

Chiral conformationally restricted arachidonic acid analogs based on a 1,3-dioxolan core

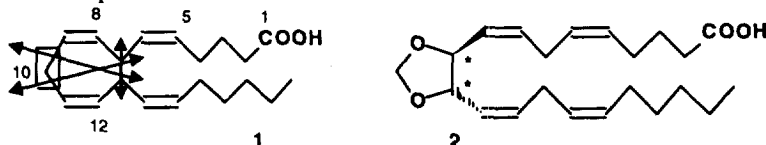
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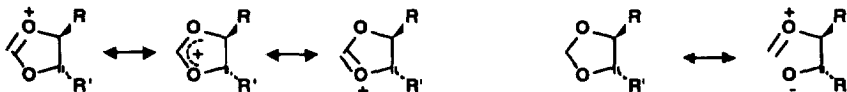
Abstract: Controlled Wittig condensations onto chiral building blocks derived from L-diethyl tartrate led to various chiral arachidonic acid analogs based on a dioxolan core.
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There is still a need to obtain analogs that mimic the various metabolites of the arachidonic acid cascade.¹ In recent years the trend in this field has been to prepare analogs that are somehow rigidified² and to introduce heteroatoms either along the chain of the acid or within a ring.³ Little interest has been devoted to chirality although this parameter was found to be crucial in other areas.⁴

In this article we describe the synthetic approach that allows the preparation of chiral arachidonic acid **1** analogs, having 2–4 double bonds including methylene interrupted moieties linked to a 1,3-dioxolan core. Such an oxygenated heterocycle would bridge the 7–13, 7–10, 10–13 positions in **1** or block the 10 position as shown in **2**, and allows the introduction of chirality by control of the appendage substitution pattern.



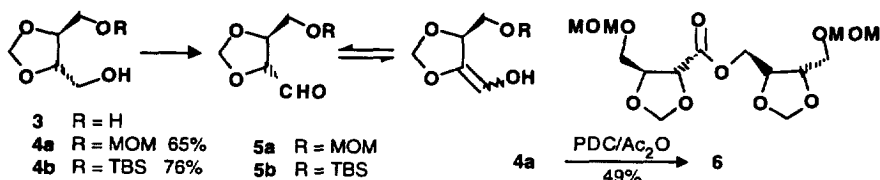
The dioxolan ring is stable in mild acidic media and, upon partial ionization, may mimic a sliding double bond either via a formoxonium ion^{5a} or, in valence bond terms, via a double bond/no-bond resonance.^{5b}



Our synthetic approach starts from (4*S*,5*S*)-4,5-dihydroxymethyl-1,3-dioxolan **3**, a chiral building block efficiently derived (96% for a two-step procedure) from (L)-diethyl tartrate.⁶ Differentiation of the two primary alcohols was achieved by mono protection of **3** either as methoxymethyl ether **4a** or tertibutyl dimethylsilyl ether **4b**.⁷ Oxidation of the remaining alcohol proved to be crucial and required a full study. For instance, oxidation by TPAP/NMO led to the corresponding aldehyde **5a** that did not survive the required silica gel filtration. Oxidation of **4a** by the PDC/Ac₂O reagent led to dimeric ester **6** in yields of up to 49%.⁸

Finally, Swern oxidation afforded crude aldehyde **5a** that can be used as such.⁹ IR spectra of **5a** indicated that the aldehyde is in the enol form with loss of an asymmetric center. This stereogenic center was fully recovered during the next step, the threo isomer of the aldehyde being much more stable than the erythro form. There was no loss of configurational integrity in the process (*vide infra*).

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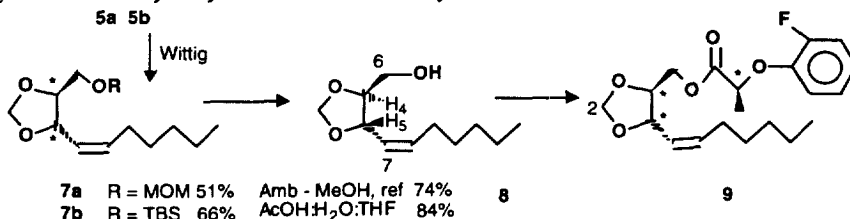


Introduction of the olefinic appendages utilized the strategy based on totally stereoselective Wittig condensations. Wittig condensation of hexyl-triphenylphosphonium bromide in the presence of $\text{NaN}(\text{TMS})_2$ as the base under carefully controlled conditions such as high dilution of the reactants in oxygen free THF (~ 0.05 M in aldehyde) and addition of the aldehyde at low temperature (-100°C) afforded single olefin **7a** in 51% yield from alcohol **4a**. NMR analysis clearly indicated the *Z* stereochemistry of the newly formed double bond with a coupling constant of 11 Hz between the olefinic protons. No trace of the *E* isomer could be detected.

Methanolysis of the MOM ether in **7a** returned the hydroxyl group in 74% yield. A NOESY experiment on alcohol **8** confirmed the threo substitution of the dioxolan ring. A cross peak between H4 and vinylic H7 and another between H5 and H6 indicated that both protons of each pair are located on the same face of the dioxolan.

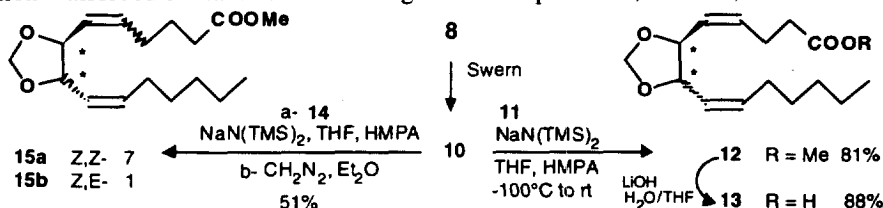
The synthesis of alcohol **8** could be improved if diol **3** is mono protected as a silyl ether,¹⁰ though deprotection of the latter via the fluoride ion was rather inefficient. Rather mild acidic treatment of **7b** selectively cleaved the TBS ether respecting the formacetal.¹¹

The enantiomeric purity of alcohol **8** was ensured by forming its fluoroaryl lactic ester.¹² Ester **9** proved to be one pure diastereomer by comparison of NMR spectra with the well differentiated 1:1 mixture obtained from racemic diol **3** and chiral fluoroaryl lactic acid. The methylene acetal protons (H2) signals are particularly well resolved: two single lines at 5.02 and 4.89 ppm for **9** versus two single lines at 5.05 and 4.96 ppm for the other diastereomer. This rather strong difference indicates that the aryl lactic moiety may lie near the heterocycle.



Swern oxidation of alcohol **8** to crude aldehyde **10** followed by Wittig addition of C4 phosphonium salt **11** under the optimal conditions that favor pure *Z*-olefin formation led to ester **12** in 81% yield. Mild saponification of **12** with LiOH led to dioxa-C17 acid analog **13** in 30% overall yield from diol **3**.

The same sequence using commercially available C5 phosphonium salt **14** then diazomethane esterification^{4c} afforded dioxa-C18 ester analog **15** as unseparable *Z,Z*- and *Z,E*- isomers in 7:1 ratio.



The natural C8 head group synthon was introduced stereochemically pure via the phosphonium salt **16** (Table 1) which was used for the synthesis of EPA¹³ and dihydroxy eicosatrienic acid.^{4b}

Thus treatment of crude aldehyde **10** with the ylid of **16** afforded the pure all-*Z*- dioxa-C21 ester **17**, mildly saponified to all-*Z*- 1,4,8-trienic, dioxa-C21 acid analog **18**. No trace of conjugated pentadiene

Table 1. Reactants and products in the controlled Wittig reactions

Substrate	Phosphonium salt	Product
 5b	 11	 7b 66%
 10	 11	 12
 10	 14	 13
		 15
 10	 16	 17
		 18
 5b	 19	 20
		 21
 22	 11	 23 58%
 22	 16	 24 54%

nor *E*- double bond isomers could be detected by 400 MHz NMR ^1H and ^{13}C analysis in this pinched analog, again obtained in 30% overall yield from **3**.

The trienic regioisomer and tetraenic analogs could be synthesized from aldehyde **5b** by applying the same strategy with the appropriate ylids. Condensation of phosphorane obtained from salt **19**¹⁴ onto aldehyde **5b** followed by careful hydrolysis of TBS ether **20** afforded dienic alcohol **21**. All reaction media in this series were carefully deoxygenated to avoid autoxidation of the pentadienic moiety. Swern oxidation of **21** followed by Wittig reaction of the ylid corresponding to phosphonium salt **11** with crude aldehyde **22** led to all-*cis* trienic ester **23**, while Wittig reaction of the ylid derived from phosphonium salt **16** led to tetraenic ester **24** (Table 1).

Ester **23** corresponds to a C₂₀, 6,10-bonded, 7,9-dioxa- arachidonic analog with three real double bonds and a floating virtual double bond. Ester **24** has two *cis*-skipped (*cis*-1,4-) pentadienic synthons and represents arachidonic acid in which the 10 position has been replaced by a dioxolan ring.

The stereochemically controlled Wittig strategy applied onto chiral building block **3** along two directions allowed the efficient synthesis of stable chiral heterocyclic pinched (or crab-like) analogs of arachidonic acid and PUFAs. Several intermediates synthesized in this work provided data to establish

a method to predict the chemical shift of ethylenic carbon atoms in polyfunctionalized polyenes.¹⁵ This simple strategy also provides various oxo chiral building blocks that may find wider applications in asymmetric synthesis.

Experimental

Melting points are uncorrected. Infrared spectra were recorded on a Perkin–Elmer IR FT-1605 spectrophotometer. The ¹H and ¹³C NMR spectra were recorded on an AC 200 or AMX 400 Bruker instrument, in CDCl₃ as internal reference for chemical shifts, respectively 7.24 and 77.1, expressed as δ values in ppm and coupling constants in Hz. Optical rotations were measured on a Perkin–Elmer 341 polarimeter at the sodium D line, at the designated concentration in g per ml. Chromatography was carried out on columns packed with Merck silica gel 60 (70–230 mesh).

(2*S*,3*S*)-2,3-O-Methylene threitol **3** was prepared according to Dulphy *et al.*⁶

(4*S*,5*S*)-4-Methoxymethoxymethyl-5-hydroxymethyl-1,3-dioxolan **4a**

Sodium hydride (46 mg, 1.92 mmol) was dissolved in dry THF (1 ml), and dry diol **3** (117 mg, 0.87 mmol) in THF (1.5 ml) was added at 0°C. After stirring for 30 min, methoxymethyl chloride (70 μl, 0.92 mmol) was added at –80°C and the reaction mixture was warmed to rt under stirring. The mixture was hydrolyzed with brine and extracted with CH₂Cl₂. The solvents were distilled off under vacuum and the residue was flash chromatographed to afford monoMOM **4a** (100 mg, 64%). IR (CDCl₃), cm⁻¹: 3700, 3630, 3495, 1240, 1185, 1160, 1040. ¹H NMR: 4.98 (1H, s), 4.96 (1H, s), 4.60 (2H, s), 3.96 (1H, dt, *J*=5.1 and 6.4), 3.85 (1H, ddd, *J*=3.6, 5.0 and 6.4), 3.80–3.71 (2H, m), 3.62 (2H, ddd, *J*=5.0, 5.3, 10.4), 3.31 (3H, s), 2.41 (OH, t, *J*=6.1). ¹³C NMR: 96.7, 95.2, 78.9, 76.2, 62.4, 67.3, 55.4. [α]_D²⁰ –12.0 (c 22.10⁻³, CCl₄). Anal. Calcd: C, 47.19; H, 7.92. Found: C, 47.16; H, 7.94.

(4*S*,5*S*)-4-(tert-Butyldimethylsilyloxymethyl)-5-hydroxymethyl-1,3-dioxolan **4b**

Sodium hydride (128 mg, 5.33 mmol) was dissolved in dry DME (3 ml), and dry diol **3** (650 mg, 4.85 mmol) in DME (10 ml) was added at 0°C. After stirring for 30 min, *tert*-butyldimethylsilyl chloride (842 mg, 5.58 mmol) in DME (4.5 ml) was added and the solution stirred at rt for 24 h. The mixture was hydrolyzed with brine and extracted with CH₂Cl₂. The solvents were distilled off under vacuum and the residue was flash chromatographed to afford monoTBS **4b** (910 mg, 76%). IR (CDCl₃), cm⁻¹: 3445, 2932, 2858, 1468, 1392, 1255, 1091, 975. ¹H NMR: 5.02 (1H, s), 4.97 (1H, s), 3.94 (1H, dt, *J*=5.3 and 9.8), 3.85–3.78 (2H, m), 3.76–3.66 (3H, m), 2.12 (OH, m), 0.87 (9H, s), 0.06 (6H, m). ¹³C NMR: 95.3, 79.5, 77.6, 63.3, 62.7, 25.9, 18.3, –5.43 (2C). [α]_D²⁰ –2.9 (c 16.10⁻³, CHCl₃).

Dimeric ester **6**

Alcohol **4a** (29 mg, 0.163 mmol) in dry CH₂Cl₂ (0.5 ml) was oxidized with PDC (55 mg, 0.146 mmol) and acetic anhydride (17 μl, 0.179 mmol) at rt in the presence of crushed activated 3 Å molecular sieve (130 mg). After all the starting material was consumed the mixture was diluted with Et₂O and the solution filtered through silica gel. Chromatography afforded ester **6** (14.5 mg, 50%) as a colorless oil. IR (film), cm⁻¹: 2949, 2888, 1758, 1449, 1205, 1153, 1040, 982. ¹H NMR: 5.19 (1H, s), 5.02 (1H, s), 4.66 (2H, s), 4.41 (1H, d, *J*=5.7), 4.24 (1H, dt, *J*=4.0 and 5.4), 3.80–3.68 (2H, ddd, *J*=3.9, 5.3 and 11), 3.36 (3H, s), 5.04 (1H, s), 4.99 (1H, s), 4.62 (2H, s), 4.32 (2H, d, *J*=4.4), 4.08 (1H, dt, *J*=4.5 and 5.8), 3.94 (1H, dt, *J*=5.4), 3.69–3.59 (2H, ddd, *J*=5.3 and 10.5), 3.34 (3H, s). ¹³C NMR: 96.8 (2C), 96.7, 78.8, 76.6, 67.2, 55.5 (2C), 170.4, 95.5, 76.1, 75.0, 67.0, 64.7. [α]_D¹⁹ –30.0 (c 10.10⁻³, CCl₄). Anal. Calcd: C, 47.73; H, 6.87. Found: C, 47.77; H, 6.81.

(4*S*,5*S*)-(Z)-4-Hydroxymethyl-5-(hept-1-enyl)-1,3-dioxolan **8**

From MOM ether **7a**: MOM ether **7a** (38 mg) in MeOH/CH₂Cl₂ (0.46 ml/0.46 ml) was refluxed for 29 h in the presence of acidic resin Amberlyst IR50 (2 mg). Chromatography on silica gel afforded **8** (24 mg, 74% yield) along with unreacted **7a** (4 mg).

From TBS ether **7b**: TBS ether **7b** (260 mg, 0.776 mmol) in a mixture of THF:H₂O:AcOH (0.8 ml:0.8 ml:2.3 ml) was magnetically stirred for 18 h at rt. The solution was neutralized with aq. NaHCO₃ before extraction with Et₂O. Chromatography afforded **8** (126 mg, 81% yield). IR (film), cm⁻¹: 3443, 3014, 2926, 2857, 1659, 1461, 1380, 1088, 980. ¹H NMR: 5.71 (1H, ddd, *J*=10.9, 8.0, 1.0), 5.41 (1H, dd, *J*=10.8, 9.0), 5.07 (1H, s), 5.04 (1H, s), 4.60 (1H, bt, *J*=8.1), 3.66 (1H, ddd, *J*=7.3, 4.5, 2.8), 3.84 (1H, ddd, *J*=5.3, 5.1, 2.7), 3.60 (1H, dt, *J*=7.2, 4.6), 2.13 (1H, ddd, *J*=14.7, 7.8, 1.4), 2.06 (1H, ddd, *J*=14.4, 7.2, 1.5), 1.82 (OH, dd, *J*=7.2, 5.5), 1.39–1.22 (6H, m), 0.89 (3H, t, *J*=6.8). ¹³C NMR: 136.7, 125.5, 95.1, 81.7, 73.1, 61.2, 29.3, 27.7, 22.4, 14.0. [α]²⁰_D -2.9 (c 16.10⁻³, CHCl₃). [α]²⁰_D -5.2 (c 16.10⁻³, CHCl₃). Anal. Calcd: C, 65.97; H, 10.07. Found: C, 65.87; H, 10.80.

General procedure for the Swern oxidation of alcohols 4b, 8, 21 to aldehydes 5b, 10, 22

(4S,5S)-4-(tert-Butyldimethylsilyloxymethyl)-5-formyl-1,3-dioxolan 5b

To a solution of oxalyl chloride (177 μl, 2.06 mmol) in CH₂Cl₂ (1 ml) cooled to -70°C were successively added DMSO (310 μl, 4.12 mmol) in CH₂Cl₂ (1 ml) and a solution of alcohol **4b** (465 mg, 1.87 mmol) in CH₂Cl₂ (3.5 ml). The reaction flask was immediately transferred to a -30°C cooling bath for 1 h then, again, cooled to -70°C before addition of triethylamine (1.3 ml, 9.37 mmol). The mixture was allowed to reach rt, diluted with petroleum ether then filtered through Celite. The crude aldehyde was used as such in the next step.

Alcohol **8** (54 mg, 0.27 mmol) was oxidized to crude aldehyde **10** (54 mg).

Alcohol **21** (45 mg, 0.188 mmol) was oxidized to crude aldehyde **22** (44 mg).

General procedure for the stereoselective Wittig olefinations

The reactions were carried out under an argon atmosphere and with efficient magnetic stirring. Phosphonium salts were dried three times by azeotropic distillation of benzene under vacuum. The phosphonium salt solutions (or suspension) in dry THF as well as the aldehyde in THF were carefully degassed (O₂ must be excluded)¹⁶ via argon bubbling.

A 0.6 M toluene solution of sodium bis(trimethylsilyl)amide (3 equiv.) was added at 0°C to the phosphonium salt in THF (~0.2 M, 3 equiv.). The orange ylid solution was stirred at rt for 1 h, then cooled to -100°C. The crude aldehyde in solution in THF (~0.2 M, 1 equiv.) was slowly added before the temperature was allowed to warm up to rt. Saturated aqueous NH₄Cl solution and water were added and the mixture was thrice extracted with Et₂O. The combined organic layers were washed with brine and dried over MgSO₄ for 5 min. Filtration over silica gel followed by column chromatography afforded pure olefinic adducts.

(4S,5S)-(Z)-4-(tert-Butyldimethylsilyloxymethyl)-5-(hept-1-enyl)-1,3-dioxolan 7b

Aldehyde **5b** (1.87 mmol crude) led to olefin **7b** (338 mg, 54% yield from the alcohol). IR (film), cm⁻¹: 2929, 2858, 1651, 1464, 1387, 1255, 1140, 1094, 986, 838. ¹H NMR: 5.66 (1H, ddd, *J*=10.9, 7.5), 5.41 (1H, dd, *J*=10.7, 9.0), 5.05 (1H, s), 4.98 (1H, s), 4.65 (1H, dd, *J*=8.5), 3.79–3.58 (3H, m), 2.18–2.00 (2H, m), 1.39–1.15 (6H, m), 0.88 (9H, s), 0.83 (3H, t, *J*=6.5), 0.05 (6H, s). ¹³C NMR: 136.0, 126.1, 95.3, 81.7, 73.4, 62.2, 31.5, 29.4, 27.8, 25.9 (3C), 22.6, 18.3, 14.0, -5.3 (2C). [α]²⁰_D -7.5 (c 15.1⁻³, CCl₄). Anal. Calcd: C, 46.15; H, 7.75. Found: C, 46.08; H, 7.82.

(4S,5S)-(Z)-4-Methoxymethoxymethyl-5-(hept-1-enyl)-1,3-dioxolan 7a

Aldehyde **5a** (0.292 mmol crude) led to olefin **7a** (36 mg, 50% yield from the alcohol). IR (CCl₄), cm⁻¹: 2920, 2780, 1659, 1467, 1356, 1178, 1043. ¹H NMR: 5.70 (1H, ddd, *J*=10.9, 7.6, 7.4), 5.42 (1H, dd, *J*=10.7, 9.1), 5.06 (1H, s), 5.04 (1H, s), 4.66 (2H, s), 4.53 (1H, dd, *J*=8.7, 7.3), 3.75 (1H, ddd, *J*=7.5, 5.8, 3.5), 3.64 (2H, dd, *J*=5.8, 3.6), 3.36 (3H, s), 2.17–2.03 (2H, m), 1.43–1.22 (6H, m), 0.86 (3H, t, *J*=6.5). ¹³C NMR: 136.4, 125.7, 96.7, 95.1, 80.3, 73.7, 66.5, 55.3, 29.2, 27.7, 22.5. [α]²¹_D +1.83 (c 18.1⁻³, CCl₄).

Methyl (4S,5S)-(Z)-5-[(Z)-5-(hept-1-enyl)-1,3-dioxolan-4-yl]pent-4-enoate 12

Aldehyde **10** (0.43 mmol crude) led to olefin **12** (98 mg, 81% yield). IR (film), cm^{-1} : 2928, 2859, 1740, 1651, 1440, 1363, 1258, 1165, 1089, 987. ^1H NMR: 5.70 (1H, dt, $J=10.8, 7.6$), 5.64 (1H, dt, $J=10.9, 7.5$), 5.50–5.35 (2H, m), 5.06 (2H, s), 4.32–4.28 (2H, m), 3.64 (3H, s), 2.40–2.30 (4H, m), 2.08 (2H, m), 1.34–1.22 (6H, m), 0.85 (3H, t, $J=6.6$). ^{13}C NMR: 173.2, 137.0, 133.9, 126.9, 125.0, 95.3, 77.2 (2C), 51.8, 34.0, 31.5, 29.4, 28.0, 23.5, 22.6, 14.1. $[\alpha]_{\text{D}}^{20} +112.9$ (c 22.1 $^{-3}$, CHCl_3). Anal. Calcd: C, 68.06; H, 9.28. Found: C, 67.80; H, 9.45.

Methyl (Z)-6-[(4S,5S)-5-(hept-1-enyl)-1,3-dioxolan-4-yl]hex-5-enoate 15ab

Aldehyde **10** (0.23 mmol crude) and phosphonium salt **14** led to the corresponding olefin (50 mg, crude). The aldehyde was diluted in Et_2O and a solution of diazomethane was added until complete conversion of the starting material. Concentration and chromatography afforded ester **15ab** (35 mg, 51% yield from the alcohol). IR (film), cm^{-1} : 3015, 2927, 2858, 1740, 1657, 1457, 1370, 1208, 1162, 1090, 988. ^1H NMR: 5.69 (1H, dt, $J=10.2, 7.2$), 5.65 (1H, dt, $J=11.0, 7.4$), 5.49–5.33 (2H, m), 5.07 (2H, s), 4.35–4.25 (2H, m), 3.64 (3H, s), 2.28 (2H, t, $J=7.5$), 2.19–1.97 (4H, m), 1.68 (2H, q, $J=7.5$), 1.41–1.22 (6H, m), 0.85 (3H, t, $J=6.5$). ^{13}C NMR: 173.8, 136.8, 135.0, 126.5, 125.1, 95.1, 77.1 (2C), 51.5, 33.4, 31.4, 29.3, 27.9, 27.3, 24.8, 22.5, 14.0. $[\alpha]_{\text{D}}^{20} +97.9$ (c 34.1 $^{-3}$, CHCl_3). Anal. Calcd: C, 68.89; H, 9.52. Found: C, 68.82; H, 9.49.

Methyl (Z,Z)-9-[(4S,5S)-(Z)-5-(hept-1-enyl)-1,3-dioxolan-4-yl]nona-5,8-dienoate 17

Aldehyde **10** (0.2 mmol crude) led to olefin **17** (59 mg, 87% yield). IR (film), cm^{-1} : 3015, 2927, 2858, 1739, 1659, 1457, 1370, 1208, 1162, 1090, 988. ^1H NMR: 5.68 (1H, dt, $J=11.0, 7.4$), 5.61 (1H, dt, $J=10.9, 7.3$), 5.46–5.37 (2H, m), 5.37–5.27 (2H, m), 5.07 (2H, s), 4.36–4.29 (2H, ABX, $J=6.3, 6.1$), 3.64 (3H, s), 2.86–2.73 (2H, m), 2.32–2.25 (2H, t, $J=7.4$), 2.10–1.97 (4H, m), 1.74–1.63 (2H, q, $J=7.3$), 1.35–1.20 (6H, m), 0.85 (3H, t, $J=6.4$). ^{13}C NMR: 173.9, 136.7, 134.2, 125.5, 124.9, 95.0, 77.1, 77.0, 51.5, 33.4, 31.4, 29.2, 27.9, 26.2, 25.5, 24.7, 22.5, 14.0. $[\alpha]_{\text{D}}^{20} +112$ (c 28.1 $^{-3}$, CHCl_3). Anal. Calcd: C, 71.39; H, 9.59. Found: C, 71.31; H, 9.55.

(4S,5S)-(Z,Z)-4-(tert-Butyldimethylsilyloxymethyl)-5-(deca-1,4-dienyl)-1,3-dioxolan 20

Aldehyde **5b** (0.41 mmol crude) led to olefin **20** (90 mg, 60% yield). IR (film), cm^{-1} : 2929, 2858, 1651, 1464, 1387, 1255, 1140, 1094, 986, 838. ^1H NMR: 5.62 (1H, dtd, $J=10.9, 7.4, 0.9$), 5.45 (1H, dtd, $J=10.9, 8.8, 1.6$), 5.41 (1H, dtd, $J=10.9, 7.2, 1.5$), 5.29 (1H, dtt, $J=10.7, 7.0, 1.5$), 5.06 (1H, s), 4.99 (1H, s), 4.67 (1H, ddd, $J=8.7, 6.7, 0.9$), 3.78 (1H, dd, $J=11.0, 3.8$), 3.68 (1H, dd, $J=11.0, 4.3$), 3.64 (1H, dt, $J=6.8, 4.0$), 2.93 (1H, dt, $J=15.5, 7.6$), 2.81 (1H, dt, $J=15.4, 7.3$), 2.02 (2H, dd, $J=7.1$), 1.38–1.22 (6H, m), 0.88 (9H, s), 0.87 (3H, t, $J=6.7$), 0.06 (3H, s), 0.05 (3H, s). ^{13}C NMR: 134.1, 131.3, 126.8, 126.4, 95.3, 81.7, 73.5, 62.3, 31.6, 29.3, 27.3, 26.1, 25.9, 22.6, 18.4, 14.1, –5.28, –5.36. $[\alpha]_{\text{D}}^{20} -2.4$ (c 37.1 $^{-3}$, CHCl_3).

Methyl (Z)-5-[(4S,5S)-(Z,Z)-5-(deca-1,4-dienyl)-1,3-dioxolan-4-yl]pent-4-enoate 23

Aldehyde **22** (0.188 mmol crude) led to olefin **23** (35 mg, 58% yield). IR (film), cm^{-1} : 3013, 2953, 2857, 1740, 1659, 1439, 1361, 1198, 1090, 985. ^1H NMR: 5.71–5.58 (2H, m), 5.51–5.35 (3H, m), 5.32–5.19 (1H, m), 5.07 (2H, s), 4.34–4.30 (2H, ABX, $J=6.4$), 3.66 (3H, s), 2.89–2.74 (2H, ABXX', $J=15.7, 8.2$), 2.39–2.32 (4H, m), 2.00–1.94 (2H, q, $J=6.7$), 1.40–1.26 (6H, m), 0.86 (3H, t, $J=6.6$). ^{13}C NMR: 173.1, 134.8, 133.9, 131.2, 126.8, 126.6, 125.2, 95.2, 77.1 (2C), 51.7, 39.9, 31.5, 29.3, 27.3, 26.3, 23.4, 22.6, 14.1. $[\alpha]_{\text{D}}^{20} +111.2$ (c 35.1 $^{-3}$, CHCl_3). Anal. Calcd: C, 70.77; H, 9.38. Found: C, 70.72; H, 9.35.

Methyl (Z,Z)-9-[(4S,5S)-(Z,Z)-5-(deca-1,4-dienyl)-1,3-dioxolan-4-yl]nona-5,8-dienoate 24

Aldehyde **22** (0.2 mmol crude) led to olefin **24** (41 mg, 55% yield). IR (film), cm^{-1} : 3200, 2854, 1712, 1663, 1174, 1131, 1090, 933. ^1H NMR: 5.66 (1H, dt, $J=10.7, 7.4$), 5.61 (1H, dt, $J=10.7, 7.4$), 5.33 (6H, m), 5.07 (2H, s), 4.34–4.31 (2H, m), 3.65 (3H, s), 2.79 (4H, m), 2.28 (2H, t, $J=7.4$), 2.02

(4H, m), 1.66 (2H, m), 1.26 (6H, m), 0.85 (3H, t, $J=5.1$). ^{13}C NMR: 174.0, 134.7, 134.3, 131.1, 129.6, 127.9, 125.6, 125.4, 125.2, 95.1, 77.0 (2C), 51.5, 33.4, 31.5, 29.2, 27.2, 26.5, 26.2 (2C), 24.6, 22.5, 14.0. $[\alpha]_{\text{D}}^{20} +76.5$ (c 29.1 $^{-3}$, CHCl_3). Anal. Calcd: C, 73.37; H, 9.64. Found: C, 73.28; H, 9.67.

(4S,5S)-(Z,Z)-4-Hydroxymethyl-5-(deca-1,4-dienyl)-1,3-dioxolan 21

TBS ether **20** (36 mg, 0.1 mmol) in a mixture of THF (degassed and distilled): H_2O :AcOH (0.1 ml:0.1 ml:0.4 ml) was magnetically stirred for 24 h at rt with protection against light. The solution was neutralized with aq. NaHCO_3 before extraction with Et_2O . Chromatography afforded alcohol **21** (22 mg, 90% yield). IR (film), cm^{-1} : 3446, 3012, 2929, 2858, 1653, 1459, 1087, 978, 851. ^1H NMR: 5.67 (1H, dtd, $J=10.8, 7.6, 0.9$), 5.44 (1H, dtd, $J=10.7, 8.8, 1.6$), 5.41 (1H, dtd, $J=10.8, 1.7$), 5.28 (1H, dtd, $J=10.7, 1.6$), 5.07 (H, s), 5.04 (1H, s), 4.62 (1H, ddd, $J=8.7, 7.4, 0.9$), 3.83 (1H, ddbr, $J=11.9, 3.0$), 3.62 (1H, ddd, $J=11.6, 6.7, 4.9$), 3.67 (1H, ddd, $J=7.3, 4.5, 2.8$), 2.91 (1H, dtbr, $J=15.6, 7.8$), 2.82 (2H, dtbr, $J=15.5, 7.5$), 2.02 (2H, dd, $J=7.1$), 1.95 (OH, m), 1.37–1.22 (6H, m). ^{13}C NMR: 134.7, 131.4, 126.4, 125.7, 95.2, 81.6, 73.0, 62.2, 31.5, 29.2, 27.3, 26.1, 22.6, 14.1. $[\alpha]_{\text{D}}^{20} -1.8$ (c 17.1 $^{-3}$, CHCl_3). Anal. Calcd: C, 69.67; H, 10.44. Found: C, 69.63; H, 10.45.

General procedure for the saponification of esters to carboxylic acids

A 0.15 M solution of the ester in THF was magnetically stirred in the presence of LiOH (2.5 equiv., solution 0.5 M) at rt for 9 h. A 5% solution of HCl was slowly added until pH 4–5. The mixture was saturated with NaCl then extracted with ether. After drying over magnesium sulfate the concentrated residue was filtered over silica gel.

(Z)-5-[(4S,5S)-(Z)-5-(Hept-1-enyl)-1,3-dioxolan-4-yl]pent-4-enoic acid 13

88% yield. IR (film), cm^{-1} : 3200, 2854, 1712, 1663, 1174, 1131, 1090, 933. ^1H NMR: 5.70 (1H, m), 5.64 (1H, m), 5.52–5.40 (2H, m), 5.07 (2H, s), 4.32–4.29 (2H, mAB), 2.38 (2H, m), 2.04 (2H, dt, $J=8.5, 7.3$), 1.34–1.18 (6H, m), 0.85 (3H, t, $J=6.4$). ^{13}C NMR: 178.5, 136.9, 133.5, 126.9, 124.8, 95.0, 77.0 (2C), 33.9, 31.3, 29.3, 27.8, 23.3, 22.4, 13.9. $[\alpha]_{\text{D}}^{20} +117.1$ (c 20.1 $^{-3}$, CHCl_3). Anal. Calcd: C, 67.14; H, 9.01. Found: C, 67.09; H, 9.12.

(Z,Z)-9-[(4S,5S)-(Z)-5-(Hept-1-enyl)-1,3-dioxolan-4-yl]nona-5,8-dienoic acid 18

85% yield. IR (film), cm^{-1} : 3200, 2854, 1712, 1663, 1174, 1131, 1090, 933. ^1H NMR: 5.68 (1H, dt, $J=10.8, 7.4$), 5.61 (1H, dt, $J=10.9, 7.3$), 5.42 (2H, m), 5.33 (2H, m), 5.08 (1H, s), 5.07 (1H, s), 4.34 and 4.30 (2H, mAB), 2.38 (2H, m), 2.33 (2H, t, $J=7.4$), 2.06 (4H, m), 1.70 (2H, q, $J=7.3$), 1.26 (6H, m), 0.85 (3H, t, $J=6.5$). ^{13}C NMR: 179.3, 136.7, 134.1, 129.4, 128.1, 125.4, 124.8, 95.0, 77.0 (2C), 33.2, 31.3, 29.2, 27.8, 26.4, 26.2, 24.3, 22.4, 13.9. $[\alpha]_{\text{D}}^{20} +114.6$ (c 24.1 $^{-3}$, CHCl_3). Anal. Calcd: C, 70.77; H, 9.38. Found: C, 70.70; H, 9.45.

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