Enantioselective Synthesis of Paraconic Acids

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Dedicated to Professor Volker Jäger on the occasion of his 60th birthday

Abstract: The development of a new method for the enantioselective synthesis of disubstituted γ-butyrolactones is reported. Based on this strategy, the total synthesis of three paraconic acids, that is (−)-roccellaric acid, (−)-nephrosteranic acid and (−)-protopraesorediosic acid, and the formal total synthesis of (−)-methylenolactocin and (−)-protolichesterinic acid is described, which are important because of their antibiotic and antitumor properties. Key steps of the synthesis are copper(I)-catalyzed asymmetric cyclopropanations of furans, highly diastereoselective Sakurai allylations, Lewis acid or Lewis base catalyzed retroaldol/lactonization cascades, and ruthenium(II)-catalyzed, intermolecular cross metathesis reactions.

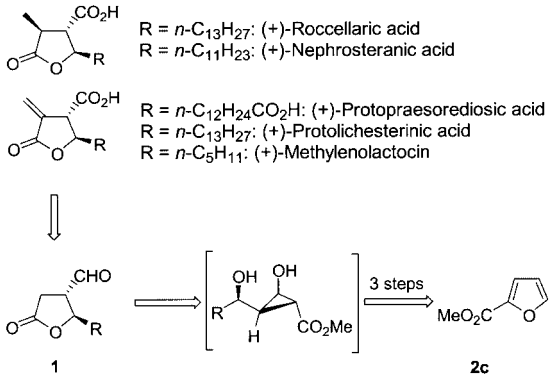
Keywords: asymmetric synthesis · lactones · metathesis · natural products · total synthesis

Introduction

γ-Butyrolactones are a most frequently occurring structural element in organic compounds and are present in about 10% of all natural products.[1] They are equivalent to 4-hydroxycarbonyl compounds (homoaldols),[2] but in comparison to the vast methodology available for the synthesis of aldol compounds[3] (3-hydroxycarbonyl compounds), there are relatively few asymmetric methods known for their de novo synthesis.[4]

Trisubstituted γ-butyrolactones,[5] especially paraconic acids (= 3-carboxylic acid substituted γ-butyrolactones) have attracted considerable interest because of their antibiotic and antitumor properties.[6] Therefore a number of syntheses have been developed leading to these natural products either in racemic[7] or enantiopure form using starting materials from the chiral pool,[8] chiral auxiliaries,[9] or applying catalytic asymmetric methodology.[10] We present here a strategy for the catalytic asymmetric synthesis of *anti*-2,3-disubstituted γ-butyrolactones **1** from furancarboxylic methyl esters **2** (Scheme 1) and the subsequent synthesis of a several paraconic acids.[11]

Vicinal substituted hydroxycyclopropane carboxylates have been widely recognized as versatile surrogates for acyclic



Scheme 1. Retrosynthetic analysis of paraconic acids.

building blocks.[12] Most relevant to our work, Reißig et al. have elegantly demonstrated the use of cyclopropanols (*rac*)-**4** for the synthesis of lactols (*rac*)-**3** as precursors to paraconic acids (Scheme 2).[13] While in the latter approach all cyclopropyl carbon atoms of (*rac*)-**3** end up in the lactol ring, our synthesis of γ-butyrolactones **5** or **6**, respectively, is achieved from the cyclopropanol **7** utilizing two of the cyclopropane ring carbons while the third atom forms the exocyclic carboxylic acid function as the decisive structural element found in all paraconic acids. What makes this strategy especially attractive is the fact that **7** and consequently **5** and **6** can be readily synthesized in a highly diastereo- and enantioselective manner in both optical forms from furan-2-carboxylic ethyl ester using an asymmetric copper-catalyzed cyclopropanantion as the key step.

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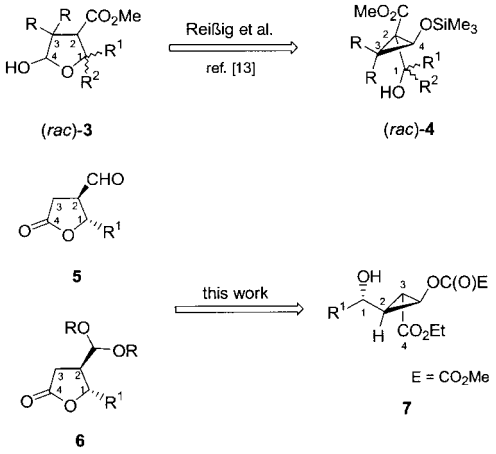
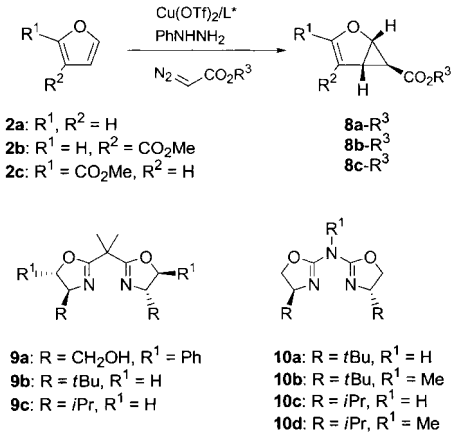


Scheme 2. Cyclopropanols as precursors to γ-butyrolactols and γ-butyrolactones.

Asymmetric cyclopropanation of furans: The copper(I)- or rhodium(II)-catalyzed cyclopropanation of furans with diazo esters[14] or diazomethane[15] has been described to yield 2-oxa[3.1.0]bicyclohexenes. We have been able to render this process asymmetric by treating furans **2** with methyl diazoacetate in the presence of catalytic amounts of chiral copper(I) bisoxazoline complexes[16] (Scheme 3, Table 1). However, furan **2a** proved to be a poor substrate both in terms of yield



Scheme 3. Asymmetric cyclopropanation of **2** with diazoacetates.

Abstract in German: *Aufbauend auf einer neuen, allgemein anwendbaren Strategie zur Synthese von disubstituierten γ-Butyrolactonen gelang die enantioselektive Totalsynthese von drei verschiedenen Paraconsäuren, (−)-Roccellarinsäure, (−)-Nephrosteraninsäure und (−)-Protopraesoridiosinsäure, sowie die formale Totalsynthese von (−)-Methylenolactocin und (−)-Protolichesterinsäure, die aufgrund ihrer antibiotischen und Antitumoreigenschaften von Bedeutung sind. Schlüsselschritte der Synthesen sind Kupfer-katalysierte, asymmetrische Cyclopropanierungen von Furanen, hoch diastereoselektive Sakurai Allylierungen, Lewissäure- oder basenkatalysierte Retroaldol-Lactonisierungskaskaden sowie Ruthenium-katalysierte, intermolekulare Metathese Reaktionen.*

Table 1. Asymmetric cyclopropanation of **2** with diazoacetates.[a]

Entry	Furan **2**	Diazoaceate R^3	Ligand	Product	Yield[b] [%]	Selectivity[c] [%] *ee*
1	**2a**	Me	**9a**	**8a**-Me	7	51
2	**2b**	Et	**9a**	**8b**-Et	27	74
3	**2b**	Et	**9b**	**8b**-Et	22	74
4	**2c**	Me	**9a**	**8c**-Me	45	69
5	**2c**	Me	**9b**	**8c**-Me	55	85
6	**2c**	Et	**9b**	**8c**-Et	63	91[f]
7[d]	**2c**	Et	**9c**	**8c**-Et	35 (77)[e]	81[f]
8[d]	**2c**	Et	(*ent*)-(**9c**)	(*ent*)-**8c**-Et	33 (71)[e]	75[f]
9	**2c**	*t*Bu	**9c**	**8c**-*t*Bu	38	95[f]
10	**2c**	Me	**10a**	**8c**-Me	23	94
11	**2c**	Me	**10b**	**8c**-Me	36	91
12	**2c**	Me	**10c**	**8c**-Me	18	91
13	**2c**	Me	**10d**	**8c**-Me	31	85

[a] 3 equiv **2c**, 1 equiv diazoacetate, 2.0 mol% $Cu(OTf)_2$, 2.5 mol% ligand. [b] Isolated yield based on diazoacetate. [c] Measured by HPLC. [d] 1 equiv **2c**, 1 equiv diazoacetate, 0.66 mol% $Cu(OTf)_2$, 0.83 mol% ligand. [e] Isolated yield based on conversion of **2c**. [f] > 99% *ee* after single crystallization [isolated yield 53% (entry 6), 32% (entry 7), 29% (entry 8) and 27% (entry 9)].

as well as selectivity (entry 1). We therefore turned our attention to substituted furans **2b** and **2c** following the precedent set by Anderson et al. for the asymmetric cyclopropanation of 2,3-dihydrofurans.[17]

The reaction proceeds regioselectively for furans **2b** and **2c**; only the less-substituted double bond was cyclopropanated, as well as diastereoselectively, orienting the ester group exclusively on the convex face of the bicyclic framework. We have not been able to detect any of the corresponding *endo*-diastereomers or products that would be expected to have formed by a retro-Claisen rearrangement.[18] The apparent high diastereoselectivity was somewhat surprising since *endo*-products were always observed in the cyclopropanation of 2,3-dihydrofurans.[17] Last but not least, chiral ligands such as the bisoxazolines **9**[19] or the azabisoxazoline **10**[20] promoted the reaction with high enantioselectivity. The ester group at 2-position of the furan proved to be advantageous compared to the one in 3-position, both, in terms of yield as well as enantioselectivity. Thus, **8c**-Me (Table 1, entries 4–5, 10–13) was obtained in up to 94% *ee* (entry 10), but the best result was obtained with bisoxazoline **9b**, which gave **8c**-Et with 91% *ee* and in good yield (entry 6). Moreover, in contrast to **8c**-Me, **8c**-Et is a crystalline adduct, which allows isolation of enantiomerically pure material by a remarkably effective and single crystallization. Therefore, for large-scale preparation of **8c** or (*ent*)-**8c** the use of the ligands **9c** or its enantiomer (*ent*)-**9c** or **10d**, with still good selectivities of 75–85% *ee* (entries 7, 8, 13), might be advantageous since they are obtained from inexpensive valine readily available in both enantiomers, while **9b** and **10b** are derived from the considerable more expensive *tert*-butyl leucine. Thus, **8c**-Et or (*ent*)-**8c**-Et were prepared on a 20–60 g scale in the presence of 0.66 mol% $Cu(OTf)_2$/0.83 mol% **9c** or (*ent*)-**9c**. Moreover, furan **2c** was readily reisolated by distillation, giving rise to up to 77% yield of **8c**-Et or (*ent*)-**8c**-Et based on conversion of **2c**. Using *tert*-butyl diazoacetate[21] as the carbene source even higher enantioselectivities can be achieved (cf. entries 7 and 9). Nevertheless, the preparation of ethyl diazoacetate is more

convenient[22] especially on large scale making the latter the reagent of choice for the synthesis of **8c**.

The absolute configuration of **8c**-Et was unambiguously proven by X-ray structure analysis (Figure 1);[23] its subsequent transformations to paraconic acids have already been described in the literature.[9, 10] The configuration of all other derivatives **8** was assigned by analogy.

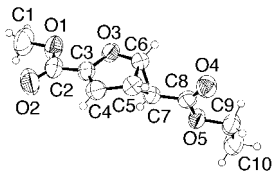
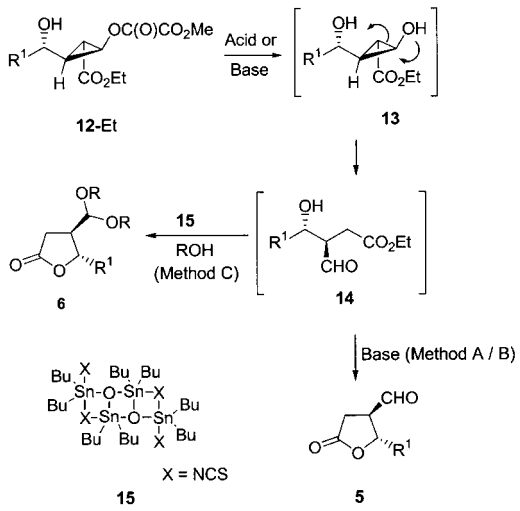


Figure 1. Ortep drawing of **8c**-Et.

Compound **8c**-Et was readily transformed to the cyclopropane carbaldehyde **11** by ozonolysis, followed by reductive work up (Scheme 4). We already demonstrated that nucleophiles can selectively be added to (*rac*)-**11**, giving the Felkin – Anh[24] adduct (*rac*)-**12** with diastereoselectivities of 80:20 to $\geq$95:5.[25] It occurred to us that if a retro-aldol reaction in **12** can be initiated, thus breaking the bond between C-4 and C-6, γ-butyrolactones should be obtained by lactonization of the hydroxyl group at C-2 with the C-5 carbon of the ethyl ester group.

Indeed, we were able to develop two different protocols leading selectively either to **5** or **6** (Schemes 4 and 5, Table 2). Addition of allylsilanes or silyl enol ethers to **11** catalyzed by $BF_3 \cdot Et_2O$ resulted in the adducts **12** with diastereoselectivities $\geq$95:5, which were directly converted to the lactones **5** or **6** without the need of isolation. Upon treatment of crude **12** with base the lactones **5** were obtained, having the aldehyde group available in unprotected form for further synthetic transformations.

Alternatively, using Otera's Sn^{IV} catalyst[26] **15** in the presence of ethylene glycol resulted in the smooth formation of **6**, in which saponification to **13** followed by ring opening to **14**, acetalization of the aldehyde group and lactonization, all had taken place in a single step (Scheme 5, Table 2). In all cases, the diastereomeric ratio of the cyclopropanes **12** (Felkin-Anh/*anti*-Felkin-Anh at C-2) and the lactones **5** or **6** (*anti*/*syn*) was identical, which indicates that no epimerization during the retroaldol/lactonization sequences occurs.

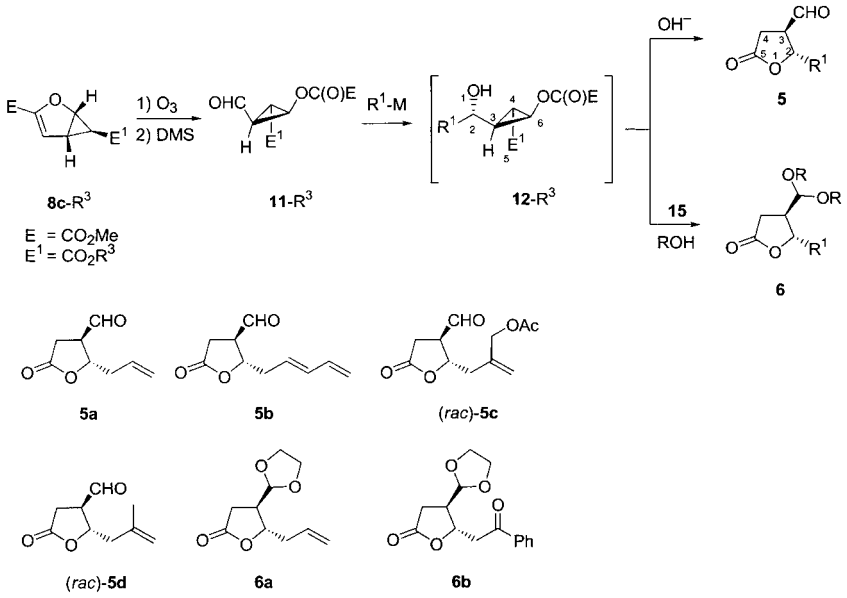


Scheme 5. Formation of lactones **5** or **6** through retroaldol/lactonization of **13**.

The lactones **5a**, **b** and **6a** seemed to be ideal precursors for the synthesis of a broad variety of the enantiomeric series of natural occurring paraconic acids.[27]

Most easily, the formal synthesis of (−)-methylenolactocin (**18**) was accomplished by hydrogenation of the diene **5b** (Scheme 6) followed by oxidation of the aldehyde with $NaClO_2$ using the variant introduced by Dalcanale.[28] The resulting product was recrystallized to remove the minor *cis*-diastereomer giving rise to the known carboxylic acid **17** in diastereomeric and enantiomeric pure form in 86% yield. The final introduction of an *exo*-methylene group into **18** to yield (−)-methylenolactocin (**17**) had been already reported.[9e]

For the synthesis of paraconic acids being substituted with alkyl chains of various lengths the lactones **5a** or **6a** were employed (Scheme 7). We envisioned that the allyl group could be used in metathesis reactions to directly introduce the desired side chains. While ring-closing metathesis (RCM)[29] has been widely used in organic synthesis, there are considerably fewer examples for intermolecular reactions,[30] most likely due to the potential formation of homocoupled dimers at the expense of the desired heterocoupled products.



Scheme 4. Synthesis of lactones **5** or **6** via cyclopropane carbaldehyde **11**.

Compound **6a** (*trans*/*cis* ratio 95:5) was treated with 1-dodecene in the presence of Grubb's catalyst **23**. In order to avoid the homocoupling of **6a**, 1.5 equivalents of the alkene had to be employed (Scheme 8). Thus, only the homocoupling product of 1-dodecene was produced as an unpolar, thus readily removable by-

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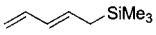
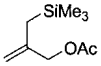
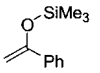
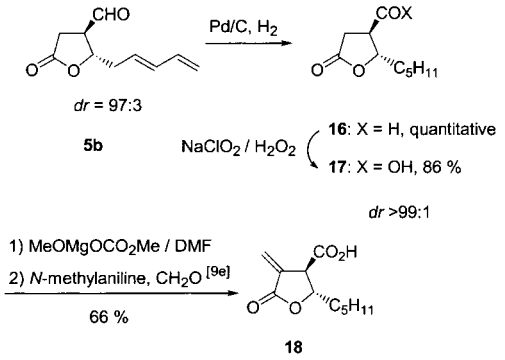
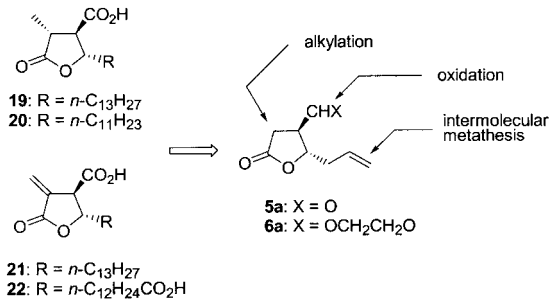
Table 2. γ-Butyrolactone synthesis **5** or **6** by addition of nucleophiles R^1M to **11** followed by retroaldol/lactonization sequence.

Entry	Aldehyde	R^1M	Method[a]	ROH	Lactone	Yield [%]	*trans*/*cis* ratio
1	**11**-Et		A	n/a	**5a**	64	95:5
2	**11**-Et		B	n/a	**5a**	49	95:5
3	**11**-Et		C	$HOCH_2CH_2OH$	**6a**	72	95:5
4	**11**-Et		A	n/a	**5b**	66	97:3
5	(*rac*)-**11**-Me		A	n/a	(*rac*)-**5c**	73	80:20
6	(*rac*)-**11**-Me		C	$HOCH_2CH_2OH$	(*rac*)-**6b**	26	95:5
7	(*rac*)-**11**-Me		A	n/a	(*rac*)-**5d**	44	96:4

[a] Allylation to **12**: **11** (1.0 equiv), $BF_3 \cdot Et_2O$ (1.0–1.25 equiv), corresponding allylsilanes (1.0–1.25 equiv), CH_2Cl_2, $-78\,^\circ C$; saponification and ring-opening to **5** or **6**: method A: $Ba(OH)_2 \cdot 8H_2O$ (1 equiv), MeOH, $0\,^\circ C$; method B: NaOMe (1 equiv), MeOH, $0\,^\circ C$; method C: **15** (0.05 mol%), ROH.

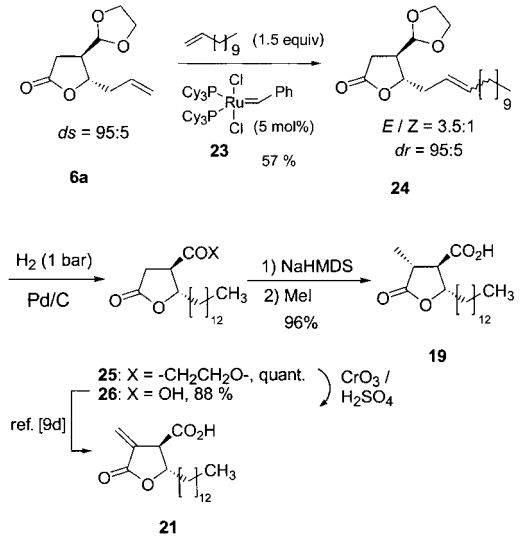


Scheme 6. Formal synthesis of methylenolactocin (**18**).



Scheme 7. Retrosynthetic analysis for **19** to **22**.

product along with the desired **24** as a 3.5:1 *E*/*Z*-mixture. The latter was without consequence, since the double bond in **24** was subsequently hydrogenated to **25**, followed by simultaneous cleavage and oxidation of the acetal under acidic conditions. Compound **26** was obtained in this way as a single stereoisomer after one recrystallization, which removed the minor *cis*-diastereomer. Its structure could be unequivocally established by X-ray structure analysis (Figure 2).[31] Moreover, **26** was synthesized before and subsequently transformed to (−)-protolichesterinic acid (**21**)[9d] and to (−)-roccellaric acid (**19**) as depicted in Scheme 8.[9c] We were able to improve the conversion of **26** to **19** (96% yield instead of 55%) by employing NaHMDS (2.2 equiv) and an excess of methyl iodide.



Scheme 8. Total synthesis of (−)-roccellaric acid (**19**) and (−)-protolichesterinic acid (**21**).

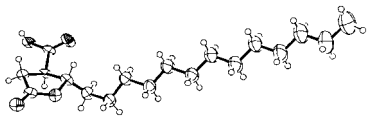
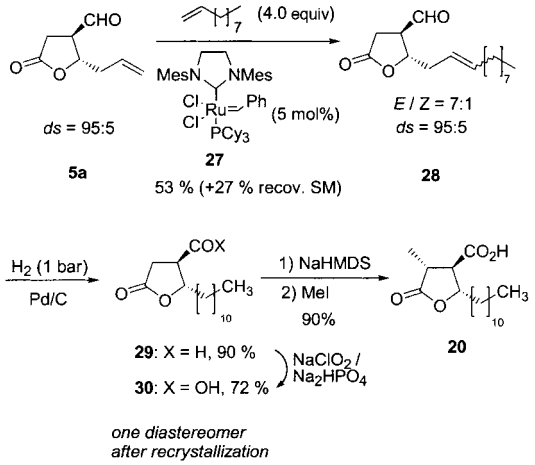


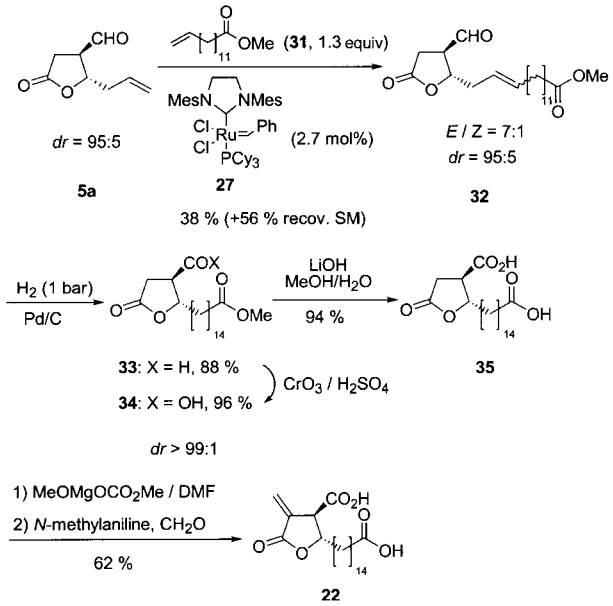
Figure 2. Ortep drawing of **26**.

In an analogous way, (−)-nephrosteranic acid (**20**) was synthesized starting from the lactone **5a** (Scheme 9). The unprotected aldehyde group in **5a** dictated the use of the more active metathesis catalyst **27**,[32] nevertheless, **28** was only obtained in 45% yield along with 30% recovered starting material using 1.5 equivalents of 1-decene. Attempts to improve this yield by using a total of 4 equiv of 1-decene in the cross metathesis were only moderately successful: In this case, **28** was isolated in 53% yield along with 27% of recovered **5a**. It should be noted that catalyst **27** gave a much higher (*E*)-selectivity in the cross coupling product than **23** (cf. Scheme 8).

Finally, the first total synthesis of protopraesorediosic acid (**22**) was accomplished (Scheme 10) starting with the cross metathesis of lactone **5a** and the alkene **31**. The heterocoupled alkene **32** was obtained in a clean reaction, although the



Scheme 9. Total synthesis of (−)-nephrosteranic acid (**20**).



Scheme 10. Total synthesis of (−)-protopraesorediosic acid (**22**).

conversion of **5a** was again low. After hydrogenation and oxidation following the examples outlined above, the ester **34** was saponified to the diacid **35** in high yield. For the final introduction of the *exo*-methylene group into a lactone various methods are known in the literature.[33] In our hands the procedure described by Greene et al.[33a] worked best to give **22** in 62% yield.

In conclusion, we have developed an asymmetric synthesis towards γ-butyrolactones using catalytic asymmetric methodology in the key step. The utility of this method was demonstrated in the synthesis of a variety of paraconic acids, which are obtained in 7–9 steps in overall yields of 7–21% from inexpensive furan carboxylic methyl ester as starting material.

Experimental Section

General remarks: Reactions with moisture-sensitive chemicals were performed under nitrogen in a flame-dried reaction flask. Solvents were dried by standard methods. Chromatography: Macherey–Nagel silica gel (0.03–0.06 mm). Enantiomeric excesses were determined by analytical HPLC using a "Chiracel OD-H" column (50 × 4.6 mm, 10 µm, flow: 1 mL min^{-1}, 20 °C) and a UV detector at 254 nm. TLC: commercially precoated silica gel aluminium sheets 60 F_{254} (Merck). Uncorrected melting point: Büchi SMP 20. IR: Mattson Genesis series FT-IR, Perkin–Elmer 298, Bruker IFS 66, $\tilde{\nu}$ in cm^{-1}. ^{1}H NMR and ^{13}C NMR: Bruker ARX 400, Avance 300, AC 250 F, δ in ppm, J in Hz. Multiplicities were determined by DEPT (distortionless enhancement by polarization transfer) measurements. MS: Finnigan MAT 95, Varian MAT 311A. Elemental analysis: Heraeus CHN-Rapid. XRD: Stoe Imaging Plate System, Siemens Stoe AED2. Optical rotation: Perkin–Elmer polarimeter PE 241.

(1*S*,5*R*,6*S*)-2-Oxabicyclo[3.1.0]hex-3-ene-4,6-dicarboxylic 6-ethyl ester-3-methyl ester (8b-Et): Phenylhydrazine (1 drop) in CH_2Cl_2 (1 mL) was added under nitrogen at 0 °C to a mixture of **2b** (1.14 g, 9.0 mmol, 3.0 equiv), $Cu(OTf)_2$ (22 mg, 0.06 mmol, 2.0 mol%) and **9b** (66 mg, 0.075 mmol, 2.5 mol%). After 5 min, a solution of ethyl diazoacetate (342 mg, 3.0 mmol, 1 equiv) in dry CH_2Cl_2 (10 mL) was added slowly with a syringe pump over 8 h. The reaction mixture was filtered through a short pad of basic alumina and solvent was evaporated in vacuo. The residue was purified by chromatography on silica gel (hexanes/ethyl acetate 10:1) to provide **8b**-Et as a pale yellow oil (140 mg, 22%, 74% *ee*). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.14 (ddd, J = 2.9, 1.0, 0.5 Hz, 1H, 6-H), 1.27 (t, J = 7.1 Hz, 3H, CH_3), 3.10 (ddd, J = 5.7, 2.9, 0.5 Hz, 1H, 5-H), 3.77 (s, 3H, CH_3), 4.15 (q, J = 7.1 Hz, 2H, CH_2), 5.02 (ddd, J = 5.7, 1.0, 0.9 Hz, 1H, 1-H), 7.21 (ddd, J = 0.9, 0.6, 0.5 Hz, 1H, 3-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.2 (+, CH_3), 21.7 (+, C-5), 29.5 (+, C-6), 51.4 (+, CH_3), 61.0 (−, CH_2), 68.9 (+, C-1), 156.3 (+, C-3), 164.0 (C_{quat}, CO), 171.4 (C_{quat}, CO); IR (film): $\tilde{\nu}$ = 3109, 2986, 2957, 1730, 1604, 1031 cm^{-1}; MS (EI, 70 eV): m/z (%): 212.2 (12) [M^+], 184.1 (11), 139.1 (100), 127.1 (16), 126.1 (11), 111.1 (129), 108.1 (18), 107.1 (24), 99.1 (61), 95.1 (13), 83.1 (11), 79.1 (15), 58.1 (16), 43.1 (64), 29.1 (36); elemental analysis calcd (%) for $C_{10}H_{12}O_5$ (212.2): C 56.60, H 5.70; found C 56.64, H 5.58.

(1*S*,5*S*,6*S*)-(−)-2-Oxabicyclo[3.1.0]hex-3-ene-3,6-dicarboxylic 6-ethyl ester 3-methyl ester (8c-Et)

Method A: Phenylhydrazine (89 mg, 0.82 mmol, 2.0 mol%) was added under nitrogen at 0 °C to a mixture of **2c** (12.9 mL, 120 mmol, 3 equiv), $Cu(OTf)_2$ (297 mg, 0.82 mmol, 2.0 mol%) and **9b** (303 mg, 1.02 mmol, 2.5 mol%). After 30 min, a solution of ethyl diazoacetate (4.685 g, 41.1 mmol, 1 equiv) in dry CH_2Cl_2 (70 mL) was added continuously with a syringe pump over 12 h in four equal amounts. After each addition, CH_2Cl_2 was evaporated by passing nitrogen through the flask. Excess of furan-2-carboxylic methyl ester was evaporated under high vacuum at room temperature, and the residue was purified by chromatography on silica gel (hexanes/EE 10:1) to provide **8c**-Et as a colorless oil (5.494 g, 63%). Enantiopure product **8c**-Et could be obtained by recrystallization from *n*-pentane (4.622 g, 53%).

Method B: Phenylhydrazine (241 µL, 2.44 mmol, 0.83 mol%) was added under nitrogen at 0 °C to a solution of **2c** (37.0 g, 0.293 mol, 1.0 equiv), $Cu(OTf)_2$ (700 mg, 1.94 mmol, 0.66 mol%) and (−)-**9c** (649 mg, 2.44 mmol, 0.83 mol%). After 20 min, a solution of ethyl diazoacetate (30.6 mL, 0.293 mol, 1.0 equiv) in dry CH_2Cl_2 (200 mL) was added through a dropping funnel over 13 h. The reaction mixture was filtered through a short pad of basic alumina and solvent was evaporated in vacuo. Unconverted **2c** was removed by distillation (5 mbar, b.p. 63–64 °C, 20.0 g, 54%) and the residue was purified by kugelrohr distillation (10^{-4}–10^{-5} mbar, 88 °C) to provide **8c**-Et as a yellowish oil (22.0 g, 35% yield, 77% yield based on conversion of **2c**, 81% *ee*) which after crystallization from *n*-pentane appeared as yellowish crystals (20.12 g, 32%, 99% *ee*). R_f (PE/EE 5:1) = 0.14; m.p. 42 °C; $[\alpha]_D^{20} = -272$ (c = 1.0, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.16 (dd, J = 2.7, 1.1 Hz, 1H, 6-H), 1.23 (t, J = 7.1 Hz, 3H, CH_3), 2.87 (ddd, J = 5.3, 2.9, 2.7 Hz, 1H, 5-H), 3.78 (s, 3H, OCH_3), 4.12 (q, J = 7.1 Hz, 2H, CH_2), 4.97 (dd, J = 5.3, 1.1 Hz, 1H, 1-H), 6.39 (d, J = 2.9 Hz, 1H, 4-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.2 (+, CH_3), 21.5 (+, C-6), 31.9 (+, C-5), 52.1 (+, OCH_3), 61.0 (−, CH_2), 67.5 (+, C-1), 116.0 (+, C-4), 149.3 (C_{quat}, C-3), 159.5 (C_{quat}, CO), 171.7 (C_{quat}, CO); IR (KBr): $\tilde{\nu}$ = 3118, 2956, 1720, 1617, 1428, 1380, 1297, 1166, 1124, 1041, 954, 831, 725 cm^{-1}; MS (70 eV, EI): m/z (%): 212.1 [M^+] (9.8), 153.0 [$M^+ - CO_2Me$] (11.5), 139.0 [$M^+ - CO_2Et$] (100), 124.9 (24.4), 98.9 (28.6), 96.9 (31.7), 78.9 (11.3), 59.0 (13.5), 52.1 (11.5); elemental analysis calcd (%) for $C_{10}H_{12}O_5$ (212.2): C 56.60, H 5.70; found C 56.51, H 5.73.

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(1*S*,5*S*,6*S*)-(−)-2-Oxabicyclo[3.1.0]hex-3-ene-3,6-dicarboxylic 6-*tert*-butyl ester 3-methyl ester (8c-*t*Bu): Phenylhydrazine (11.5 μL, 116.77 mmol, 0.83 mol %) was added under nitrogen at 0 °C to a mixture of **2c** (1.77 g, 14.07 mmol, 1.0 equiv), $Cu(OTf)_2$ (33.6 mg, 92.85 mmol, 0.66 mol %) and **9c** (31.1 mg, 116.77 mmol, 0.83 mol %). After 30 min, a solution of *tert*-butyl diazoacetate (2.0 g, 14.07 mmol, 1.0 equiv) in dry CH_2Cl_2 (30 mL) was added slowly with a syringe pump over 9 h. The reaction mixture was filtered through a short pad of basic alumina and solvent was evaporated in vacuo. The residue was purified by chromatography on silica gel (hexanes/EE 10:1) to provide **8c**-*t*Bu as a yellowish crystals (1.30 g, 38 %, 95 % *ee*) which after crystallization from dichloromethane and n-pentane appeared as white needle crystals (0.92 g, 27 %, >99 % *ee*). R_f (PE/EE 5:1) = 0.16; m.p. 68 °C; $[\alpha]_D^{20} = -226$ ($c = 1.0$, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.08$ (dd, $J = 2.7$, 1.1 Hz, 1.1 Hz, 1H, 6-H), 1.44 (s, 9H, $C(CH_3)_3$), 2.79 (ddd, $J = 5.3$, 2.9, 2.7 Hz, 1H, 5-H), 3.80 (s, 3H, OCH_3), 4.90 (dd, $J = 5.3$, 1.1 Hz, 1H, 1-H), 6.37 (d, $J = 2.9$ Hz, 1H, 4-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 22.5$ (+, C-6), 28.2 (+, $C(CH_3)_3$), 31.6 (+, C-5), 52.1 (+, OCH_3), 67.4 (+, C-1), 81.4 (C_{quat}, $C(CH_3)_3$), 116.3 (+, C-4), 149.2 (C_{quat}, C-3), 159.6 (C_{quat}, CO), 171.0 (C_{quat}, CO); IR (KBr): $\tilde{\nu} = 3056$, 2983, 1729, 1698, 1621, 1440, 1384, 1309, 1162, 1110, 1022, 971, 879, 829, 750, 715 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 240.1 (3.83) [M^+], 183.9 (16.8), 166.9 (16.8), 151.9 (11.5), 138.9 (70.8), 124.8 (36.8), 96.9 (39.0), 57.1 (100), 52.1 (14.5), 41.1 (26.6); elemental analysis calcd (%) for $C_{12}H_{16}O_5$ (240.3): C 59.99, H 6.71; found C 60.04, H 6.76.

(1*S*,2*S*,3*S*)-(−)-Oxalic acid 2-ethoxycarbonyl 3-formyl-cyclopropyl ester methyl ester (11-Et): A solution of (−)-**8c**-Et (2.50 g, 11.78 mmol) in dry CH_2Cl_2 (125 mL) was cooled to −78 °C and treated with ozone until the mixture turned blue. Excess ozone was expelled by passing oxygen through the solution, followed by addition of dimethyl sulfide (4.3 mL, 58.91 mmol, 5.0 equiv). The reaction mixture was allowed to warm to room temperature and stirring was continued for 24 h. Saturated $NaHCO_3$ (10 mL) was added and layers were separated. The organic layer was washed with water (2 × 10 mL), dried, filtered and evaporated. The residue was recrystallized from Et_2O at −27 °C to yield (−)-**11**-Et as a colorless solid (2.70 g, 94 %). M.p. 52 °C; $[\alpha]_D^{20} = -37.7$ ($c = 1.0$, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta =$ 1.28 (t, $J = 7.1$ Hz, 3H, CH_2CH_3), 2.79 (ddd, $J = 7.3$, 6.0, 4.0 Hz, 1H, 2-H), 2.90 (dd, $J = 6.0$, 3.6 Hz, 1H, 3-H), 3.91 (s, 3H, CO_2CH_3), 4.19 (q, $J = 7.1$ Hz, 2H, CH_2CH_3), 4.83 (dd, $J = 7.3$, 3.6 Hz, 1H, 1-H), 9.45 (d, $J = 4.0$ Hz, 1H, CHO); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 14.1$ (+, CH_3), 26.4 (+, C-3), 34.9 (+, C-2), 54.0 (+, CO_2CH_3), 58.9 (+, C-1), 62.0 (−, $CO_2CH_2CH_3$), 156.6 (C_{quat}, CO), 156.9 (C_{quat}, CO), 168.1 (C_{quat}, $CO_2CH_2CH_3$), 192.7 (+, CHO); IR (KBr): $\tilde{\nu} = 3066$, 3015, 2963, 2892, 1785, 1751, 1735, 1706, 1445, 1345, 1313, 1210, 1167, 1086, 1011, 963, 867, 790, 715, 613, 495 cm^{-1}; MS (DCI, NH_3): *m*/*z* (%): 262.0 [M^++NH_4] (100), 176.0 (20), 160.0 (55), 120.9 (15); elemental analysis calcd (%) for $C_{10}H_{12}O_7$ (244.2): C 49.19, H 4.95; found C 49.22, H 4.99.

(2*S*/*R*,3*R*)-2-Allyl-5-oxotetrahydrofuran-3-carbaldehyde (5a): A solution of **11**-Et (5.00 g, 20.5 mmol) in dry CH_2Cl_2 (200 mL) was treated with $BF_3 \cdot Et_2O$ (3.0 mL, 20.5 mmol) at −78 °C. After 10 minutes allyltrimethylsilane (5.0 mL, 30.75 mmol, 1.5 equiv) was added and stirring was continued for 24 h. The reaction was quenched with saturated $NaHCO_3$ (6.0 mL) and the mixture was allowed to warm to 0 °C. After separation of the organic layer and drying with $MgSO_4$, the solvent was evaporated under vacuo to yield the corresponding alcohol **12a** as a colorless oil (5.82 g, 100 % crude yield, *dr* 95:5). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.25$ (t, $J = 7.0$ Hz, 3H, CH_3), 1.81–1.92 (m, 1H, 2-H), 2.15 (dd, $J = 6.2$, 2.7 Hz, 1H, 3-H), 2.31–2.51 (m, 4H), 3.70 (ddd, $J = 7.3$, 7.3, 5.4 Hz, 1H, 1′-H), 3.88 (s, 3H, CO_2CH_3), 4.13 (q, $J = 7.0$ Hz, 2H, $CO_2CH_2CH_3$), 4.72 (dd, $J = 7.5$, 2.8 Hz, 1H, 1-H), 5.14–5.22 (m, 2H, 4′-H), 5.76–5. 93 (m, 1H, 3′-H), characteristic signals of the diastereomer: $\delta = 4.14$ (q, $J = 7.0$ Hz, 2H, $CO_2CH_2CH_3$), 4.67 (dd, $J = 6.9$, 3.0 Hz, 1H, 1-H).

Method A: The alcohol **12a** (5.78 g, 20.0 mmol) was dissolved in methanol (200 mL) at 0 °C and treated dropwise with a solution of $Ba(OH)_2 \cdot 8H_2O$ (3.15 g, 10.0 mmol, 0.5 equiv) in methanol (200 mL). CH_2Cl_2 (100 mL) and H_2O (100 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (10 × 100 mL). The combined organic layers were dried, filtered and concentrated in vacuo. Chromatography on silica gel (hexane/EE 1:1) yielded **5a** as a colorless oil (2.02 g, 64 %, *dr* 95:5).

Method B: The alcohol **12a** (1.842 g, 6.77 mmol, 1 equiv) was dissolved in dry methanol (30 mL) at 0 °C and treated dropwise with a suspension of NaOMe (0.365 g, 6.77 mmol, 1 equiv) in dry methanol (15 mL). After 135 min, the solvent was evaporated under vacuo. The residue was dissolved in CH_2Cl_2 (40 mL) and washed with water (2 × 20 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 30 mL). The combined organic layers were dried, filtered and concentrated in vacuo. Chromatography on silica gel (hexane/EE 1:1) yielded **5a** as a colorless oil (0.510 g, 49 %, *dr* 95:5). R_f (hexanes/EE 1:1) = 0.17; $[\alpha]_D^{20} = -31.7$ ($c = 1.35$ in CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 2.35-2.59$ (m, 2H, 1′-H), 2.71 (dd, $J = 18.2$, 9.9 Hz, 1H, 3-H), 2.89 (dd, $J = 18.2$, 7.5 Hz, 1H, 3-H), 3.19 (dddd, $J = 10.0$, 7.3, 6.0, 1.2 Hz, 1H, 4-H), 4.74 (dd, $J = 11.9$, 6.2 Hz, 1H, 5-H), 5.10–5.27 (m, 2H, 3′-H), 5.75 (dddd, $J = 17.3$, 10.0, 7.0, 3.5 Hz, 1H, 2′-H), 9.69 (d, $J = 1.2$ Hz, 1H, CHO), characteristic signals of the diastereomer (2*R*): $\delta = 3.00$ (dd, $J = 17.7$, 5.8 Hz, 1H, 3-H), 9.82 (d, $J = 1.7$ Hz, 1H, CHO); IR (film): $\tilde{\nu} = 3080$, 2980, 2939, 2841, 1774, 1727, 1642, 1419, 1359, 1193, 1111, 1000, 924 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 154.2 (5) [M^+], 113.1 (100) [$M^+ - C_3H_5$], 85.1 (95), 57.1 (95); elemental analysis calcd (%) for $C_8H_{10}O_3$ (154.2): C 62.33, H 6.54; found: C 62.36, H 6.83.

(2*S*/*R*,3*R*)-(−)-3-Formyl-5-oxo-2-(pentadien-2′,4′-yl)-tetrahydrofuran (5b): A solution of **11**-Et (527 mg, 2.16 mmol, 1.0 equiv) in dry CH_2Cl_2 (10 mL) was cooled to −78 °C. $BF_3 \cdot Et_2O$ (340 μL, 2.66 mmol, 1.25 equiv) and 1,3-pentadienyltrimethylsilane (379 mg, 2.66 mmol, 1.25 equiv) were added through a syringe and the solution was stirred for 12 h at −78 °C. Saturated $NaHCO_3$ solution (0.4 mL) was added and the mixture was warmed to 0 °C. After separating the layers the organic layer was dried, filtered and concentrated in vacuo to yield **12b** (762 mg, 2.37 mmol, quant.) as a colorless oil (*dr* 97:3). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.25$ (t, $J =$ 7.0 Hz, 3H, CH_3), 1.81–1.92 (m, 1H, 2-H), 2.15 (dd, $J = 6.2$, 2.7 Hz, 1H, 3-H), 2.31–2.51 (m, 4H), 3.70 (ddd, $J = 7.3$, 7.3, 5.4 Hz, 1H, 1′-H), 3.88 (s, 3H, CO_2CH_3), 4.13 (q, $J = 7.0$ Hz, 2H, $CO_2CH_2CH_3$), 4.72 (dd, $J = 7.5$, 2.8 Hz, 1H, 1-H), 5.14–5.22 (m, 2H, 4′-H), 5.76–5.93 (m, 1H, 3′-H), characteristic signals of the diastereomer (2*R*): $\delta = 4.14$ (q, $J = 7.0$ Hz, 2H, $CO_2CH_2CH_3$), 4.67 (dd, $J = 6.9$, 3.0 Hz, 1H, 1-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 14.1$ (+, CH_3), 24.7 (+, C-3), 31.3 (+, C-2), 41.7 (−, C-2′), 53.8 (+, CO_2CH_3), 58.8 (+, C-1), 61.3 (−, $CO_2CH_2CH_3$), 67.8 (+, C-1′), 118.8 (−, C-4′), 133.4 (+, C-3′), 157.2 (C_{quat}, CO), 157.2 (C_{quat}, CO), 170.6 (C_{quat}, CO_2CH_3), characteristic signals of the diastereomer (2*R*): $\delta = 25.1$ (+, C-3), 41.3 (−, C-2′), 53.6 (+, CO_2CH_3), 58.6 (+, C-1), 61.2 (−, $CO_2CH_2CH_3$), 68.6 (+, C-1′), 118.6 (−, C-4′), 133.5 (+, C-3′).

The alcohol **12b** (762 mg) was dissolved in methanol (20 mL) at 0 °C and treated dropwise with a solution of $Ba(OH)_2 \cdot 8H_2O$ (340 mg, 1.08 mmol, 0.5 equiv) in methanol (15 mL). Then CH_2Cl_2 (20 mL) and H_2O (20 mL) were added and layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 15 mL). The combined organic layers were dried, filtered and concentrated in vacuo. Chromatography on silica gel (hexanes/EE 1:1) yielded **5b** as a colorless oil (258 mg, 66 %, *dr* 97:3). R_f (hexanes/EE 1:1) = 0.17; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 2.56-2.63$ (m, 2H, 1′-H), 2.74 (dd, $J = 18.0$, 10.0 Hz, 1H, 4-H), 2.92 (dd, $J = 18.0$, 7.5 Hz, 1H, 4-H), 3.19 (dddd, $J = 10.0$, 7.5, 6.2, 1.3 Hz, 1H, 3-H), 4.75 (dd, $J = 12.0$, 6.0 Hz, 1H, 2-H), 5.04–5.24 (m, 2H, 5′-H), 5.62 (dt, $J = 14.4$, 7.3 Hz, 1H, 2′-H), 6.12–6.39 (m, 2H, 3′-H, 4′-H), 9.73 (d, $J = 1.2$ Hz, 1H, CHO), characteristic signals of the diastereomer (2*R*): $\delta = 9.84$ (d, $J = 1.6$ Hz, 1H, CHO); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 28.9$ (−, C-4), 37.9 (−, C-1′), 51.4 (+, C-3), 78.1 (+, C-2), 117.8 (−, C-5′), 125.8 (+, C-2′), 136.1 (+, C-3′), 136.2 (+, C-4′), 173.8 (C_{quat}, C-5), 197.1 (+, CHO); MS (EI, 70 eV): *m*/*z* (%): 180.2 [M^+] (10), 113.1 [$M^+ - C_5H_7$] (80), 85.1 (100), 57.1 (90), 29.1 (75); HRMS: calcd for $C_{10}H_{16}NO_3$: 198.11302 [M^++NH_4], found: 198.11285.

(2*S/*R**,3*R**)-3-Formyl-5-oxo-2-(2′-acetoxymethyl-propen-2′-yl)-tetrahydrofuran (5c)**: A solution of (*rac*)-**11**-Me (1.150 g, 5.00 mmol, 1 equiv) in dry CH_2Cl_2 (25 mL) was cooled to −78 °C. $BF_3 \cdot Et_2O$ (690 μL, 5.50 mmol, 1.1 equiv) and 2-acetoxymethyl allyltrimethylsilane (1.025 g, 5.50 mmol, 1.1 equiv) were added through a syringe and the solution was stirred for 12 h at −78 °C. Saturated $NaHCO_3$ solution (1 mL) was added and the mixture was warmed to 0 °C. After separating the layers the organic layer was dried, filtered and concentrated in vacuo to yield **12c** as a colorless oil in quantitative yield (*trans*/*cis* 80:20).

^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.81-1.91$ (m, 1H, 2-H), 2.04 (s, 3H, CH_3), 2.14 (dd, $J = 6.1$, 2.7 Hz, 1H, 3-H), 2.32–2.44 (m, 2H, 2′-H), 2.89 (br s, 1H, OH), 3.66 (s, 3H, CO_2CH_3), 3.72 (m, 1H, 1′-H), 3.86 (s, 3H, CO_2CH_3), 4.51 (m, 2H, CH_2), 4.67 (dd, $J = 7.4$, 2.7 Hz, 1H, 1-H), 5.05 (m, 1H, 4′-H), 5.13 (m, 1H, 4′-H), characteristic signals of the diastereomer: $\delta = 1.86-1.96$ (m, 1H, 2-H), 2.05 (s, 3H, CH_3), 2.17 (dd, $J = 6.1$, 2.7 Hz, 1H,

3-H), 3.67 (s, 3H, CO_2CH_3), 3.87 (s, 3H, CO_2CH_3), 4.65 (dd, $J = 7.4$, 2.7 Hz, 1H, 1-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 20.7$ (+, CH_3), 24.8 (+, C-3), 31.6 (+, C-2), 41.5 (−, C-2′), 52.2 (+, CO_2CH_3), 53.7 (+, CO_2CH_3), 58.7 (+, C-1), 66.5 (−, CH_2), 67.4 (+, C-1′), 116.1 (−, C-4′), 140.1 (C_{quat}, C-3′), 157.0 (C_{quat}, CO), 157.1 (C_{quat}, CO), 170.5 (C_{quat}, CO_2CH_3), 170.8 (C_{quat}, CO_2CH_3), characteristic signals of the diastereomer: $\delta = 20.9$ (+, CH_3), 25.2 (+, C-3), 31.5 (+, C-2), 41.0 (−, C-2′), 52.2 (+, CO_2CH_3), 53.8 (+, CO_2CH_3), 58.4 (+, C-1), 66.9 (−, CH_2), 67.8 (+, C-1′), 116.2 (−, C-4′), 157.5 (C_{quat}, CO), 170.6 (C_{quat}, CO_2CH_3), 170.7 (C_{quat}, CO_2CH_3); IR (film): $\tilde{\nu}$ = 3506, 2957, 1779, 1736, 1442, 1374, 1315, 1234, 1201, 1160, 1028, 980, 915, 860 cm^{-1}; MS (DCI, NH_3): *m*/*z* (%): 362.2 (100) [M^++NH_4], 258.1 (69), 200.1 (18); HRMS (DCI): calcd for $C_{15}H_{24}NO_9$: 362.1451 [M^++NH_4], found: 362.1438.

The crude product was dissolved in MeOH (50 mL). At 0 °C a solution of $Ba(OH)_2 \cdot 8H_2O$ (1.735 g, 5.50 mmol, 1.1 equiv) in MeOH (30 mL) was added dropwise. Then H_2O (50 mL) was added and the mixture was extracted with CH_2Cl_2 (10 × 30 mL). The combined organic layers were dried and concentrated in vacuo. Chromatography on silica gel (hexanes/EE 1:1) yielded **5c** as a colorless oil (828 mg, 73%, *trans*/*cis* 80:20). R_f (PE/EE 1:1) = 0.07; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 2.08$ (s, CH_3, 3H), 2.47 (dd, $J = 14.7$, 6.0 Hz, 1H, 1′-H), 2.61 (dd, $J = 14.7$, 7.0 Hz, 1H, 1′-H), 2.76 (dd, $J = 18.0$, 10.0 Hz, 1H, 4-H), 2.90 (dd, $J = 17.9$, 7.7 Hz, 1H, 4-H), 3.21 (dddd, $J = 9.9$, 7.7, 6.4, 1.3 Hz, 1H, 3-H), 4.54 (s, 2H, CH_2OAc), 4.87 (dd, $J = 13.0$, 6.4 Hz, 1H, 2-H), 5.13 (s, 1H, C=CH), 5.25 (s, 1H, C=CH), 9.71 (d, $J = 1.3$ Hz, 1H, CHO), characteristic signals of the diastereomer: $\delta = 9.82$ (d, $J = 1.7$ Hz, 1H, CHO); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 20.8$ (+, CH_3), 28.9 (−, C-4), 39.0 (−, C-1′), 51.7 (+, C-3), 66.6 (−, CH_2OAc), 77.2 (+, C-2), 117.7 (−, C=CH_2), 138.3 (C_{quat}, C-2′), 170.5 (C_{quat}, CO), 173.7 (C_{quat}, CO), 197.2 (C_{quat}, CO), characteristic signals of the diastereomer: $\delta = 28.9$ (−, C-4), 66.6 (−, CH_2OAc), 117.7 (−, C=CH_2), 197.9 (C_{quat}, CO); IR (film): $\tilde{\nu}$ = 3090, 2938, 1777, 1736, 1655, 1436, 1373, 1233, 1029, 920 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 226.2 [M^+] (5), 113.1 (40), 85.1 (50), 57.1 (40), 43.1 (100); elemental analysis calcd (%) for $C_{11}H_{14}O_5$ (226.2): C 58.40, H 6.24; found: C 58.61, H 6.87.

(2*S/*R**,3*R**)-2-(2-Methylallyl)-5-oxotetrahydrofuran-3-carbaldehyde (5d)**: A solution of (*rac*)-**11**-Me (500 mg, 2.17 mmol, 1.0 equiv) in dry CH_2Cl_2 (11 mL) was cooled to −78 °C. $BF_3 \cdot Et_2O$ (273 μL, 2.17 mmol, 1.0 equiv) and trimethyl-(2-methyl-allyl)-silane (279 mg, 2.17 mmol, 1.0 equiv) were added through a syringe and the solution was stirred for 16 h at −78 °C. Saturated $NaHCO_3$ solution (1.0 mL) was added and the mixture was warmed to 0 °C. After drying with $MgSO_4$ the reaction mixture was filtered and concentrated in vacuo to yield the corresponding alcohol **12d** as a colorless oil. The alcohol was directly dissolved in methanol (17 mL) at 0 °C and treated dropwise with a solution of $Ba(OH)_2 \cdot 8H_2O$ (720 mg, 2.28 mmol, 1.05 equiv) in methanol (10 mL). CH_2Cl_2 (20 mL) and H_2O (35 mL) were added and layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were dried, filtered and concentrated in vacuo. Chromatography on silica gel (hexanes/EE 1:1) yielded **5d** as a colorless oil (162 mg, 44%, *trans*/*cis* 96:4). ^{1}H NMR (300 MHz, CD_3OD): $\delta = 1.79$ (s, 3H, CH_3), 2.40 (dd, $J = 14.1$, 7.0 Hz, 1H, CH_2-C1′), 2.59 (dd, $J = 14.1$, 6.5 Hz, 1H, CH_2-C1′), 2.76 (dd, J = 18.0, 9.9 Hz, 1H, CH_2-C4), 2.92 (ddd, $J = 18.0$, 7.5, 0.5 Hz, 1H, CH_2-C4), 3.22 (dddd, $J = 9.9$, 7.5, 6.2, 1.2 Hz, 1H, C3-H), 4.79–4.90 (m, 2H, C2-H, =CH_2), 4.95 (s, 1H, =CH_2), 9.72 (dd, $J = 1.1$, 0.5 Hz, 1H, CHO), characteristic signals of the diastereomer: 9.84 (d, $J = 1.7$ Hz, CHO); ^{13}C NMR (75.4 MHz, CD_3OD): $\delta = 22.66$ (+, CH_3), 28.85 (−, CH_2), 51.76 (+, CH), 77.50 (+, CH), 115.11 (−, CH_2), 139.81 (C_{quat}), 174.06 (C_{quat}), 197.51 (+, CHO), characteristic signals of the diastereomer: 198.28 (+, CHO); IR (film): $\tilde{\nu}$ = 3078, 2937, 2830, 1790, 1779, 1700, 1651, 1446, 144 cm^{-1}; MS (DCI, NH_3): *m*/*z* (%): 186.1 (100.0) [M^++NH_4]; HRMS: calcd for $C_9H_{12}O_3$: 168.0786, found 169.0865 [M^++H].

(2*S/*R**,3*R**)-3-(1,3-Dioxolan-2-yl)-5-oxo-2-(propen-2-yl)-tetrahydrofuran (6a)**: A solution of the aldehyde (*rac*)-**11**-Me (1.151 g, 5.0 mmol) in dry CH_2Cl_2 (25 mL) was treated with $BF_3 \cdot OEt_2$ (630 μL, 5.0 mmol, 1 equiv) at −78 °C. After 30 min trimethylallylsilane (159 μL, 1.0 mmol, 1 equiv) was added and stirring continued for 12 h. The reaction was quenched with saturated $NaHCO_3$ solution (1 mL) and the mixture was allowed to warm to 0 °C. After drying ($MgSO_4$) the mixture was filtered and concentrated. The intermediate product was dissolved in benzene, treated with the tin-catalyst **15** (22 mg, 1 mol%) and ethane-1,2-diol (587 μL, 10.5 mmol, 2.1 equiv) and refluxed with a Dean–Stark trap for 48 h. Toluene (40 mL) was added and the mixture was concentrated in vacuo. After chromatography on silica gel (hexanes/EE 1:1, 1 vol% NEt_3), **6a** was obtained as a pale yellow oil (712 mg, 72%, *cis*/*trans* 93:7). R_f (PE/EE 1:1) = 0.34; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 2.39$–2.67 (m, 5H, 1′-H, 3-H, 4-H), 3.83–4.01 (m, 4H, OCH_2CH_2O), 4.51 (m, 1H, CH), 4.86 (m, 1H, 2-H), 5.11–5.21 (m, 2H, 3′-H), 5.79 (ddt, $J = 16.7$, 10.6, 6.9 Hz, 1H, 2′-H), characteristic signals of the diastereomer: $\delta = 4.06$–4.18 (m, 4H, OCH_2CH_2O), 4.60 (ddd, $J = 8.3$, 6.7, 5.8 Hz, 1H, 2-H), 4.98 (d, $J = 3.7$ Hz, 1H, CH), 5.85 (ddt, $J = 7.2$, 10.2, 6.7 Hz, 1H, 2′-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 29.6$ (−, C-4), 39.2 (−, C-1′), 42.5 (+, C-4), 65.4, 65.5 (−, OCH_2CH_2O), 79.7 (+, C-2), 103.5 (+, CH), 119.3 (−, C-3′), 132.0 (+, C-2′), 175.9 (C_{quat}, CO), characteristic signals of the diastereomer: $\delta = 29.26$ (−, CH_2), 34.9 (−, C-1′), 41.4 (+, C-4), 65.1, 65.6 (−, OCH_2CH_2O), 80.3 (+, C-2), 101.8 (+, CH), 118.3 (−, C-3′), 133.2 (+, C-2′); IR (film): $\tilde{\nu}$ = 3078, 2953, 2890, 2760, 1782, 1642, 1420, 1356, 1187, 1131, 1025, 994, 945, 922 cm^{-1}; MS (DCI, NH_3): *m*/*z* (%): 250.3 [MH$^+$ − 3NH_3] (10), 233.2 [MH$^+$+2NH_3] (5), 216.2 [M^++NH_4] (100); elemental analysis calcd (%) for $C_{10}H_{14}O_4$ (198.2): C 60.59, H 7.12; found: C 60.76, H 7.12.

(2*S/*R**,3*R**)-3-(1,3-dioxolan-2-yl)-5-oxo-2-(2-oxo-2-phenylethyl)-tetrahydrofuran (6b)**: A solution of (*rac*)-**11**-Me (230 mg, 1.0 mmol) in dry CH_2Cl_2 (5 mL) was treated with $BF_3 \cdot OEt_2$ (126 μL, 1.0 mmol, 1 equiv) at −78 °C. After 30 min 1-phenylvinyl trimethylsilyl ether (226 μL, 1.1 mmol, 1 equiv) was added and stirring continued for 12 h. The reaction was quenched with saturated $NaHCO_3$ solution (0.2 mL) and the mixture was allowed to warm to 0 °C. After drying ($MgSO_4$) the mixture was filtered and concentrated. The intermediate product was dissolved in benzene, treated with the tin-catalyst **15** (2.4 mg, 0.56 mol%) and ethane-1,2-diol (123 μL, 2.2 mmol, 2.2 equiv) and refluxed with a Dean-Stark trap for 6 h. The organic layer was washed with saturated $NaHCO_3$ solution (10 mL) and with H_2O (2 × 10 mL). The combined aqueous layers were extracted with Et_2O (3 × 10 mL). The combined organic layers were dried, filtered and concentrated at 20 °C. After chromatography on silica gel (hexanes/EE 1:1, 1 vol% NEt_3), **6b** was obtained as a colorless solid (71 mg, 26%). R_f (PE/EE 1:1) = 0.21; m.p. 94–95 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 2.57$–2.80 (m, 3H, 3-H, 4-H), 3.37 (dd, $J = 17.4$, 5.7 Hz, 1H, 1′-H), 3.49 (dd, $J = 17.4$, 6.1 Hz, 1H, 1′-H), 3.83–4.03 (m, 4H, OCH_2CH_2O), 5.01 (d, $J = 3.4$ Hz, 1H, CH), 5.08 (dd, $J =$ Hz, 11.2, 5.6 Hz, 1H, 2-H), 7.41–7.51 (m, 2H, Ar-H), 7.55–7.63 (m, 1H, Ar-H), 7.88–7.99 (m, 2H, Ar-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 29.5$ (−, C-4), 43.3 (−, C-1′), 42.4 (−, C-4), 65.3, 65.4 (−, OCH_2CH_2O), 76.3, 76.7 (+, C-2), 103.4 (+, CH), 128.0, 128.7, 133.6, 136.4 (Ar-C), 175.6 (C_{quat}, CO), 196.2 (C-2′); IR (KBr): $\tilde{\nu}$ = 2961, 2882, 2360, 2342, 1769, 1685, 1387, 1196, 1013, 939 cm^{-1}; MS (EI, 70eV): *m*/*z* (%): 276.1 (5) [M^+], 149.1 (15), 105.1 (70), 73.1 (100); elemental analysis calcd (%) for $C_{15}H_{16}O_5$ (276.3): C 65.21, H 5.84; found C 65.02, H 5.84.

(2*S*/*R*,3*R*)-(−)-3-Formyl-5-oxo-2-pentyl-tetrahydrofuran (16): A solution of **5b** (134 mg, 0.744 mmol, 1.0 equiv) and Pd/C (40 mg, 5 mol%) in methanol (10 mL) was stirred under hydrogen atmosphere (1 atm) at RT for 24 h. After filtration, evaporation of the solvent and chromatography on silica gel **16** was obtained as a colorless oil in quantitative yield (137 mg, *dr* 97:3). R_f (hexanes/EE 1:1) = 0.17; $[\alpha]_D^{20} = -42.9$ ($c = 1.1$ in CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.85$–0.92 (m, 3H, CH_3), 1.24–1.56 (m, 6H, CH_2), 1.65–1.82 (m, 2H, CH_2), 2.74 (dd, $J = 17.9$, 9.9 Hz, 1H, 4-H), 2.91 (dd, $J = 17.9$, 7.6 Hz, 1H, 4-H), 3.11 (dddd, $J = 9.9$, 7.6, 6.3, 1.5 Hz, 1H, 3-H), 4.65 (ddd, $J = 7.4$, 6.3, 5.5 Hz, 1H, 2-H), 9.73 (d, $J = 1.5$ Hz, 1H, CHO), characteristic signals of the diastereomer (2*R*): $\delta = 9.81$ (d, J = 2.0 Hz, CHO); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 13.9$ (+, CH_3), 22.4 (−, CH_2), 24.8 (−, CH_2), 29.0 (−, C-4), 31.3 (−, CH_2), 35.5 (−, C-1′), 52.6 (+, C-3), 79.1 (+, C-2), 174.1 (C_{quat}, C-5), 197.3 (+, CHO), characteristic signals of the diastereomer (2R): $\delta = 80.5$ (+, C-2); IR (film): $\tilde{\nu}$ = 2933, 2860, 1773, 1665, 1362, 1199 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 184.2 [M^+] (5), 113.1 [M − $C_5H_{11}^+$] (100), 85.1 (70), 57.1 (60), 43.1 (60), 29.2 (45); elemental analysis calcd (%) for $C_{10}H_{16}O_3$ (184.2): C 65.19, H 8.75; found: C 64.89, H 8.50.

(2*S*,3*R*)-(−)-Tetrahydro-5-oxo-2-pentyl-3-furan carboxylic acid (17): A solution of KH_2PO_4 (14 mg, 0.101 mmol) in H_2O (0.5 mL), $NaClO_2$ (32 mg, 0.27 mmol, 1.6 equiv) and 30% H_2O_2 (15 μL) were added at 0 °C to a solution of **16** (50 mg, 0.169 mmol, 1.0 equiv) in CH_3CN (5 mL). The mixture was stirred for 1.5 h. Then Na_2SO_3 (80 mg) was added and stirring was continued for an additional hour. The solution was acidified to pH 2 by addition of an aqueous solution of 1N KH_2SO_4 solution. The mixture was extracted with CH_2Cl_2 (10 × 5 mL), the organic layers were dried and evaporated at room temperature. After crystallization from ethyl acetate

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17 was obtained as colorless solid (29 mg, 86 %). M.p. 105 °C; $[\alpha]_D^{20} = -52$ ($c = 0.5$ in $CHCl_3$), lit.:[10c] -52 ($c = 0.52$ in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.90$ (t, $J = 7.1$ Hz, 3H, CH_3), 1.25–1.58 (m, 6H, CH_2), 1.65–1.85 (m, 2H, CH_2), 2.83 (dd, $J = 17.9$, 9.6 Hz, 1H, 4-H), 2.95 (dd, $J = 17.9$, 8.3 Hz, 1H, 4-H), 3.10 (ddd, $J = 9.5$, 8.3, 7.1 Hz, 1H, 3-H), 4.63 (ddd, $J = 7.6$, 7.1, 4.8 Hz, 1H, 2-H), 8.64 (brs, 1H, COOH); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 13.9$ (+, CH_3), 22.4 (−, CH_2), 24.8 (−, CH_2), 31.3 (−, CH_2), 31.9 (−, CH_2), 35.3 (−, CH_2), 45.4 (+, C-3), 81.9 (+, C-2), 174.6 (C_{quat}, C-5), 176.4 (C_{quat}, CO_2H); MS (EI, 70 eV): m/z (%): 201.2 [MH$^+$] (2), 182.2 [$M^+ - H_2O$] (5), 129.1 [$M^+ - C_5H_{11}$] (60), 101.1 (100), 55.0 (70).

(*E*)/(*Z*)-(4*R*,5*S*/*R*)-(−)-4-[1,3]Dioxolan-2-yl-5-tridec-2-enyl-dihydrofuran-2-one (24): Compound **5a** (327 mg, 1.65 mmol), 1-dodecene (550 μL, 2.48 mmol, 1.5 equiv) and **23** (68 mg, 5 mol %) were given into dry CH_2Cl_2 (25 mL), refluxed for 8 h and stirred for additional 10 h at 30 °C. After chromatography on silica gel (hexanes/EE 2:1), **24** was obtained as colorless oil (317 mg, 57 %, *dr* 95:5, *E*/*Z* 3.5:1). R_f (hexanes/EE 1:1) = 0.50; $[\alpha]_D^{20} = -13.4$ ($c = 0.85$, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.86$ (t, $J = 6.5$ Hz, 3H, CH_3), 1.23 (brs, 16H, CH_2), 1.99 (ddt, $J = 7.0$, 7.0, 0.4 Hz, 2H, 4′-H), 2.27–2.60 (m, 5H, 1′-H, 3-H, 4-H), 3.81–4.03 (m, 4H, OCH_2CH_2O), 4.43–4.57 (m, 1H, CH), 4.86 (dt, $J = 2.3$, 1.3 Hz, 1H, 5-H), 5.37 (dtt, $J = 15.2$, 6.9, 1.2 Hz, 1H, =CH-), 5.58 (dtt, $J = 15.2$, 6.6, 1.2 Hz, 1H, =CH-), characteristic signals of the diastereomer: $\delta = 4.99$ (d, $J = 3.6$ Hz, 1H, CH), Major diastereomer: ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 14.1$ (+, CH_3), 22.7 (−, CH_2), 29.16 (−, CH_2), 29.26 (−, CH_2), 29.32 (−, CH_2), 29.47 (−, CH_2), 29.51 (−, CH_2), 29.60 (−, C-3, CH_2), 31.9 (−, CH_2), 32.62 (−, CH_2), 38.0 (−, CH_2), 42.2 (+, C-4), 65.3, 65.4 (−, OCH_2CH_2O), 80.22 (+, C-5), 103.6 (+, CH), 122.9 (+, =CH-), 135.8 (+, =CH-), 176.1 (C_{quat}, CO), characteristic signals of the diastereomer: $\delta = 29.15$ (−, CH_2), 29.23 (−, CH_2), 29.9 (−, C-3), 33.7 (−, CH_2), 34.9 (−, C-1′), 41.4 (+, C-4), 65.1, 65.6 (−, OCH_2CH_2O), 80.94 (+, C-5), 101.9 (+, CH), 124.1 (+, =CH-), 134.7 (+, =CH-), characteristic signals of the diastereomer: $\delta = 27.5$ (−, CH_2), 29.30 (−, CH_2), 29.43 (−, CH_2), 29.62 (−, CH_2), 32.60 (−, CH_2), 42.5 (+, C-4), 80.24 (+, C-5), 122.2 (+, =CH-), 134.4 (+, =CH-), 175.9 (C_{quat}, CO), characteristic signals of the diastereomer: $\delta = 80.76$ (+, C-5), 123.1 (+, =CH-); IR (film): $\tilde{\nu} = 2924$, 2853, 1781, 1465, 1421, 1354, 1181, 1133, 1031, 974, 945, 920 cm^{-1}; MS (EI, 70 eV): m/z (%): 338.0 [M^+] (1), 210.0 (3), 154.9 (9), 98.9 (4), 82.9 (3), 72.9 (100), 55.0 (6), 45.0 (7), 43.0 (6); elemental analysis calcd (%) for $C_{20}H_{34}O_4$ (338.5): C 70.97, H 10.12; found: C 70.70, H 10.02.

(4*R*,5*S*/*R*)-(−)-4-[1,3]Dioxolan-2-yl-5-tridecyl-dihydrofuran-2-one (25): A solution of **24** (280 mg, 0.83 mmol) and Pd/C (50 mg, 5 mol %) in methanol (50 mL) was stirred under H_2 atmosphere at room temperature for 24 h. After filtration and evaporation of the solvent, **25** was obtained as a colorless solid (281 mg, quant., *dr* 95:5). R_f (hexanes/EE 2:1) = 0.30; m.p. 46 °C; $[\alpha]_D^{20} = -26.5$ ($c = 1.0$, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.86$ (t, $J = 6.5$ Hz, 3H, CH_3), 1.25 (brs, 22H, CH_2), 1.61–1.72 (m, 2H, CH_2), 2.42–2.69 (m, 3H, 3-H, 4-H), 3.87–4.03 (m, 4H, OCH_2CH_2O), 4.46 (dt, $J = 7.3$, 5.0 Hz, 1H, CH), 4.88 (d, $J = 4.9$ Hz, 1H, 2-H), characteristic signals of the diastereomer: $\delta = 4.98$ (d, $J = 3.8$ Hz, 1H, CH); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 14.1$ (+, CH_3), 22.7 (−, CH_2), 25.6 (−, CH_2), 29.25 (−, CH_2), 29.33 (−, CH_2), 29.43 (−, CH_2), 29.51 (−, CH_2), 29.63 (−, C-3, CH_2), 29.66 (−, CH_2), 31.9 (−, CH_2), 35.6 (−, CH_2), 43.6 (+, C-4), 65.36, 65.41 (−, OCH_2CH_2O), 81.0 (+, C-5), 103.6 (+, CH), 176.1 (C_{quat}, CO), characteristic signals of the diastereomer: $\delta = 26.3$ (−, CH_2), 29.35 (−, CH_2), 29.46 (−, CH_2), 29.52 (−, CH_2), 29.61 (−, CH_2), 29.9 (−, C-3), 31.9 (−, CH_2), 41.6 (+, C-4), 65.1, 65.6 (−, OCH_2CH_2O), 81.4 (+, C-5), 102.1 (+, CH); IR (KBr): $\tilde{\nu} = 2919$, 2849, 1764, 1466, 1427, 1214, 1153, 1063, 982, 941, 721 cm^{-1}; MS (DCI, NH_3): m/z (%): 358.5 [M^++NH_4] (100), 344.5 [M^+] (2), 136.2 (6); elemental analysis calcd (%) for $C_{20}H_{36}O_4$ (340.5): C 70.55, H 10.66, found: C 70.37, H 10.60.

(2*S*,3*R*)-(−)-5-Oxo-2-tridecyltetrahydrofuran-3-carboxylic acid (26): A solution of the **25** (259 mg, 0.761 mmol) in acetone (10 mL) was treated with freshly prepared Jones reagent (760 mg CrO_3 + 0.75 mL H_2SO_4 + 1.5 mL H_2O) at 0 °C. After 48 h of stirring at 0 °C (TLC), 2-propanol (10 mL) was added to destroy the excess reagent. The reaction mixture was diluted with H_2O (10 mL) and acetone was removed under reduced pressure. The residue was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were concentrated, taken up in ethyl acetate and washed with H_2O (3 × 5 mL). The organic layer was dried, filtered and concentrated. After chromatography on silica gel ($CHCl_3$/EE/HOAc 90:8:2), **26** was obtained as a colorless solid (209 mg, 88 %). R_f ($CHCl_3$/EE/HOAc 90:8:2) = 0.24; m.p. 108 °C, lit.:[9d] 109–111 °C, $[\alpha]_D^{20} = -40.5$ ($c = 0.32$, $CHCl_3$), lit.:[9d] -41 ($c = 0.5$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 6.7$ Hz, 3H, CH_3), 1.26 (brs, 18H, CH_2), 1.40–1.60 (m, 2H, CH_2), 1.72–1.83 (m, 2H, CH_2), 2.83 (dd, $J = 17.9$, 9.6 Hz, 1H, 4-H), 2.95 (dd, $J = 17.9$, 8.3 Hz, 1H, 4-H), 3.10 (ddd, $J = 9.6$, 8.3, 7.2 Hz, 1H, 3-H), 4.62 (ddd, $J = 7.4$, 7.3, 4.8 Hz, 1H, 2-H), 8.64 (brs, 1H, CO_2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 14.1$ (+, CH_3), 22.7 (−, CH_2), 25.2 (−, CH_2), 29.2 (−, CH_2), 29.37 (−, CH_2), 29.42 (−, CH_2), 29.52 (−, CH_2), 29.63 (−, CH_2), 29.67 (−, CH_2), 29.70 (−, CH_2), 31.91 (−, CH_2), 31.94 (−, CH_2), 35.40 (−, CH_2), 45.4 (+, C-3), 81.8 (+, C-2), 174.2 (C_{quat}, CO), 175.9 (C_{quat}, CO).

(2*S*,3*R*,4*R*)-(−)-4-Methyl-5-oxo-2-tridecyltetrahydrofuran-3-carboxylic acid, roccellaric acid (19): A solution of **26** (20 mg, 0.064 mmol) in dry THF (1.4 mL) was added to a solution of sodium bis(trimethylsilyl)amide (1 M in THF, 140 μL, 0.140 mmol, 2.2 equiv) at −78 °C under Argon over 30 minutes. The mixture was stirred at −78 °C for 3 h. Methyl iodide (40 μL, 0.61 mmol, 9.6 equiv) was slowly added and the mixture was stirred for additional 12 h. The mixture was allowed to warm to −20 °C. 2 N HCl (2 mL) was added, the mixture was extracted with Et_2O (5 × 2 mL) and the combined organic layers was washed with saturated Na_2SO_3 solution and dried. **27** was obtained as a colorless solid (20 mg, 96 %). R_f ($CHCl_3$/EE/HOAc 90:8:2) = 0.25; m.p. 110 °C, lit.:[8b] 108 °C; $[\alpha]_D^{20} = -26$ ($c = 0.5$, $CHCl_3$), lit.:[8b] -26 ($c = 1.93$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 6.5$ Hz, 3H, CH_3), 1.18–1.47 (m, 21H, CH_2), 1.37 (d, $J = 7.1$ Hz, 3H, CH_3), 1.48–1.59 (m, 1H, 1′-H), 1.65–1.77 (m, 1H, 1′-H), 1.78–1.88 (m, 1H, 1′-H), 2.70 (dd, $J = 11.4$, 9.1 Hz, 1H, 3-H), 2.99 (dq, $J = 11.4$, 7.1 Hz, 1H, 4-H), 4.48 (ddd, $J = 9.1$, 8.7, 4.1 Hz, 1H, 2-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 14.1$ (+, CH_3), 14.5 (+, CH_3), 22.7 (−, CH_2), 25.3 (−, CH_2), 29.22 (−, CH_2), 29.34 (−, CH_2), 29.38 (−, CH_2), 29.50 (−, CH_2), 29.60 (−, CH_2), 29.64 (−, CH_2), 29.67 (−, CH_2), 31.91 (−, CH_2), 34.92 (−, CH_2), 39.8 (+, C-3), 53.8 (+, C-4), 79.3 (+, C-2), 175.3 (C_{quat}, CO), 176.5 (C_{quat}, CO).

(*E*)/(*Z*)-(2*S*/*R*,3*R*)-(−)-5-Oxo-2-undec-2-enyltetrahydrofuran-3-carbaldehyde (28): A mixture of **5a** (310 mg, 2.01 mmol), 1-decene (800 μL, 95 % purity (Acros), 4.03 mmol, 2.0 equiv) and **27** (51.2 mg, 3 mol %) in dry CH_2Cl_2 (40 mL) was heated under reflux for 7 h. Since the TLC showed still starting material, **27** (34 mg, 2 mol %) and 1-decene (400 μL, 1.0 equiv) were added and refluxing continued for 23 h. 1-Decene (400 μL, 1.0 equiv) was added again and refluxing was continued for additional 20 h. After evaporation of the solvent and chromatography on silica gel (hexanes/EE 1:1), **28** (284 mg, 53 %, *dr* 95:5, *E*/*Z* 7:1) as an oil and **5a** (85 mg, 27 %) [R_f (hexanes/EE 1:1) = 0.25] were obtained (conversion yield = 73 %). R_f (hexanes/EE 1:1) = 0.36; $[\alpha]_D^{20} = -13.4$ ($c = 1.55$ in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 6.5$ Hz, 3H, CH_3), 1.25 (m, 12H, CH_2), 2.01 (ddt, $J = 6.9$, 6.9, 0.4 Hz, 2H, 4′-H), 2.41–3.23 (m, 5H, 1′-H, 4-H, 3-H), 4.71 (dt, $J = 6.1$, 2.3, 1H, 2-H), 5.37 (dtt, $J = 15.3$, 7.0, 1.2 Hz, 1H, =CH-), 5.67 (dtt, $J = 15.3$, 6.8, 1.2 Hz, 1H, =CH-), 9.71 (d, $J = 1.29$ Hz 1H,): major diastereomeric aldehyde (2*S*); 9.73 (d, $J = 1.26$ Hz): minor diastereomeric aldehyde (2*R*); ^{13}C NMR (62.9 MHz $CDCl_3$): $\delta = 14.05$ (+, CH_3), 22.65 (−, CH_2), 28.87 (−, CH_2), 29.16 (−, 2C, CH_2), 29.24 (−, CH_2), 29.39 (−, CH_2), 51.25 (+, C-3), 78.54 (+, C-2), 121.75 (+, =CH-), 137.17 (+, =CH-), 174.06 (C_{quat}), 197.25 (+, -CHO); IR (film): $\tilde{\nu} = 3427$, 2925, 2854, 2360, 1772, 1457, 1363, 1194, 1024, 927 cm^{-1}; HRMS: calcd for $C_{16}H_{26}O_3$: 266.1900, found: 266.1881.

(2*S*,3*R*)-(−)-5-Oxo-2-undecyltetrahydrofuran-3-carbaldehyde (29): 1.4 mol % Pd/C (15 mg) was added to a solution of **28** (266 mg, 1 mmol) in methanol (50 mL) and stirred under hydrogen atmosphere at room temperature for 24 h. After filtration, evaporation of the solvent and recrystallization from ethyl acetate **29** was obtained as a viscous oil (240 mg, 90 %). R_f ($CHCl_3$/MeOH 95:5) = 0.35; $[\alpha]_D^{20} = -24.8$ ($c = 1.70$ in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 6.5$ Hz, 3H, CH_3), 1.25 (m, 18H, CH_2), 1.62–1.81 (m, 2H, CH_2), 2.69–3.15 (m, 3H, 3-H, 4-H), 4.66 (dt, $J = 7.0$, 6.3 Hz, 1H, 2-H), 9.73 (s, 1H, CHO); ^{13}C NMR (100 MHz): $\delta = 13.66$ (+, CH_3), 22.63 (−, CH_2), 25.09 (−, CH_2), 28.98 (−, CH_2), 29.15 (−, CH_2), 29.29 (−, CH_2), 29.35 (−, CH_2), 29.45 (−, CH_2), 29.55 (−, CH_2), 31.80 (−, CH_2), 35.61 (−, CH_2), 52.13 (+, C-3)), 78.91 (+, C-2), 174.07 (C_{quat}), 197.15 (+,-CHO); IR (film): $\tilde{\nu} = 3418$, 2922, 2852, 1731, 1651, 1466, 1417, 1377, 1221, 1103 cm^{-1}; HRMS: calcd for $C_{16}H_{28}O_3$: 268.2000; found: 268.2038.

(2*S*,3*R*)-(−)-5-Oxo-2-undecyltetrahydrofuran-3-carboxylic acid (30): A solution of KH_2PO_4 (96 mg, 0.72 mmol) in H_2O (1 mL), $NaClO_2$ (166 mg, 1.8 mmol) and 30 % H_2O_2 (42 mg) was added at 0 °C to a solution of **29**

(150 mg, 0.56 mmol) in CH_3CN (13 mL). The mixture was stirred for 48 h. Then Na_2SO_3 (114 mg) was added and stirring was continued for an additional hour. The solution was acidified to pH 2 by addition of an aqueous solution of 1N KH_2SO_4 solution. The mixture was extracted with CH_2Cl_2 (200 mL), the organic layers were dried and evaporated at room temperature. After crystallization from ethyl acetate **30** was obtained as colorless microcrystals (114.6 mg, 72%). R_f ($CHCl_3$/EE/HOAc 90:8:2) = 0.24; m.p. 121 °C; $[\alpha]_D^{20} = -47.4$ ($c = 0.35$ in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 6.5$ Hz, 3H, CH_3), 1.26 (m, 18H, CH_2), 1.66–2.11 (m, 2H, CH_2), 2.70–2.90 (m, 2H, 4-H), 3.37–3.40 (m, 1H, 3-H), 4.61 (m, 1H, 2-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 14.65$ (+, CH_3), 23.56 (−, CH_2), 26.53 (−, CH_2), 30.31 (−, CH_2), 30.36 (−, CH_2), 30.46 (−, CH_2), 30.52 (−, CH_2), 30.59 (−, CH_2), 30.61 (−, CH_2), 32.91 (−, CH_2), 34.39 (−, CH_2), 36.44 (−, CH_2), 49.41 (+, C-3), 85.60 (+, C-2), 174.18 (C_{quat}), 174.86 (C_{quat}); IR (KBr): $\tilde{\nu} = 3442$, 2922, 2853, 1749, 1599, 1466, 1424, 1236, 1095, 1020 cm^{-1}; HRMS: calcd for $C_{16}H_{28}O_4$ 284.200; found: 284.1987.

(2*S*,3*R*,4*R*)-(−)-4-Methyl-5-oxo-2-tridecyltetrahydrofuran-3-carboxylic acid, nephrosteranic acid (20): A solution of **30** (50 mg, 0.176 mmol) in dry THF (30 mL) was added to sodium bis(trimethylsilyl)amide (1M solution in THF, 630 μL, 0.63 mmol, 3.6 equiv) at −78 °C under argon over 30 minutes. The mixture was stirred at −78 °C for 24 h. Methyliodide (2.71 mmol, 200 μL) was slowly added and the mixture was stirred for additional 24 h. The mixture was allowed to warm to −20 °C. HCl (1N, 3.1 mL) was added, the mixture was extracted with Et_2O (3 × 10 mL) and the organic layer was washed with brine and dried. **20** was obtained as colorless microcrystals (47.2 mg, 90%). R_f ($CHCl_3$/ethyl acetate/HOAc 90:80:2) = 0.25; m.p. 109 °C; $[\alpha]_D^{20} = -27.7$ ($c = 0.90$ in $CHCl_3$), $[\alpha]_D^{20} = -28.1$ ($c = 1.02$ in $CHCl_3$);[9b] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 6.5$ Hz, 3H, CH_3), 1.20–1.47 (m, 20H, CH_2), 1.38 (d, $J = 7.1$ Hz, 3H, CH_3), 2.65–2.75 (m, 1H, 4-H), 2.93–3.08 (m, 1H, 3-H), 4.48 (ddd, $J = 9.0$, 8.7, 4.2 Hz, 1H, 2-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 14.10$ (+, CH_3), 14.50 (+, CH_3), 22.65 (−, CH_2), 25.34 (−, CH_2), 29.24 (−, CH_2), 29.32 (−, CH_2), 29.40 (−, CH_2), 29.51 (−, CH_2), 29.61 (−, CH_2), 31.91 (−, CH_2), 34.94 (−, CH_2), 39.34 (+, C-3), 53.55 (+, C-4), 79.05 (+, C-2), 175.58 (C_{quat}), 176.66 (C_{quat}); IR (KBr): $\tilde{\nu} = 3456$, 2921, 2852, 1748, 1469, 1260, 1201, 1172. 1100, 1026, 802 cm^{-1}; HRMS: calcd for $C_{17}H_{30}O_4$: 298.2100; found: 298.2144.

Tetradec-13-enoic-acid methylester (31): A solution of tetradec-13-enoic acid (4.17 g, 18.4 mmol) and conc. H_2SO_4 (1 mL) in MeOH (100 mL) was refluxed for 12 h. The mixture was concentrated to half of its original volume, diluted with H_2O (250 mL), and the remaining methanol was evaporated. The mixture was extracted with pentane (500 mL), and the organic layer was washed with saturated $NaHCO_3$ solution and concentrated. After chromatography on silica gel (hexanes/EE 10:1), **31** was obtained as colorless oil (4.0 g, 90%). R_f (hexanes/EE 1:1) = 0.74; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.23$ (brs, 16H, CH_2), 1.54–1.71 (m, 2H, CH_2), 1.97–2.10 (m, 2H, CH_2), 2.30 (t, $J = 7.6$ Hz, 2H, CH_2), 3.67 (s, 3H, OCH_3), 4.91 (ddt, $J = 10.1$, 2.3, 1.2 Hz, 1H, 14-H), 4.98 (ddt, $J = 17.1$, 2.2, 16. Hz, 1H, 14-H), 5.80 (ddt, $J = 17.1$, 10.1, 6.7 Hz, 1H, 13-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.92$ (−, CH_2), 28.91 (−, CH_2), 29.10 (−, CH_2), 29.11 (−, CH_2), 29.22 (−, CH_2), 29.40 (−, CH_2), 29.45 (−, CH_2), 29.53 (−, CH_2), 33.79 (−, CH_2), 34.08 (−, CH_2), 51.38 (+, CH_3), 114.03 (−, CH_2), 139.18 (+, CH), 174.3 (+, CO); IR (film): $\tilde{\nu} = 3077$, 2926, 2854, 1743, 1641, 1436, 1362, 1247, 1196, 1171, 1117, 994, 909 cm^{-1}; HRMS: calcd for $C_{15}H_{28}O_2$: 249.2100; found: 240.2089; elemental analysis calcd (%) for $C_{15}H_{28}O_2$ (240.21): C 74.95; H 11.74 found: C 74.89; H 11.82.

(*E*)/(*Z*)-(2*S*/*R*,3*R*)-(−)-15-(3-Formyl-5-oxo-tetrahydrofuran-2-yl)-pentadec-13-enoic acid methylester (32): Compound **5a** (500 mg, 3.25 mmol, *dr* = 95:5), **31** (1.0 g, 4.16 mmol, 1.3 equiv) and **27** (75 mg, 2.7 mol%) were added into dry CH_2Cl_2 (60 mL) and the resulting soltuion was heated under reflux for 24 h. After chromatography on silica gel (hexanes/EE 1:1), **30** was obtained as an oil (448 mg, 38%, *dr* 95:5, *E*/*Z* 7:1) and **5a** (282 mg, 56%) were recovered (conversion yield = 86%). R_f (hexanes/EE 1:1) = 0.37; $[\alpha]_D^{20} = -9.5$ ($c = 2.45$ in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.26$ (brs, 16H, CH_2), 1.51–1.70 (m, 2H, CH_2), 1.94–2.09 (m, 2H, CH_2), 2.30 (t, $J = 7.4$ Hz, 2H, 2′-H), 2.39–2.62 (m, 2H, CH_2), 2.71 (dd, $J = 17.8$, 9.9 Hz, 1H, 4-H), 2.92 (dd, $J = 18.0$, 7.3 Hz, 1H, 4-H), 3.19 (dddd, $J = 9.9$, 7.3, 6.0, 1.3 Hz, 1H, 3-H), 3.67 (s, 3H, OCH_3), 4.66–4.76 (m, 1H, 3-H), 5.28–5.42 (m, 1H, =CH-), 5.57–5.72 (m, 1H, =CH-), 9.70 (d, $J = 1.3$ Hz, 1H, -CHO) characteristic signals of the diastereomer (2*R*): 9.72 (d, $J = 1.3$ Hz, CHO); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 24.90$ (−, CH_2), 24.81 (−, CH_2), 28.90 (−, CH_2), 29.14 (−, CH_2), 29.18 (−, CH_2), 29.19 (−, CH_2), 29.24 (−, CH_2), 29.42 (−, CH_2), 29.43 (−, CH_2), 29.55 (−, 2C, CH_2), 32.63 (−, CH_2), 34.12 (−, CH_2), 38.09 (−, CH_2), 51.23 (+, CH), 51.39 (+, CH_3), 78.51 (+, CH), 121.73 (+, =CH), 137.13 (+, =CH), 174.07 (C_{quat}), 174.33 (C_{quat}), 197.27 (+, -CHO); IR (film) $\tilde{\nu} = 3442$, 2926, 2854, 1777, 1739, 1594, 1437, 1363, 1196, 1114, 1022, 973 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 366.2 (2.0) [M^+], 334.1 (15.7), 316.2 (31.0), 113.0 (100.0), 85.0 (65.9); HRMS: calcd $C_{21}H_{34}O_5$: 366.2406; found: 366.2409 [M^+].

(2*S*,3*R*)-15-(3-Formyl-5-oxotetrahydrofuran-2-yl)-pentadecanoic methyl ester (33): Pd/C (57 mg, 5 mol%) was added to a solution of **32** (392 mg, 1.07 mmol) in methanol (40 mL), and stirred under H_2 atmosphere at room temperature for 18 h. After filtration and evaporation of the solvent **33** was obtained as a colorless oil (347 mg, 88%). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.21–1.84$ (m, 28H, CH_2), 2.30 (t, $J = 7.6$ Hz, 2H, CH_2CO_2Me), 2.76 (dd, $J = 17.8$, 9.9 Hz, 1H, 4-H), 2.92 (dd, $J = 17.8$, 7.7 Hz, 1H, 4-H), 3.12 (dddd, $J = 9.9$, 7.7, 6.3, 1.5 Hz, 1H, 3-H), 3.67 (s, 3H, CH_3), 4.66 (m, 1H, 2-H), 9.74 (d, $J = 1.5$ Hz, 1H, CHO); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 24.97$ (−, CH_2), 25.15 (−, CH_2), 29.03 (−, CH_2), 29.16 (−, CH_2), 29.19 (−, CH_2), 29.27 (−, CH_2), 29.39 (−, CH_2), 29.45 (−, CH_2), 29.48 (−, CH_2), 29.59 (−, 2C, CH_2), 29.61 (−, CH_2), 29.62 (−, CH_2), 34.14 (−, CH_2), 35.58 (−, CH_2), 51.47 (+, CH_3), 52.57 (+, CH), 79.14 (+, CH), 174.11 (C_{quat}), 174.43 (C_{quat}), 197.30 (+, CHO); MS (DCI): *m*/*z* (%): 369.3 (29.6) [*M*H$^+$], 337.2 (100.0, ΔCH_3OH); HRMS: calcd for $C_{21}H_{36}O_5$: 369.2641; found: 369.2640 [M^+].

(2*S*,3*R*)-(−)-2-(14-Methoxycarbonyl-tetradecyl)-5-oxo-tetrahydrofuran-3-carboxylic acid (34): A solution of the **33** (309 mg, 0.839 mmol) in acetone (7 mL) was treated with 2 mL of freshly prepared Jones reagent (2.5 g CrO_3 + 3 mL H_2SO_4 + 25 mL H_2O) at 0 °C until the color was presisted. After 7 h of stirring at 0 °C (controlled by TLC), 2-propanol (7 mL) was added to destroy the excess reagent. The reaction mixture was diluted with H_2O (5 mL) and acetone was removed under reduced pressure. The residue was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were washed with brine (30 mL), dried and concentrated in vacuo to give **34** as colorless solid (311 mg, 96%). R_f ($CHCl_3$/MeOH 9:1) = 0.22; m.p. 120–124 °C; $[\alpha]_D^{20} = -26.0$ ($c = 0.75$ in $CHCl_3$); ^{1}H NMR (250 Hz, $CDCl_3$): $\delta = 1.25$ (brs, 24H, CH_2), 1.55–1.82 (m, 2H, 15′-H), 2.3 (t, $J = 7.5$ Hz, 2H, 2′-H), 2.75–3.14 (m, 3H, 4-H, 3-H), 3.67 (s, 3H, OCH_3), 4.56–4.67 (m, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.90$ (−, CH_2), 25.10 (−, CH_2), 29.09 (−, CH_2), 29.18 (−, CH_2), 29.28 (−, CH_2), 29.34 (−, CH_2), 29.38 (−, CH_2), 29.40 (−, CH_2), 29.47 (−, CH_2), 29.50 (−, CH_2), 29.52 (−, CH_2), 29.53 (−, CH_2), 31.90 (−, CH_2), 34.10 (−, CH_2), 35.31 (−, CH_2), 45.00 (+, CH), 51.27 (+, CH_3), 81.75 (+, CH), 174.45 (C_{quat}), 174.69 (C_{quat}), 175.71 (C_{quat}); IR (film): $\tilde{\nu} = 3449$, 3116, 2921, 2850, 1748, 1464, 1436, 1394, 1358, 1239, 1194, 1171, 1114, 973 cm^{-1}; HRMS: calcd for $C_{21}H_{36}O_6$: 384.2500; found: 383.2428 [$M^+ - H$].

(2*S*,3*R*)-(−)-2-(14-Carboxy-tetradecyl)-5-oxo-tetrahydrofuran-3-carboxylic acid (35): Compound **34** (100 mg, 0.3 mmol) was added to a mixture of MeOH (60 mL) and saturated aqueous LiOH solution (10 mL) and the mixture was stirred for 2 d. The mixture was acidified with 20% HCl solution and saturated with NaCl (pH ≥ 7). The mixture was extracted with CH_2Cl_2 several times (TLC), dried and concentrated to get the crude product which after chromatography on silica gel ($CHCl_3$/MeOH/AcOH 9:8:2) gave **35** as a colorless solid (91 mg, 94%). R_f ($CHCl_3$/MeOH 9:1) = 0.12; m.p. 128 °C; $[\alpha]_D^{20} = -15.0$ ($c = 0.90$ in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD): $\delta = 1.28$ (brs, 22H, CH_2), 1.59–1.64 (m, 2H, CH_2), 1.69–1.88 (m, 2H, CH_2), 2.29 (t, $J = 7.5$ Hz, 2H, 2′-H), 2.81 (dd, $J = 17.9$, 9.6 Hz, 1H, 4-H), 2.93 (dd, $J = 17.9$, 8.1 Hz, 1H, 4-H), 3.09 (ddd, $J = 9.6$, 8.3, 6.9 Hz, 1H, 3-H), 4.62–4.70 (m, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD): $\delta = 24.31$ (−, CH_2), 24.60 (−, CH_2), 28.47 (−, CH_2), 28.55 (−, CH_2), 28.63 (−, CH_2), 28.75 (−, CH_2), 28.80 (−, CH_2), 28.83 (−, CH_2), 28.91 (−, 2C, CH_2), 28.94 (−, 2C, CH_2), 31.41 (−, CH_2), 33.44 (−, CH_2), 34.65 (−, CH_2), 44.93 (+, CH), 82.32 (+, CH), 172.62 (C_{quat}), 175.71 (C_{quat}), 176.10 (C_{quat}); IR (film): $\tilde{\nu} = 3448$, 3140, 2921, 2849, 2679, 1747, 1718, 1462, 1436, 1278, 1238, 1194, 1114, 857 cm^{-1}; HRMS: calcd for $C_{20}H_{34}O_6$: 370.2400; found: 369.2281 [$M^+ - H$].

(2*S*,3*R*)-(−)-2-(14-Carboxytetradecyl)-4-methylen-5-oxo-tetrahydrofuran-3-carbonic acid, (−)-protopraesorediosic acid (22): Magnesium methylcarbonate (5.6 mL, 11.28 mmol, 38.0 equiv, 2M in DMF (Stiles reagent)) was added under argon atmosphere to **35** (110 mg, 0.297 mmol, 1.0 equiv) and the solution was stirred at 135 °C for 66 h. After cooling CH_2Cl_2 (35 mL) was added and the solution was acidified with cold 10% HCl. The aqueous layer was extracted with CH_2Cl_2 (4 × 30 mL) and the combined organic

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layers were washed with saturated NaCl solution (20 mL), and concentrated in vacuo. The residue was treated with 1.85 mL of a freshly prepared Stock solution (20 mL HOAc, 15 mL 37% formaldehyde in water, 5.2 mL *N*-methylaniline and 600 mg NaOAc) and stirred under argon for 2.5 h at room temperature. Et_2O (20 mL) and sat. NaCl solution (10 mL, containing 1 mL conc. HCl) were added and the aqueous layer was extracted with Et_2O (4×15 mL). The combined organic layers were washed with sat. NaCl solution (15 mL, containing 10 drops conc. HCl) and aqueous layer was re-extracted with Et_2O (2×15 mL). The combined organic layers were dried and the solvent was evaporated. After recrystallization from $CHCl_3$/pentane **22** was obtained as colorless microcrystals (71 mg, 62%, 0.1856 mmol). R_f ($CHCl_3$/MeOH/HOAc 90:8:2) = 0.25; m.p. 123 °C; $[\alpha]_D^{20} = -8.9$ ($c = 1.12$ in MeOH), $[\alpha]_D^{20} = +9.1$ (MeOH) for the enantiomer.[34] ^{1}H NMR (250 MHz, CD_3OD): $\delta = 1.30$ (br s, 24H, CH_2), 1.52–1.66 (m, 2H, CH_2), 1.68–1.78 (m, 2H, CH_2), 2.27 (t, $J = 7.4$ Hz, 2H, 2′-H), 3.71 (ddd, $J = 5.7$, 3.0, 2.7 Hz, 1H, 3-H), 4.78 (dt, $J = 5.7$, 6.4 Hz, 1H, 2-H), 5.99 (d, $J = 2.7$ Hz, 1H, $=CH_2$), 6.31 (d, $J = 3.0$ Hz, 1H, $=CH_2$); ^{13}C NMR (62.9 MHz, CD_3OD): $\delta = 26.01$ (−, CH_2), 26.12 (−, CH_2), 30.26 (−, CH_2), 30.35 (−, CH_2), 30.44 (−, CH_2), 30.58 (−, CH_2), 30.62 (−, CH_2), 30.65 (−, CH_2), 30.72 (−, CH_2), 30.73 (−, CH_2), 30.74 (−, CH_2), 30.75 (−, CH_2), 34.97 (−, CH_2), 36.59 (−, CH_2), 51.03 (+, CH), 81.29 (+, CH), 125.21 (−, $=CH_2$), 135.64 (C_{quat}), 170.65 (C_{quat}), 172.58 (C_{quat}), 177.73 (C_{quat}); IR (film): $\tilde{\nu} = 3442$, 2922, 2852, 1744, 1714, 1257 cm^{-1}; HRMS: calcd for $C_{21}H_{34}O_6$: 382.2355 (381.2275 for $[M - H^+]$, found: 381.2275.

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