(+)-2-phenylcyclohexyl benzoate.[13]

(26) Isolation of the crude product was generally accomplished by pouring the reaction mixture into water and then thoroughly extracting the separated aqueous phase with the specified solvent. After being washed with 10% aqueous HCl and/or $NaHCO_3$ (if required), water, and saturated aqueous NaCl, the combined organic phases were dried over anhyd $Na_2SO_4$ or $MgSO_4$ and then filtered and concentrated under reduced pressure on a Büchi Rotovapor to yield the crude reaction product. Tetrahydrofuran was distilled from sodium–benzophenone, ether was distilled from lithium aluminum hydride, and $CH_2Cl_2$, pyridine, and TMEDA were distilled from calcium hydride. Thin-layer chromatography was performed on Merck $60F_{254}$ (0.2 mm) sheets, which were visualized with molybdophosphoric acid in ethanol. Merck 70–230 silica gel 60 was employed for column chromatography. A Perkin-Elmer 397 spectrophotometer was used to record IR spectra (neat or as Nujol films). Brucker WPSY 80, AC 200, and AM 300 spectrometers were used for the $^1H$ and $^{13}C$ NMR spectra ($CDCl_3$ solutions). Mass spectra were obtained on an AEI MS-30 mass spectrometer (70 eV, direct insert probe). Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Melting points were obtained with a Buchi-Tottoli apparatus and are not corrected. Microanalyses were performed by the Central Service of the CNRS.

being stirred for an additional 1 h, the mixture was treated at 0 °C with 6.3 mL of saturated aqueous $K_2CO_3$ and stirred for an additional 15 min at 0 °C. The mixture was then diluted with ether and filtered through 50 g of alumina (neutral, pretreated with 3.0 mL of saturated aqueous $K_2CO_3$ and 2.5 mL of triethylamine) with 0.5% triethylamine–ether. The crude product was further purified by dry-column silica gel chromatography ($SiO_2$ pretreated with 2.5% (v/v) of triethylamine) with hexane to afford 1.93 g (86%) of pure **3**: $[\alpha]^{21}_D$ −25° (*c* 3.1, $CHCl_3$); $^1H$ NMR (200 MHz) δ 7.4–7.0 (m, 8H), 6.9–6.8 (m, 2H), 4.97 (t, *J* = 7.1 Hz, 1H), 3.63 (dt, *J* = 3.9, 10.2 Hz, 1H), 2.72 (dt, *J* = 3.9, 10.1 Hz, 1H), 2.17–1.10 (m, 32 H), 0.88 (t, *J* = 6.7 Hz, 3H); $^{13}C$ NMR (50.3 MHz) δ 151.7, 144.4, 135.8, 128.3, 128.0, 127.8, 127.2, 126.6, 126.2, 116.2, 79.6, 50.7, 33.4, 32.3, 31.9, 29.7, 29.4, 25.9, 24.7, 22.7, 14.1; IR 3050, 3020, 1645, 1600, 1440, 1060 $cm^{-1}$; mass spectrum (EI), *m/z* 460 ($M^+$), 302, 158, 91. Approximately 6% of the *E* isomer was also isolated (4.82 ppm, t, *J* = 7.6 Hz).

Anal. Calcd for $C_{33}H_{48}O$: C, 86.03; H, 10.50. Found: 86.27; H, 10.46.

**(5*S*)-(+)-3-Chloro-4-phenyl-5-tridecyl-2(5*H*)-furanone (6).** To a stirred mixture of 1.32 g (2.87 mmol) of enol ether **3** and 2.90 g (ca. 45 mmol) of Zn–Cu couple in 26 mL of ether under argon was added over 1.5 h 1.24 mL (2.02 g, 11.1 mmol) of freshly distilled trichloroacetyl chloride in 13 mL of ether, and the resulting mixture was stirred overnight. The ether solution was then separated from the excess couple and added to hexane, and the resulting mixture was partially concentrated under reduced pressure in order to precipitate the zinc chloride. The supernatant was decanted and washed successively with an aqueous solution of sodium bicarbonate, water, and brine and then dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure left 1.64 g of crude (2*S*,3*S*)-4,4-dichloro-3-phenyl-3-(((1*R*,2*S*)-2-phenylcyclohexyl)oxy)-2-tridecylcyclobutanone (**4**): $^1H$ NMR (200 MHz) δ 7.5–6.8 (m, 10H), 3.81 (dd, *J* = 3.6, 10.0 Hz, 1H), 3.23 (dt, *J* = 3.7, 10.0 Hz, 1H), 2.59 (m, 1H), 2.2–1.0 (m, 32H), 0.89 (t, *J* = 6.4 Hz, 3H): IR 3050, 3020, 1815, 1600, 1440 $cm^{-1}$. Approximately 10% of the diastereomer was also present (4.10 ppm, m).

A mixture of 1.64 g of the above crude cyclobutanone, 3.50 g (41.7 mmol) of sodium bicarbonate, and 3.40 g (70–75%, ca. 14.3 mmol) of 3-chloroperoxybenzoic acid in 290 mL of $CH_2Cl_2$ was stirred overnight at 20 °C and then processed with $CH_2Cl_2$ in the usual manner to give 1.68 g of crude (4*R*,5*S*)-3,3-dichlorodihydro-4-phenyl-4-(((1*R*,2*S*)-2-phenylcyclohexyl)oxy)-5-tridecyl-2(3*H*)-furanone (**5**): $^1H$ NMR (200 MHz) δ 7.6–6.8 (m, 10H), 4.84 (d, *J* = 7.5 Hz, 1H), 3.87 (dt, *J* = 3.4, 8.5 Hz, 1H), 2.55 (dt, *J* = 4.1, 8.5 Hz, 1H), 2.0–1.1 (m, 32 H), 0.88 (t, *J* = 7.1 Hz, 3H); IR 3060, 3030, 1810, 1220 $cm^{-1}$. Approximately 10% of the diastereomer was also present (5.04 ppm, d, *J* = 9.6 Hz).

To a solution of the above crude lactone (1.68 g) in 190 mL of acetone at 0 °C under argon was added over 1 h 38 mL of a ca. 1.6 M aqueous solution of chromium(II) perchlorate. After the addition, the crude product was isolated with ether in the usual way and was purified by dry-column silica gel chromatography with 3% ethyl acetate–hexane to provide 396 mg (78% recovery) of the inductor and 790 mg (73% overall) of **6**: mp 55–57 °C; $[\alpha]^{21}_D$ +49° (*c* 0.2, $CHCl_3$); $^1H$ NMR (200 MHz) δ 7.7–7.5 (m, 5H), 5.49 (m, 1H), 2.0–1.1 (m, 24 H), 0.88 (t, *J* = 6.8 Hz, 3H); $^{13}C$ NMR (50.3 MHz) δ 185.0, 168.2, 156.6, 131.0, 129.0, 127.8, 117.9, 81.6, 33.2, 31.8, 29.5, 29.3, 29.2, 29.0, 24.1, 22.6, 14.0; IR 1780, 1630, 1200, 1030 $cm^{-1}$; mass spectrum (EI) *m/z* 376 ($M^+$), 341, 207, 194, 165.

Anal. Calcd for $C_{23}H_{33}O_2Cl$: C, 73.33; H, 8.82. Found: C, 73.48; H, 8.84.

**(2*S*,3*R*)-(−)-Tetrahydro-5-oxo-2-tridecyl-3-furancarboxylic Acid (8).** A 550-mg (1.46 mmol) sample of lactone **6** and 359 mg (4.38 mmol) of sodium acetate in 40 mL of methanol were stirred under an $H_2$ atmosphere in the presence of 37 mg of 10% Pd–C at 20 °C for 20 h. The mixture was then filtered and concentrated under reduced pressure, and the resulting solid material was triturated with ethyl acetate, which in turn was filtered and concentrated to provide 502 mg of crude (4*RS*,5*S*)-dihydro-4-phenyl-5-tridecyl-2(3*H*)-furanone (**7**): IR 3060, 3030, 1780, 1600, 1460, 1180 $cm^{-1}$. This lactone (502 mg) in $CCl_4$ (3.0 mL)–$CH_3CN$ (3.0 mL)–$H_2O$ (4.5 mL) was stirred with 4.65 g (21.75 mmol) of $NaIO_4$ and 17 mg (0.08 mmol) of anhyd $RuCl_3$ at 38 °C for 96 h, whereupon the reaction mixture was diluted with ether, stirred for 10 min, and then carefully acidified with 10% aqueous HCl to pH = 3. The product was isolated with ethyl acetate in the usual manner to provide the crude acid, which was esterified with $CH_2N_2$ in ether to give 358 mg of the crude methyl ester. This material was stirred with 0.50 g (3.28 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in 15 mL of $CH_2Cl_2$ at 20 °C under argon for 72 h. The crude product was isolated with ethyl acetate in the usual way and was purified by dry-column silica gel chromatography with 3% ether–hexane to afford 286 mg of the trans isomer and 35 mg of the cis, which, retreated with DBU, provided an additional 13 mg (63% total yield) of the trans isomer, methyl (2*S*,3*R*)-(−)-tetrahydro-5-oxo-2-tridecyl-3-furancarboxylate (**8**, methyl ester): $[\alpha]^{21}_D$ −78° (*c* 1.0, $CHCl_3$); $^1H$ NMR (200 MHz) δ 4.57 (ps q, *J* = 5.5, 7.0 Hz, 1H), 3.77 (s, 3H), 3.1–2.7 (m, 3H) 1.8–1.1 (m, 24H), 0.88 (t, *J* = 6.8 Hz, 3H); $^{13}C$ NMR (50.3 MHz) δ 174.3, 171.5, 81.8, 52.6, 45.6, 35.2, 32.1, 31.8, 29.6, 29.5, 29.4, 29.3, 29.1, 25.1, 22.6, 14.0; IR 1780, 1740, 1460, 1200 $cm^{-1}$; mass spectrum (EI) *m/z* 327 ($M^+$ + 1), 294, 267, 132, 115, 55.

Anal. Calcd for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 69.81; H, 10.48.

A solution of 286 mg (0.88 mmol) of the above ester in 10 mL of dioxane and 4.0 mL of 6 N aqueous hydrochloric acid was refluxed for 6 h under argon. The product was isolated with $CH_2Cl_2$ in the normal manner to provide 268 mg (98%) of acid. Recrystallization of this material from ethyl acetate–cyclohexane gave 177 mg (65%) of enantiomerically pure acid **8**: mp 109–111 °C; $[\alpha]^{21}_D$ −41° (*c* 0.5, $CHCl_3$); $^1H$ NMR (200 MHz) δ 4.62 (ps q, *J* = 5.2, 7.0 Hz, 1H), 3.2–2.7 (m, 3H), 1.76 (m, 2H), 1.6–1.1 (m, 24H), 0.88 (t, *J* = 6.8 Hz, 3H); $^{13}C$ NMR (50.3 MHz) δ 176.4, 174.6, 81.8, 45.3, 35.3, 31.8, 29.6, 29.4, 29.3, 29.1, 25.1, 22.6, 14.0; IR (Nujol) 3600–2300, 1755, 1725, 1240 $cm^{-1}$; mass spectrum (EI) *m/z* 313 ($M^+$ + 1), 294, 266, 253, 118, 55, 43.

Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.33. Found: C, 68.92; H, 10.40.

**(*S*)-Mosher Ester of (*S*)-*N*,*N*-Diethyl-4-hydroxyheptadecanamide (10b).** A solution of 52 mg (0.17 mmol) of acid **8**, 9.0 mg (0.05 mmol) of acridine, and 0.20 mL of *t*-$C_4H_9SH$ in 9.0 mL of benzene was irradiated under nitrogen with a Hanau TQ 150 high-pressure Hg arc lamp (Pyrex filter) for 3 h. The solvents were then evaporated under reduced pressure, and the residue was purified by dry-column silica gel chromatography with 20% ethyl acetate in cyclohexane to give 25 mg (56%) of (*S*)-(−)-γ-heptadecanolactone (**9**): $[\alpha]^{21}_D$ −28.5° (*c* 1.0, $CH_3OH$) (lit.[21] $[\alpha]^{21}_D$ −28.2°); $^1H$ NMR (200 MHz) δ 4.49 (m, 1H), 2.58–2.24 (m, 4H), 2.0–1.1 (m, 24H), 0.88 (t, *J* = 6.7 Hz, 3H).

To a solution of 14.6 mg (0.20 mmol) of diethylamine in 0.50 mL of $CH_2Cl_2$ at room temperature under argon was slowly added 0.10 mL (0.20 mmol) of a 2.0 M solution of trimethylaluminum in hexane. The mixture was stirred for 15 min, and 18 mg (0.07 mmol) of the above lactone was then added. After being stirred at 40 °C overnight, the reaction mixture was treated with 10% aqueous HCl and then processed with $CH_2Cl_2$ in the usual way. The resulting crude product was purified by dry-column silica gel chromatography with ether in hexane to provide (*S*)-*N*,*N*-diethyl-4-hydroxyheptadecanamide (**10a**): $^1H$ NMR (200 MHz) δ 3.7–3.3 (m, 6H), 2.50 (ps q, *J* = 6.2, 7.0 Hz, 2H), 2.0–1.0 (m, 32H), 0.88 (t, *J* = 6.5 Hz, 3H). $^{19}F$ NMR analysis of the (*S*)-Mosher ester (**10b**) of this alcohol and of the corresponding racemic alcohol ((*R*)-(−)-2-methoxy-2-phenyl-2-(trifluoromethyl)-acetyl chloride, pyridine) confirmed the enantiomeric purity (≥99%) of **9**.

**(2*S*,3*R*)-(−)-Tetrahydro-4-methylene-5-oxo-2-tridecyl-3-furanecarboxylic Acid (Protolichesterinic Acid (1)).** A 100-mg (0.32 mmol) sample of acid **8** in 6 mL (12 mmol) of 2 M methyl methoxymagnesium carbonate in DMF was stirred under argon at 135–140 °C for 70 h. The reaction mixture was then added to 10% aqueous HCl in the presence of $CH_2Cl_2$, and the product was isolated with $CH_2Cl_2$ in the normal fashion (solvent evaporation at <30 °C!) to give 114 mg of crude diacid. This material was treated with 2.0 mL of a stock solution (prepared from 20 mL of acetic acid, 15 mL of 37% formaldehyde in water, 5.20 mL of *N*-methylaniline, and 600 mg of sodium acetate) and stirred under argon at 20 °C for 2 h. The crude product was isolated with ether in the usual way and was purified by dry-

column silica gel chromatography with chloroform–ethyl acetate–acetic acid (90:8:2) to give 71 mg (68%) of (−)-protolichesterinic acid (1): mp 103–105 °C (ethyl acetate) (lit.[1,4c] 104–105 °C); $[\alpha]^{21}_D$ −15° (*c* 1.0, $CHCl_3$) (lit.[11a] $[\alpha]^{22}_D$ −15° (*c* 1.0, $CHCl_3$)); $^1H$ NMR (200 MHz) δ 6.47 (d, *J* = 2.9 Hz, 1H), 6.02 (d, *J* = 2.5 Hz, 1H), 4.81 (ps q, *J* = 6.0, 6.2 Hz, 1H), 3.63 (m, 1H) 1.8–1.2 (m, 24H), 0.88 (t, *J* = 6.7 Hz, 3H); $^{13}C$ NMR (75.5 MHz) δ 174.2 (C), 166.1 (C), 132.3 (C), 125.8 ($CH_2$), 78.8 (CH), 49.4 (CH), 35.7 ($CH_2$), 31.6 ($CH_2$), 31.5 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 29.3 ($CH_2$), 29.1 ($CH_2$), 24.7 ($CH_2$), 22.6 ($CH_2$), 14.0 ($CH_3$); IR (Nujol) 3600–2400, 1750, 1710, 1660, 1250 $cm^{-1}$; mass spectrum (EI) *m/z* 324 ($M^+$), 306, 279, 261, 192, 55.

Anal. Calcd for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94. Found: C, 70.14; H, 10.02.

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