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Diastereoselective synthesis of (+)-nephrosterinic acid and (+)-protolichesterinic acid

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ABSTRACT

A diastereoselective synthesis of (+)-nephrosterinic acid and (+)-protolichesterinic acid, common members of the paraconic acids is described. The synthesis is based on a diastereoselective orthoester Johnson–Claisen rearrangement of a (*Z*)-allyl alcohol with a vicinal dioxolane moiety as key steps. The synthesis is completed in 10 steps and with overall yields of 15.9% for (+)-nephrosterinic acid and 16.4% for (+)-protolichesterinic acid.

1. Introduction

Nephrosterinic acid[1] isolated from *Centraria endocrocea* and protolichesterinic acid[2] isolated from *Cetraria islandica* and *Parmelia sinodensis* are important members of the family of paraconic acids. The latter are characterized by the presence of a highly substituted γ-butyrolactone with a β-COOH group and an α-methyl or methylene group and display varied stereochemical relationships of substituents on adjacent carbon atoms. These compounds are known for their biological activities such as antibacterial,[3] antifungal,[3b] antitumor[4] and growth-regulating effects.[5] The activity arises mainly due to the α,β-unsaturated carbonyl system which acts as a Michael acceptor to various biological nucleophiles. The syntheses of nephrosterinic acid[6] and protolichesterinic acid[7] have been reported both in racemic and either of the enantiomer forms. In the course of studies directed toward the enantioselective synthesis of bioactive molecules[8] employing the orthoester Johnson–Claisen rearrangement (JCR)[9] of allyl alcohols with a vicinal chiral dioxolane functionality, we recently completed the synthesis of (+)-nephrosteranic acid **1**, (+)-roccellaric acid **2**, (−)-methylenolactocin **3,** and (−)-phaseolinic acid **4** (Fig. 1).[8e,f] The strategy was based on the separation of diastereomeric mixture **8**/**9** (or *ent*-**8**/*ent*-**9**) obtained in a 1.1:1 to 2.5:1 ratio by the orthoester Johnson–Claisen rearrangement of (*E*)-**7** [or (*E*)-*ent*-**7**, Fig. 1]. Although the diastereomeric lactones were easily separable for further synthetic exploration, the brevity was overshadowed by the poor diastereoselectivity which was a major concern to us, and so we undertook a detailed study to improve this aspect. A stereochemical feature of **7** or *ent*-**7** available for variation apart from our earlier work was the olefin geometry. We report here a remarkable improvement in the diastereoselectivity in the orthoester

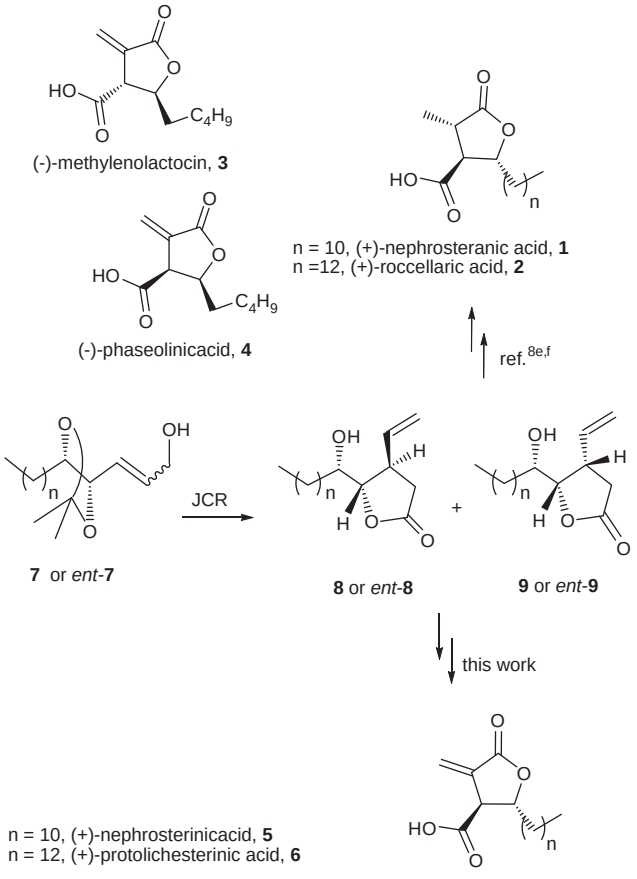

Figure 1. Strategic considerations to paraconic acids.

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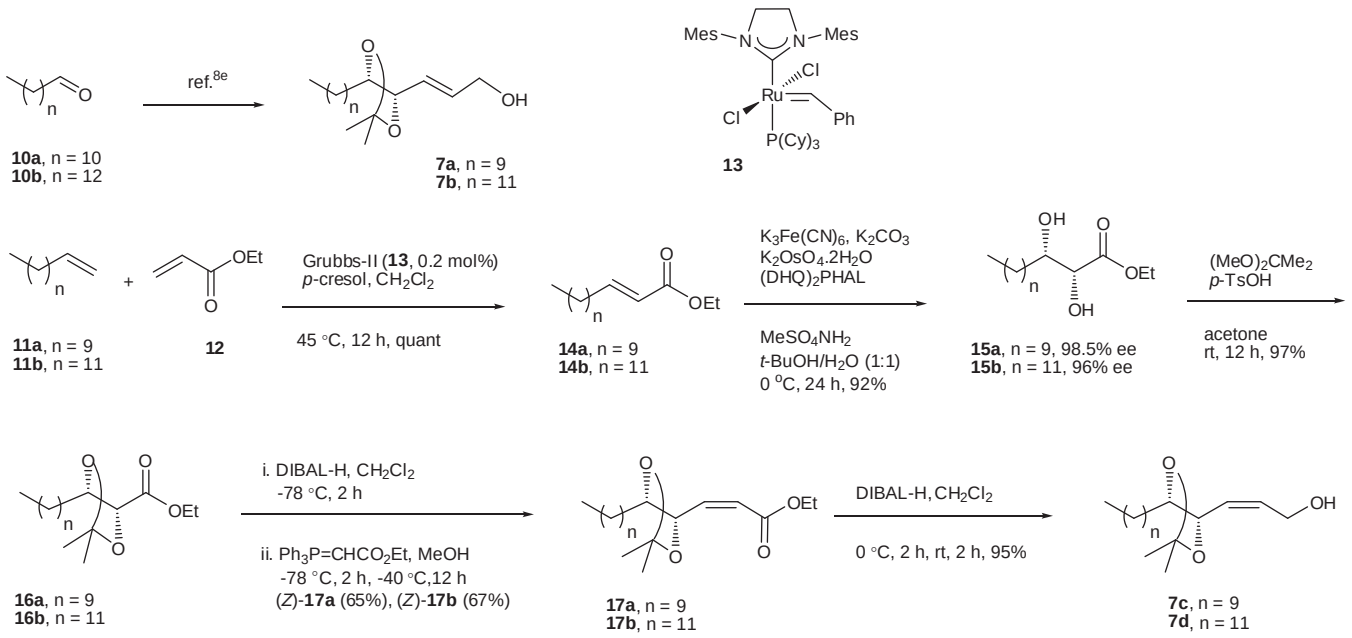
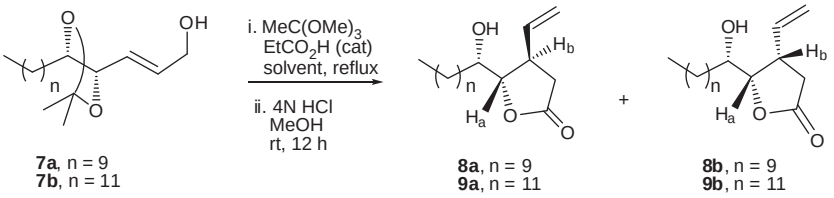


Scheme 1. Synthesis of allyl alcohols **7a**–**d**.

Table 1
Diastereoselective orthoester Johnson–Claisen rearrangement of **7a** or **7b**



Entry	Solvent (reaction time, h)	Allyl alcohol	**8a**:**8b**[a] (% yield)	**9a**:**9b**[a] (% yield)
1	Benzene (120)	**7a**	1:1 (78)	—
2	"	**7b**	—	1.3:1 (83)
3	$MeC(OMe)_3$ (44)	**7a**	1.3:1 (57)	—
4	"	**7b**	—	1.5:1 (57)
5	Toluene (24)	**7a**	2:1 (89)	—
6	"	**7b**	—	2:1 (86)
7	Xylene (4)	**7a**	1.1:1 (88)	—
8	"	**7b**	—	1.1:1 (88)
9	Mesitylene (4)	**7a**	1.2:1 (72)	—
10	"	**7b**	—	1.3:1 (71)
11	Decalin (2)	**7a**	1.1:1 (82)	—
12	"	**7b**	—	1.2:1 (78)

[a] Determined by ^1H NMR.

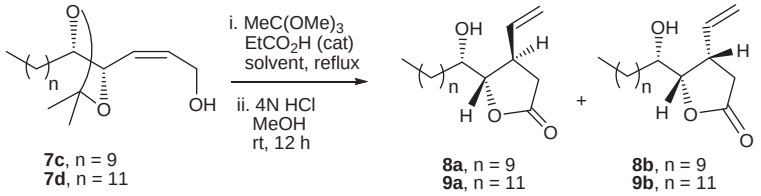
Johnson–Claisen rearrangement of allyl alcohols with a vicinal chiral dioxolane functionality and (*Z*)-olefin geometry. The results were successfully utilized in the total synthesis of (+)-nephrosterinic acid **5** and (+)-protolichesterinic acid **6**.

2. Results and discussion

We prepared the desired allyl alcohols **7a**–**d** as shown in Scheme 1. The allyl alcohols **7a** and **7b** were prepared from commercially available dodecanal **10a** and tetradecanal **10b** as reported earlier.[8e] The synthesis of **7c** and **7d** commenced from olefins **11a** and **11b** which on cross-metathesis[10] (using G-II, **13**, 0.2 mol %) with ethylacrylate **12**, provided α,β-unsaturated esters **14a**[11] and **14b**,[12] respectively, in quantitative yields and excellent (*E*)-stereoselectivity. The asymmetric dihydroxylation of **14a** and **14b** afforded the diols **15a** and **15b**, each in 92% yields and excellent enantioselectivity of 98.5%[11] and 96% ee,[13] respectively. The acetonide protection of diols provided **16a** and **16b**, each in a 97% yield. Subsequent DIBAL-H reduction of these esters to the corresponding aldehydes and (*Z*)-selective Wittig olefination with $Ph_3P{=}CHCO_2Et$ in MeOH gave (*Z*)-α,β-unsaturated esters **17a** (65%) and **17b** (67%).[14] Further reduction of the ester groups with DIBAL-H afforded the desired allyl alcohols **7c** and **7d** each in a 95% yield.

With the four allyl alcohols **7a**–**d** in hand, we subjected them to orthoester Johnson–Claisen rearrangement to investigate the

Table 2
Diastereoselective orthoester Johnson–Claisen rearrangement of **7c** or **7d**



7c, n = 9
7d, n = 11

8a, n = 9
9a, n = 11

8b, n = 9
9b, n = 11

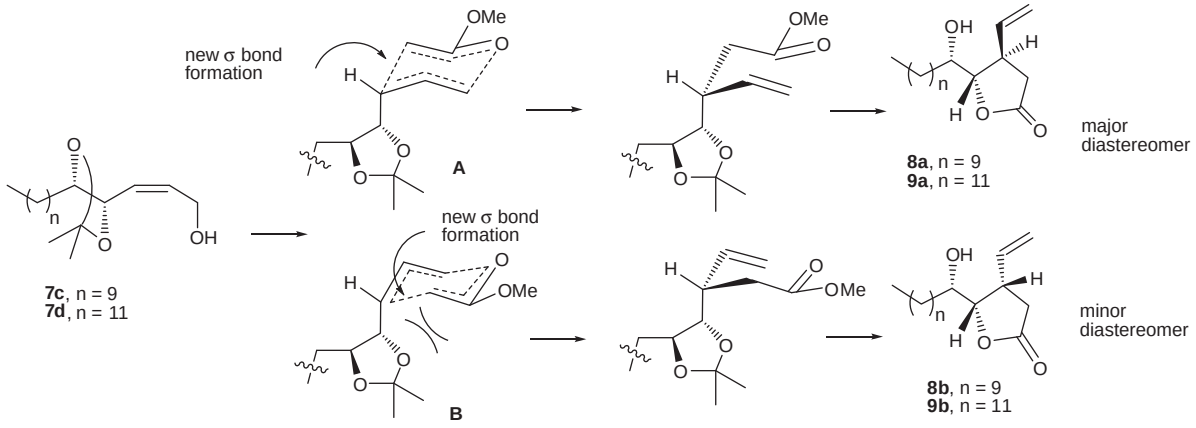
Entry	Solvent (reaction time, h)	Allyl alcohol	**8a**:**8b**[a] (% yield)	**9a**:**9b**[a] (% yield)
1	Benzene (120)	**7c**	7:1 (61)	—
2	"	**7d**	—	5:1 (60)
3	$MeC(OMe)_3$ (24)	**7c**	5:1 (88)	—
4	"	**7d**	—	6:1 (85)
5	Toluene (24)	**7c**	8:1 (89)	—
6	"	**7d**	—	8.7:1 (86)
7	Xylene (4)	**7c**	5:1 (88)	—
8	"	**7d**	—	45:1 (86)
9	Mesitylene (4)	**7c**	4:1 (89)	—
10	"	**7d**	—	4.5:1 (94)
11	Decalin (3)	**7c**	4:1 (84)	—
12	"	**7d**	—	3.5:1 (99)

[a] Determined by ^{1}H NMR.

diastereoselectivity based on the geometry of olefinic bond and the presence of a chiral vicinal dioxolane moiety. The results are shown in Tables 1 and 2. The allyl alcohol **7a** with an (*E*)-olefinic bond after orthoester Johnson–Claisen rearrangement in benzene and subsequent lactonization provided **8a** and **8b** as a 1:1 mixture (78%, entry 1, Table 1). The reaction was rather slow and required a longer time (120 h) for completion. The assignment of relative stereochemistry to lactones **8a** and **8b** comes from their ^{1}H NMR spectra. In lactone **8a** the proton H_a is *syn* to the double bond and gets shielded to δ = 4.09 ppm, while the same proton in **8b** is *anti* to the double bond and appears downfield at δ = 4.38 ppm. We have further confirmation of this stereochemistry from X-ray studies of similar lactones.[8c] The lactones **8a**/**8b** or **9a**/**9b** were easily separable by column chromatography. The allyl alcohol **7b** similarly gave **9a** and **9b** as a 1.3:1 mixture (83%, entry 2). A neat reaction in $MeC(OMe)_3$ did not improve the diastereoselectivity; and also yields of the mixture were lower (57%, entries 3 and 4). On changing the solvent to toluene and then to higher boiling solvents (entries 5–12), the diastereoselectivity did not change much except in toluene when the mixture of diastereomeric lactones were obtained in a 2:1 ratio (entries 5 and 6).

The allyl alcohol **7c** with (*Z*)-olefinic bond after orthoester Johnson–Claisen rearrangement in benzene and subsequent lactonization provided **8a** and **8b** as a 7:1 mixture (61%, entry 1, Table 2). Similarly **7d** gave **9a** and **9b** as a 5:1 mixture (60%, entry 2). The neat reaction in $MeC(OMe)_3$ gave similar results (entries 3 and 4). Changing the solvent to toluene, **7c** provided **8a** and **8b** as an 8:1 mixture and in good yields of 89% (entry 5), Similarly **7d** gave **9a** and **9b** in good diastereoselectivity of 8.7:1 and 86% yield (entry 6). With higher boiling solvents (entries 7–12), the diastereoselectivity gradually decreased. Thus the reaction in toluene over 24 h gave the best diastereoselectivity. In all cases the *anti*-diastereomer **8a** or **9a** was the major product.

The observed diastereoselectivity is in accordance with the literature reports.[9] Considering chairlike transition states, compound **7a** giving **8a** and **8b** in almost equal amounts could be due to the transition states of almost equal energy in which the chiral dioxolane moiety is placed equatorial. Similar is the case with **7b** giving **9a** and **9b** in equal amounts. However for **7c** (or **7d**) giving **8a** (or **9a**) as the major product could be due to involvement of lower energy transition state A (Scheme 2) wherein the new σ bond is formed from the side of the smaller H atom and away from the



7c, n = 9
7d, n = 11

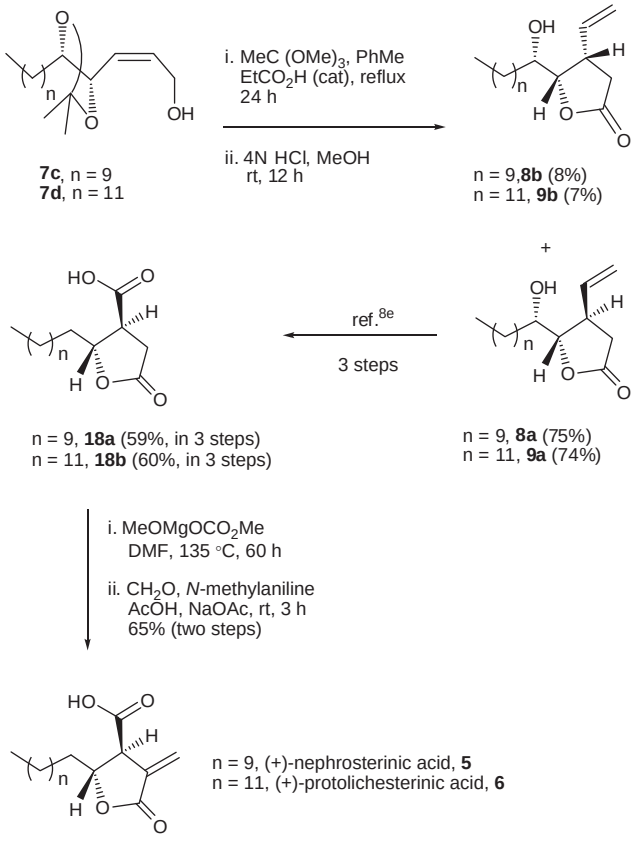
8a, n = 9
9a, n = 11

8b, n = 9
9b, n = 11

Scheme 2. Transition state models for orthoester Johnson–Claisen rearrangement of **7c** and **7d**.

axially placed dioxolane moiety. For transition state B, the new σ bond would be formed from the side of axially placed dioxolane moiety which would be sterically less favored. Hence **8b** or **9b** are minor products.

The best results of this study were further utilized to complete the total synthesis of (+)-nephrosterinic acid **5** and (+)-protolichesterinic acid **6** as shown in Scheme 3. The orthoester Johnson–Claisen rearrangement of the allyl alcohol (*Z*)-**7c** with trimethylorthoacetate in the presence of catalytic amounts of propionic acid in toluene solvent over 24 h and the same-pot hydrolysis (4 N HCl) provided a mixture of **8a** and **8b** in an 8:1 ratio. Flash column chromatography of this mixture yielded pure diastereomer **8a** in 75% and **8b** in 8% yields. Similarly, (*Z*)-**7d** gave **9a** (74%) and **9b** (7%). The lactones were fully characterized by spectroscopic and analytical data.[8e] The lactones **8a** and **9a** had the required functionality to set the β,γ-stereocenters of the target molecules **5** and **6**, respectively, while the free hydroxyl group in the side chain needs to be removed.



Scheme 3. Synthesis of (+)-nephrosterinic acid, **5** and (+)-protolichesterinic acid, **6**.

Further conversion of **8a** and **9a** to β-carboxylic acid group containing lactones **18a** and **18b**, respectively, was carried out as reported earlier in three steps[8e] in a 59% overall yield for **18a** and 60% for **18b**. The α-methylene group was very efficiently introduced following the literature procedure.[15] Thus treatment of **18a** with methoxy magnesium methylcarbonate, followed by formaldehyde and *N*-methylaniline gave (+)-nephrosterinic acid **5** in a 65% yield, $[\alpha]_D^{25} = +12.5$ (*c* 0.1, $CHCl_3$), lit.[6b] $[\alpha]_D^{32} = +13.0$ (*c* 0.6, $CHCl_3$). The introduction of α-methylene group similarly as above in **18b** provided (+)-protolichesterinic acid **6** in a 65% yield, $[\alpha]_D^{25} = +13.9$ (*c* 0.16, $CHCl_3$), lit.[7j] $[\alpha]_D^{25} = +14.2$ (*c* 0.95, $CHCl_3$). The spectral data for **5** and **6** were in full agreement with the literature data.[6b,7j]

3. Conclusions

In summary, we have synthesized varied allyl alcohols with an (*E*)- or (*Z*)-olefin geometry and having a chiral vicinal dioxolane moiety and demonstrated the strategic utility of the orthoester Johnson–Claisen rearrangement of these compounds to furnish the chiral β,γ-disubstituted-γ-lactones with good diastereoselectivity. These lactone diastereomers were efficiently separated and carried forward to complete the total synthesis of paraconic acids: (+)-nephrosterinic acid **5,** and (+)-protolichesterinic acid **6** in 10 steps and 15.9% and 16.4% overall yields, respectively. Further application of this strategy toward the synthesis of other natural products is in progress in our laboratory.

4. Experimental

4.1. General information

Dry reactions were carried out under an atmosphere of Ar or N_2. Solvents and reagents were purified by standard methods. Thin-layer chromatography was performed on EM 250 Kieselgel 60 F254 silica gel plates. The spots were visualized by staining with $KMnO_4$ or by a UV lamp. ^{1}H NMR and ^{13}C NMR were recorded on Varian Mercury Plus, AS400 spectrometer and Bruker, AVANCE III 400 spectrometer. The chemical shifts are based on TMS peak at $\delta = 0.00$ pm for proton NMR and $CDCl_3$ peak at $\delta = 77.00$ ppm (t) in carbon NMR. IR spectra were obtained on Perkin Elmer Spectrum One FT-IR spectrometer. Optical rotations were measured with Jasco P-2000 polarimeter. HRMS was recorded using Micromass: Q-Tof micro (YA-105) spectrometer. HPLC was performed with JASCO-PU-2089PLUS quaternary gradient pump with MD-2010 PLUS multiwavelength Detector.

4.1.1. (*E*)-Ethyl tridec-2-enoate 14a[11]

A solution of dodecene **11a** (1.0 g, 5.94 mmol), ethyl acrylate (1.3 mL, 12.18 mmol, 2.05 equiv), and *p*-cresol (0.321 g, 2.97 mmol, 50 mol %) in CH_2Cl_2 (20 mL) was degassed with N_2 for 20 min. Grubbs II catalyst (10.1 mg, 11.9 μmol, 0.2 mol %) was then added and the reaction mixture refluxed for 12 h. It was then concentrated and the residue purified by silica gel column chromatography using petroleum ether/EtOAc (4:1) as eluent to afford **14a** (1.42 g, quant) as a colorless oil. IR ($CHCl_3$): $\nu_{max} = 3019$, 2930, 2858, 1711, 1656, 1471, 1366, 1274, 1125, 1044, 929, 669 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, $J = 6.9$ Hz, 3H, *CH*$_3$), 1.24–1.46 (m, 19H, *CH*$_3$, *H*-5, *H*-6, *H*-7, *H*-8, *H*-9, *H*-10, *H*-11, *H*-12), 2.17–2.21 (m, 2H, *H*-4), 4.17 (q, $J = 7.1$ Hz, 2H, *OCH*$_2$), 5.80 (dt, $J = 15.7$, 1.5 Hz, 1H, *H*-2), 6.96 (dt, $J = 15.6$, 6.9 Hz, 1H, *H*-3). HRMS (ESI$^+$): Calcd for [$C_{15}H_{28}O_2$+H] 241.2168. Found: 241.2174.

4.1.2. (*E*)-Ethyl pentadec-2-enoate 14b[12]

The title compound was prepared from tetradecene **11b** (1.0 g, 5.09 mmol) by a procedure similar to that described for the conversion of **11a** to **14a** to give **14b** (1.366 g, quant) as a colorless oil. IR ($CHCl_3$): ν_{max} 3021, 2928, 2856, 1715, 1656, 1467, 1369, 1274, 1128, 1045, 981, 669 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, $J = 6.8$ Hz, 3H, *CH*$_3$), 1.22–1.46 (m, 23H, *CH*$_3$, *H*-5, *H*-6, *H*-7, *H*-8, *H*-9, *H*-10, *H*-11, *H*-12, *H*-13, *H*-14), 2.16–2.21 (m, 2H, *H*-4), 4.21 (q, $J = 7.1$ Hz, 2H, *OCH*$_2$), 5.81 (dt, $J = 15.7$, 1.5 Hz, 1H, *H*-2), 6.96 (dt, $J = 15.6$, 6.9 Hz, 1H, *H*-3). ^{13}C NMR (100 MHz, CDCl3): δ 166.8, 149.6, 121.1, 60.1, 32.2, 31.9, 29.64 (2C), 29.61, 29.5, 29.4, 29.3, 29.1, 28.0, 22.7, 14.3, 14.1. HRMS(ESI$^+$): Calcd for [$C_{17}H_{32}O_2$+H] 269.2481. Found: 269.2488.

4.1.3. (2*R*,3*S*)-Ethyl 2,3-dihydroxytridecanoate 15a[11]

To a mixture of $K_3Fe(CN)_6$ (4.11 g, 12.48 mmol, 3.0 equiv), K_2CO_3 (1.726 g, 12.48 mmol, 3.0 equiv), $MeSO_2NH_2$ (0.395 g, 4.16 mmol, 1.0 equiv), $(DHQ)_2$-PHAL (32.4 mg, 0.0416 mmol, 1.0 mol %) and $K_2OsO_4{\cdot}2H_2O$ (6.2 mg, 16.7 μmol, 0.4 mol %) in *t*-BuOH (11 mL) and water (21 mL) at 0 °C was added α,β-unsaturated ester **14a** (1.0 g, 4.16 mmol) in *t*-BuOH (10 mL). The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid Na_2SO_3 and stirred for 30 min. The solution was extracted with EtOAc (3 × 30 mL) and combined organic layers were washed with 1 M KOH (20 mL), water (25 mL), brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (1:1) as eluent to afford **15a** (1.05 g, 92%) as a white solid. Mp 63–65 °C. $[\alpha]_D^{25} = -9.9$ (*c* 1.26, $CHCl_3$). IR ($CHCl_3$): ν_{max} 3449, 3020, 2928, 2857, 1735, 1467, 1370, 1101, 1020, 930, 669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.8 Hz, 3H, *CH*$_3$), 1.26–1.41 (m, 19H, *CH*$_3$, *H*-5, *H*-6, *H*-7, *H*-8, *H*-9, *H*-10, *H*-11, *H*-12), 1.58–1.63 (m, 2H, *H*-4), 3.88 (dt, *J* = 6.3, 1.8 Hz, 1H, *H*-3), 4.09 (d, *J* = 2.0 Hz, 1H, *H*-2), 4.30 (q, *J* = 7.2 Hz, 2H, *OCH*$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 73.0, 72.5, 62.1, 33.8, 31.9, 29.6 (2C), 29.5, 29.48, 29.3, 25.7, 22.7, 14.1, 14.09. HRMS (ESI^+): Calcd for [$C_{15}H_{30}O_4$+H] 275.2223. Found: 275.2220.

4.1.4. (2*R*,3*S*)-Ethyl 2,3-dihydroxypentadecanoate 15b[13]

The title compound was prepared from **14b** (1.3 g, 4.84 mmol) by a procedure similar to that described for the conversion of **14a** to **15a** to give **15b** (1.345 g, 92%) as a white solid. Mp 70–71 °C. $[\alpha]_D^{25} = -7.8$ (*c* 1.4, $CHCl_3$). IR ($CHCl_3$): ν_{max} 3514, 3020, 2928, 2856, 1732, 1524, 1467, 1446, 1422, 1390, 1102, 1029, 929, 669, 626 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.8 Hz, 3H, *CH*$_3$), 1.26–1.42 (m, 23H, *CH*$_3$, *H*-5, *H*-6, *H*-7, *H*-8, *H*-9, *H*-10, *H*-11, *H*-12, *H*-13, *H*-14), 1.57–1.64 (m, 2H, *H*-4), 1.85 (br s, 1H, *OH*), 3.05 (br s, 1H, *OH*), 3.89 (dt, *J* = 6.8, 1.9 Hz, 1H, *H*-3), 4.08 (d, *J* = 2.0 Hz, 1H, *H*-2), 4.29 (q, *J* = 7.1 Hz, 2H, *OCH*$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 73.0, 72.5, 62.1, 33.8, 31.9, 29.64 (2C), 29.61, 29.55, 29.53, 29.5, 29.3, 25.7, 22.7, 14.1, 14.08. HRMS (ESI^+): Calcd for [$C_{17}H_{34}O_4$+H] 303.2536. Found: 303.2542.

4.1.5. (2*R*,3*S*)-Ethyl 2,3-(isopropylidenedioxy)tridecanoate 16a

To a solution of diol **15a** (0.84 g, 3.06 mmol) in acetone (25 mL) was added *p*-TsOH (catalytic) and 2,2-dimethoxypropane (0.94 mL, 7.65 mmol, 2.5 equiv) and the reaction mixture stirred at room temperature for 12 h. $NaHCO_3$ (0.2 g) was added to the reaction mixture and stirred for additional 30 min and then filtered through a pad of silica gel. The filtrate was concentrated and the residue purified by silica gel column chromatography using petroleum ether/EtOAc (3:2) as eluent to afford **16a** (0.933 g, 97%) as a colorless oil. $[\alpha]_D^{25} = -14.6$ (*c* 0.6, $CHCl_3$). IR ($CHCl_3$): ν_{max} 2988, 2928, 2857, 1755, 1660, 1466, 1382, 1373, 1216, 1099, 1034, 861, 668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.8 Hz, 3H, *CH*$_3$), 1.27–1.36 (m, 19H, *CH*$_3$, *H*-5, *H*-6, *H*-7, *H*-8, *H*-9, *H*-10, *H*-11, *H*-12), 1.48 (s, 3H, *CH*$_3$), 1.49 (s, 3H, *CH*$_3$), 1.63–1.87 (m, 2H, *H*-4), 4.11–4.13 (m, 2H, *H*-2, *H*-3), 4.24 (q, *J* = 7.0 Hz, 2H, *OCH*$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 110.7, 79.2, 79.1, 61.3, 33.5, 31.9, 29.6, 29.54, 29.5, 29.46, 29.3, 27.2, 25.64, 25.6, 22.7, 14.2, 14.1. HRMS (ESI^+): Calcd for [$C_{18}H_{34}O_4$+H] 315.2536. Found: 315.2545.

4.1.6. (2*R*,3*S*)-Ethyl 2,3-(isopropylidenedioxy)pentadecanoate 16b

The title compound was prepared from **15b** (1.2 g, 3.96 mmol) by a procedure similar to that described for the conversion of **15a** to **16a** to give acetonide ester **16b** (1.32 g, 97%) as a colorless oil. $[\alpha]_D^{25} = -10.8$ (*c* 0.74, $CHCl_3$). IR ($CHCl_3$): ν_{max} 3020, 2991, 2928, 2856, 1749, 1657, 1523, 1467, 1383, 1374, 1099, 1031, 929, 877, 857, 669, 626 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.8 Hz, 3H, *CH*$_3$), 1.25–1.31 (m, 23H, *CH*$_3$, *H*-5, *H*-6, *H*-7, *H*-8, *H*-9, *H*-10, *H*-11, *H*-12, *H*-13, *H*-14), 1.44 (s, 3H, *CH*$_3$), 1.47 (s, 3H, *CH*$_3$), 1.63–1.80 (m, 2H, *H*-4), 4.10–4.20 (m, 2H, *H*-2, *H*-3), 4.22 (q, *J* = 7.0 Hz, 2H, *OCH*$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 110.7, 79.2, 79.1, 61.2, 33.5, 31.9, 29.61 (2C), 29.6, 29.5, 29.46, 29.4, 29.3, 27.1, 25.6, 25.58, 22.6, 14.1, 14.06. HRMS (ESI^+): Calcd for [$C_{20}H_{38}O_4$+H] 343.2849. Found: 343.2855.

4.1.7. (4*S*,5*S*,*Z*)-Ethyl 4,5-(isopropylidenedioxy)pentadec-2-enoate 17a

To a solution of ester **16a** (0.8 g, 2.54 mmol) in CH_2Cl_2 (40 mL) at −78 °C was added DIBAL-H (1.54 mL, 2.69 mmol, 1.75 M solution in toluene, 1.06 equiv). The reaction mixture was stirred for 2 h and then quenched by adding a saturated aqueous solution of potassium–sodium–tartarate (5 mL) and stirred for 1 h. It was then extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were washed with water, brine, dried (Na_2SO_4), and concentrated. The crude aldehyde was dissolved in MeOH (25 mL), cooled to −78 °C and $Ph_3P{=}CHCO_2Et$ (1.062 g, 3.05 mmol, 1.2 equiv) was added. The reaction mixture was stirred at −78 °C for 2 h and then at −40 °C for 12 h. It was warmed to room temperature and concentrated. The residue was purified by flash column chromatography using petroleum ether/EtOAc (5:1) as eluent to afford **17a** (0.563 g, 65%) as a colorless oil. $[\alpha]_D^{25} = +37.1$ (*c* 0.6, $CHCl_3$). IR ($CHCl_3$): ν_{max} 3020, 2928, 2856, 1719, 1659, 1512, 1467, 1419, 1372, 1031, 929, 876, 669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.9 Hz, 3H, *CH*$_3$), 1.25–1.50 (m, 19H, *CH*$_3$, *H*-7, *H*-8, *H*-9, *H*-10, *H*-11, *H*-12, *H*-13, *H*-14), 1.42 (s, 3H, *CH*$_3$), 1.43 (s, 3H, *CH*$_3$), 1.58–1.65 (m, 2H, *H*-6), 3.68–3.73 (m, 1H, *H*-5), 4.18 (q, *J* = 7.1 Hz, 2H, *OCH*$_2$), 5.27 (dt, *J* = 8.5, 1.0 Hz, 1H, *H*-4), 5.94 (dd, *J* = 11.8, 1.0 Hz, 1H, *H*-2), 6.13 (dd, *J* = 11.7, 8.8 Hz, 1H, *H*-3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 145.4, 123.1, 109.1, 81.1, 76.1, 60.4, 32.0, 31.9, 29.7, 29.6, 29.55, 29.5, 29.3, 27.3, 27.1, 26.1, 22.7, 14.2, 14.1. HRMS (ESI+): Calcd for [$C_{20}H_{36}O_4$+H] 341.2693. Found: 341.2688.

4.1.8. (4*S*,5*S*,*Z*)-Ethyl 4,5-(isopropylidenedioxy)heptadec-2-enoate 17b

The title compound was prepared from **16b** (0.9 g, 2.63 mmol) by a procedure similar to that described for the conversion of **16a** to **17a** to give acetonide ester **17b** (0.65 g, 67%) as a colorless oil. $[\alpha]_D^{25} = +32.6$ (*c* 0.4, $CHCl_3$). IR ($CHCl_3$): ν_{max} 2986, 2927, 2855, 1725, 1657, 1466, 1418, 1380, 1371, 1193, 1047, 929, 874, 826, 668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.9 Hz, 3H, *CH*$_3$), 1.27–1.50 (m, 23H, *CH*$_3$, *H*-7, *H*-8, *H*-9, *H*-10, *H*-11, *H*-12, *H*-13, *H*-14, *H*-15, *H*-16), 1.42 (s, 3H, *CH*$_3$), 1.43 (s, 3H, *CH*$_3$), 1.60–1.65 (m, 2H, *H*-6), 3.68–3.74 (m, 1H, *H*-5), 4.18 (q, *J* = 7.1 Hz, 2H, *OCH*$_2$), 5.27 (dt, *J* = 8.5, 1.0 Hz, 1H, *H*-4), 5.94 (dd, *J* = 11.8, 1.1 Hz, 1H, *H*-2), 6.13 (dd, *J* = 11.7, 8.8 Hz, 1H, *H*-3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 145.5, 123.1, 109.1, 81.1, 76.1, 60.4, 32.0, 31.9, 29.7, 29.63 (3C), 29.6, 29.5, 29.3, 27.4, 27.1, 26.1, 22.7, 14.2, 14.1. HRMS (ESI^+): Calcd for [$C_{22}H_{40}O_4$+H] 369.3006. Found: 369.3011.

4.1.9. (4*S*,5*S*,*Z*)-4,5-(Isopropylidenedioxy)pentadec-2-en-1-ol 7c

To a solution of the acetonide ester **17a** (0.41 g, 1.204 mmol) in CH_2Cl_2 (20 mL) was added DIBAL-H (1.51 mL, 2.65 mmol, 1.75 M solution in toluene, 2.2 equiv) dropwise at 0 °C. The reaction mixture was stirred for 2 h and warmed to room temperature and stirred for 2 h. It was then quenched by adding a saturated aqueous solution of potassium–sodium–tartarate (5 mL) and stirred for 2 h. It was then extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were washed with water, brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography using petroleum ether/EtOAc (3:2) as eluent

to afford **7c** (0.34 g, 95%) as a colorless oil. $[\alpha]_D^{25} = +2.1$, (*c* 0.54, $CHCl_3$). IR ($CHCl_3$): ν_{max} 3682, 3613, 3448, 3019, 2989, 2929, 2856, 1602, 1523, 1466, 1381, 1372, 1164, 1042, 930, 876, 669, 626 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.8 Hz, 3H, *CH*$_3$), 1.15–1.70 (m, 18H, *H*-6, *H*-7, *H*-8, *H*-9, *H*-10, *H*-11, *H*-12, *H*-13, *H*-14), 1.41 (s, 3H, *CH*$_3$), 1.42 (s, 3H, *CH*$_3$), 3.65–3.70 (m, 1H, *H*-5), 4.11–4.21 (m, 1H, *H*-4), 4.31–4.36 (m, 2H, *H*-1), 5.48–5.54 (m, 1H, *H*-2), 5.85–5.92 (m, 1H, *H*-3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.2, 128.5, 108.6, 80.9, 76.7, 58.6, 31.9, 31.7, 29.7, 29.54, 29.5, 29.4, 29.3, 27.3, 27.0, 26.0, 22.6, 14.1. HRMS (ESI^+): Calcd for [$C_{18}H_{34}O_3$+H] 299.2587. Found: 299.2594.

4.1.10. (4*S*,5*S*,*Z*)-4,5-(Isopropylidenedioxy)heptadec-2-en-1-ol 7d

The title compound was prepared from **17b** (0.5 g, 1.36 mmol) by a procedure similar to that described for the conversion of **17a** to **7c** to give allyl alcohol **7d** (0.42 g, 95%) as a colorless oil. $[\alpha]_D^{25} = +2.9$ (*c* 0.6, $CHCl_3$). IR ($CHCl_3$): ν_{max} 3684, 3616, 3432, 3019, 2928, 2856, 1687, 1603, 1523, 1468, 1422, 1382, 1047, 929, 877, 669, 626 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.7 Hz, 3H, *CH*$_3$), 1.15–1.80 (m, 22H, *H*-6, *H*-7, *H*-8, *H*-9, *H*-10, *H*-11, *H*-12, *H*-13, *H*-14, *H*-15, *H*-16), 1.41 (s, 3H, *CH*$_3$), 1.42 (s, 3H, *CH*$_3$), 3.64–3.70 (m, 1H, *H*-5), 4.16–4.21 (m, 1H, *H*-4), 4.31–4.36 (m, 2H, *H*-1), 5.50–5.56 (m, 1H, *H*-2), 5.85–5.92 (m, 1H, *H*-3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.1, 128.5, 108.6, 80.9, 76.7, 58.6, 31.9, 31.7, 29.7, 29.62 (2C), 29.6, 29.5, 29.46, 29.3, 27.3, 27.0, 26.0, 22.6, 14.1. HRMS (ESI^+): Calcd for [$C_{20}H_{38}O_3$+H] 327.2900. Found: 327.2908.

4.1.11. (4*R*,5*S*)-5-[(*S*)-1-Hydroxyundecyl]-4-vinyl-4,5-dihydrofuran-2(3*H*)-one 8a and (4*S*,5*S*)-5-[(*S*)-1-hydroxyundecyl]-4-vinyl-4,5-dihydrofuran-2(3*H*)-one 8b

To a solution of allyl alcohol **7c** (0.6 g, 2.01 mmol) in toluene (15 mL) were added trimethylorthoacetate (2.41 g, 20.10 mmol, 10.0 equiv) and $EtCO_2H$ (catalytic), and the solution refluxed for 24 h. After cooling to room temperature, the volatile material was removed under reduced pressure and the residue (0.72 g) was dissolved in MeOH (30 mL). To this was added 4 N HCl (5 mL) and stirred for 12 h at room temperature. It was then quenched with powdered $NaHCO_3$ (1.0 g) and filtered. The filtrate was concentrated and the residue purified by silica gel flash column chromatography (petroleum ether/EtOAc, 9:1) to provide **8b** (45 mg, 8%) as a colorless oil. Further elution gave **8a** (426 mg, 75%) as a colorless oil. Data for **8a**: $[\alpha]_D^{25} = +37.0$ (*c* 0.32, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.5 Hz, 3H, *CH*$_3$), 1.25–1.39 (m, 16H, *H*-3′, *H*-4′, *H*-5′, *H*-6′, *H*-7′, *H*-8′, *H*-9′, *H*-10′), 1.38–1.74 (m, 3H, *H*-2′, *OH*), 2.46 (dd, *J* = 17.7, 10.3 Hz, 1H, H_A-3), 2.78 (dd, *J* = 17.7, 8.9 Hz, 1H, H_B-3), 3.21–3.25 (m, 1H, *H*-4), 3.58–3.61 (m, 1H, *H*-1′), 4.09 (d, *J* = 8.3 Hz, 1H, *H*-5), 5.16 (d, *J* = 10.7 Hz, 1H, *H*-vinyl), 5.21 (d, *J* = 17.4 Hz, 1H, *H*-vinyl), 5.71–5.78 (m, 1H, *H*-vinyl). Data for **8b**: $[\alpha]_D^{25} = +40.1$ (*c* 0.28, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.8 Hz, 3H, *CH*$_3$), 1.18–1.31 (m, 16H, *H*-3′, *H*-4′, *H*-5′, *H*-6′, *H*-7′, *H*-8′, *H*-9′, *H*-10′), 1.36–1.77 (m, 3H, *H*-2′, *OH*), 2.59 (dd, *J* = 17.2, 9.2 Hz, 1H, H_A-3), 2.69 (dd, *J* = 17.2, 9.2 Hz, 1H, H_B-3), 3.21–3.25 (m, 1H, *H*-4), 3.71–3.80 (m, 1H, *H*-1′), 4.38 (dd, *J* = 8.1, 2.9 Hz, 1H, *H*-5), 5.20 (d, *J* = 15.8 Hz, 1H, *H*-vinyl), 5.22 (d, *J* = 11.4 Hz, 1H, *H*-vinyl), 5.85–6.02 (m, 1H, *H*-vinyl). Other spectroscopic data and analysis for **8a** and **8b** are the same as reported earlier.[8e]

4.1.12. (4*R*,5*S*)-5-[(*S*)-1-Hydroxytridecyl]-4-vinyl-4,5-dihydrofuran-2(3*H*)-one 9a and (4*S*5*S*)-5-[(*S*)-1-hydroxytridecyl]-4-vinyl-4,5-dihydrofuran-2(3*H*)-one 9b

The title compounds were prepared from **7d** (0.5 g, 1.53 mmol) by a procedure similar to that described for the conversion of **7c** to **8a** and **8b**. The reaction afforded **9b** (33 mg, 7%) and **9a** (352 mg, 74%) as colorless oils. Data for **9a**: $[\alpha]_D^{25} = +37.6$ (*c* 0.22, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.9 Hz, 3H, *CH*$_3$), 1.18–1.30 (m, 20H, *H*-3′, *H*-4′, *H*-5′, *H*-6′, *H*-7′, *H*-8′, *H*-9′, *H*-10′, *H*-11′, *H*-12′), 1.35–1.75 (m, 3H, *H*-2′, *OH*), 2.47 (dd, *J* = 17.7, 10.1 Hz, 1H, H_A-3), 2.78 (dd, *J* = 17.4, 8.9 Hz, 1H, H_B-3), 3.21–3.25 (m, 1H, *H*-4), 3.56–3.61 (m, 1H, *H*-1′), 4.10 (dd, *J* = 8.3, 2.4 Hz, 1H, *H*-5), 5.18 (d, *J* = 10.7 Hz, 1H, *H*-vinyl), 5.22 (d, *J* = 17.1 Hz, 1H, *H*-vinyl), 5.72–5.79 (m, 1H, *H*-vinyl). Data for **9b**: $[\alpha]_D^{25} = +34.2$ (*c* 0.38, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.7 Hz, 3H, *CH*$_3$), 1.19–1.33 (m, 20H, *H*-3′, *H*-4′, *H*-5′, *H*-6′, *H*-7′, *H*-8′, *H*-9′, *H*-10′, *H*-11′, *H*-12′), 1.36–1.76 (m, 3H, *H*-2′, *OH*), 2.59 (dd, *J* = 17.3, 9.0 Hz, 1H, H_A-3), 2.69 (dd, *J* = 17.5, 9.0 Hz, 1H, H_B-3), 3.20–3.24 (m, 1H, *H*-4), 3.71–3.80 (m, 1H, *H*-1′), 4.38 (dd, *J* = 7.9, 2.7 Hz, 1H, *H*-5), 5.21 (d, *J* = 11.3 Hz, 1H, *H*-vinyl), 5.22 (d, *J* = 15.9 Hz, 1H, *H*-vinyl), 5.85–6.01 (m, 1H, *H*-vinyl). Other spectral data and analysis for **9a** and **9b** are same as reported earlier.[8e]

4.1.13. (2*R*,3*S*)-4-Methylene-5-oxo-2-undecyltetrahydrofuran-3-carboxylic acid/(+)-nephrosterinic acid 5

Methoxy magnesium methylcarbonate (Stiles reagent, 4.3 mL, 8.64 mmol, 38.0 equiv, 2 M solution in DMF) was added under an inert atmosphere to **18a** (64.5 mg, 0.227 mmol) and the solution stirred at 135 °C for 60 h. After cooling the reaction mixture was acidified with dropwise addition of cold 10% HCl (15 mL) at 0 °C. Then CH_2Cl_2 (25 mL) was added to the mixture and stirred for 0.5 h. The aqueous layer was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was treated with 3 mL of a freshly prepared stock solution [HOAc (10 mL), 37% formaldehyde in water (7.5 mL), *N*-methylaniline (2.6 mL) and NaOAc (0.3 g)] and stirred for 3 h at room temperature. Brine solution (20 mL, containing 2 mL conc. HCl) was added and the aqueous layer extracted with Et_2O (5 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel flash column chromatography (CH_2Cl_2/EtOAc, 19:1) to furnish **5** (43.7 mg, 65%) as a white solid. Mp 82–84 °C, $[\alpha]_D^{25} = +12.5$ (*c* 0.1, $CHCl_3$); lit.[6b] Mp 86–88 °C, $[\alpha]_D^{32} = +13.0$ (*c* 0.66, $CHCl_3$). IR ($CHCl_3$): ν_{max} 3684, 3020, 2958, 2928, 2856, 1763, 1719, 1602, 1523, 1475, 1423, 1117, 1018, 929, 850, 669, 626 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, *J* = 6.8 Hz, 3H, *CH*$_3$), 1.11–1.60 (m, 18H, *H*-2′, *H*-3′, *H*-4′, *H*-5′, *H*-6′, *H*-7′, *H*-8′, *H*-9′, *H*-10′), 1.65–1.80 (m, 2H, *H*-1′), 3.58–3.64 (m, 1H, *H*-3), 4.78–4.82 (m, 1H, *H*-2), 6.01 (d, *J* = 3.0 Hz, 1H, *H*-vinyl), 6.45 (d, *J* = 3.0 Hz, 1H, *H*-vinyl). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.2, 168.2, 132.7, 125.6, 78.9, 49.4, 35.7, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 24.8, 22.7, 14.1. HRMS (ESI^+): Calcd for [$C_{17}H_{28}O_4$+H] 297.2066. Found: 297.2072.

4.1.14. (2*R*,3*S*)-4-Methylene-5-oxo-2-tridecyltetrahydrofuran-3-carboxylic acid/(+)-protolichesterinic acid (6)

The title compound was prepared from **18b** (55 mg, 0.176 mmol) by a procedure similar to that described for the conversion of **18a** to **5** to give **6** (37.1 mg, 65%) as a white solid. Mp 101–103 °C, $[\alpha]_D^{25} = +13.9$ (*c* 0.16, $CHCl_3$); lit.[7j] Mp 103–104 °C, $[\alpha]_D^{25} = +14.2$ (*c* 0.95, $CHCl_3$). IR ($CHCl_3$): ν_{max} 3682, 3020, 2927, 2855, 1759, 1714, 1602, 1516, 1466, 1378, 1109, 1023, 929, 669, 626 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, *J* = 6.7 Hz, 3H, *CH*$_3$), 1.08–1.62 (m, 22H, *H*-2′, *H*-3′, *H*-4′, *H*-5′, *H*-6′, *H*-7′, *H*-8′, *H*-9′, *H*-10′, *H*-11′, *H*-12′), 1.65–1.81 (m, 2H, *H*-1′), 3.59–3.63 (m, 1H, *H*-3), 4.78–4.82 (m, 1H, *H*-2), 6.01 (d, *J* = 2.9 Hz, 1H, *H*-vinyl), 6.45 (d, *J* = 2.9 Hz, 1H, *H*-vinyl). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.9, 168.3, 132.7, 125.6, 79.0, 49.6, 35.7, 31.9 (2C), 29.6, 29.5 (3C), 29.4, 29.3, 29.2, 24.8, 22.7, 14.1. HRMS (ESI^+): Calcd for [$C_{19}H_{32}O_4$+H] 325.2379. Found: 325.2386.

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