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

Jean-Louis Gras,* Thierry Soto and Jacques Viala

Université D'Aix-Marseille III, Laboratoire RéSo, CNRS–UMR 6516, Faculté des Sciences St Jérôme-D12, F-13397 Marseille Cedex 20, France

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Abstract

Chiral building blocks derived from L-diethyl tartrate are derivatized into various chiral arachidonic acid analogs based on a dioxane core.

1. Introduction

Polyunsaturated fatty acids such as arachidonic acid and their metabolites such as thromboxanes or prostaglandins are of major biological importance. Several cyclic compounds have been prepared to render available more stable analogs such as, for instance, thromboxane or rigidified arachidonic acid mimics. New developments in this area include the study of thromboxane/prostaglandin receptor antagonists built on a heteroaromatic ring: pyridine, furane,[1] pyrrole,[2] pyrazole,[3] and imidazole,[4] and on a heterocyclic system: oxa-,[5,6] thia-,[7] and aza-.[8] A few ethers[9] and thioethers[10] have been tested against lipoxygenase.

We were interested in preparing analogs that bear a formacetal ring, because the methylene acetal function is stable toward many reagents and experimental conditions, including mildly acidic media. It may also be a source of hydrogen or metal bonding site and then provides, with an oxacarbenium ion intermediate,[11] a potential double bond mimic. Recent reports indicate that the 1,3-dioxane moiety attracts increasing interest, for instance as a thromboxane receptor antagonist[12] or as the aglycons of nucleoside analogs.[13] Moreover, a methylene acetal derivative of illudin S exhibited an improved antitumor activity.[14]

In the course of various studies on biomolecules and their synthetic analogs, we recently described the syntheses of chiral pinched arachidonic analogs[15] and we now report our synthetic efforts toward chiral analogs based on a 1,3-dioxane core.

* Corresponding author. E-mail: jean-louis.gras@reso.u-3mrs.fr

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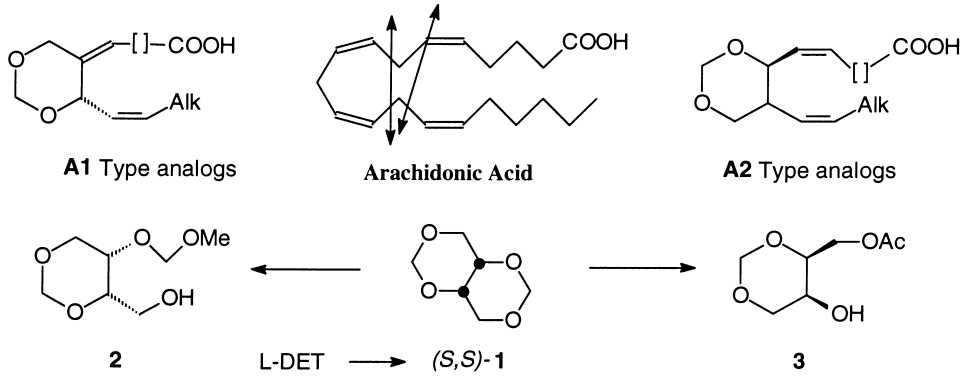
2. Results and discussion

Our basic approach was to bridge arachidonic acid between C6 or C7 and C13 to afford analogs of types A1 and A2, and related ethers. The synthetic strategy was based on the use of 4,5-disubstituted-1,3-dioxane chiral building blocks, conveniently derived from tartrate.

L-Diethyltartrate was efficiently transformed into dimethylenethreitol **1** which underwent a versatile acetolyzing cleavage to primary alcohol **2** or secondary alcohol **3**.[16] Each alcohol was converted to its fluoroaryl lactic ester.[17] NMR analysis of the esters indicated the enantiomeric purity of the chiral building blocks by comparison with the spectra of the corresponding mixture of the diastereomeric esters obtained from these racemic alcohols and chiral fluoroaryl lactic acid.

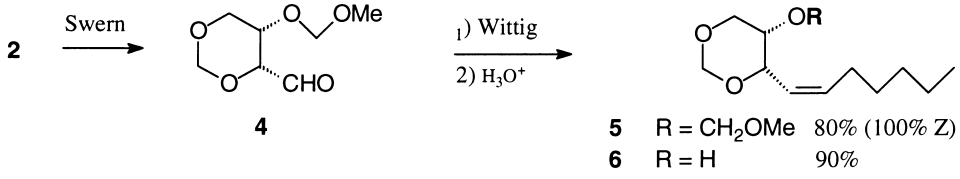


2.1. Type A1 and ether analogs derived from alcohol 2

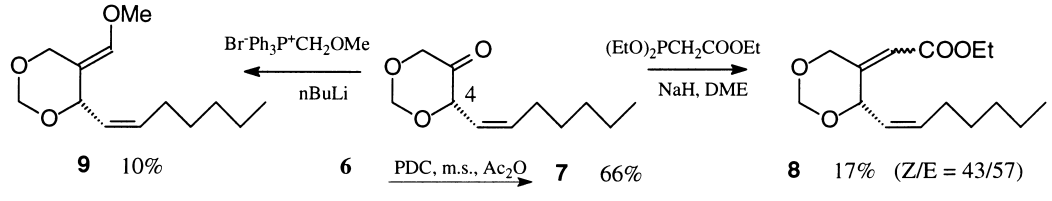
Oxidation of primary alcohol **2** to aldehyde **4** had to proceed without epimerization at C4. Catalytic oxidation using a perruthenate agent, TPAP/NMO,[18] gave good results that were not reproducible on scaling up over 2 mmol. Swern oxidation under carefully controlled conditions (i.e. reagent formed at −70°C and the oxidizing step run over 1 h at −30°C) gave the oily aldehyde **4** as a sensitive material that epimerized upon standing in $CDCl_3$. Crude aldehyde **4** was immediately submitted to Wittig addition with the ylid of hexyl-triphenylphosphonium bromide, under the optimal conditions that favor the *Z* configuration of the double bond: ylid formed at −100°C at high dilution (0.05 M) and by a lithium free base such as $NaN(TMS)_2$.[19] Olefin **5** was thus obtained in 80% yield, pure *Z* isomer as indicated by the coupling constant of 11 Hz between the two olefinic protons. The same reaction was applied to a mixture of epimers **4** and **4′** and afforded the corresponding *threo–erythro* mixture of olefins **5** and **5′**. Separation of the two epimers allowed a clear NMR identification. This was made on the basis of the nature of the signals of protons H4, H5, H6ax and on the coupling constant values that reflected the ax–eq (*threo* isomer) or ax–ax (*erythro*) relationships between H4–H5 and H5–H6ax (Table 1). Refluxing **5** in methanol in the presence of an acidic resin removed the MOM protecting group and freed the secondary alcohol function in **6**, with respect to the dioxan moiety. Again, the fluoroaryl lactic ester of **6** indicated the enantiomeric purity of the alcohol, the relative *threo* stereochemistry of C4 and C5 being indicated by NMR.

Table 1
Selected coupling constants in hertz for *erythro/threo* isomers, measured at 200 MHz

Compound	$J_{6a,5}$	$J_{4,5}$	Conformation H_4, H_5	Configuration
5'	8.3	9	ax, ax	E
5	1.5	0	ax, eq	T
18a	11	4.5	ax, ax	E
18b	2.7	0	ax, eq	T
21a	11.1	10.8	ax, ax	E
21b	8.6	3.4	ax, eq	T

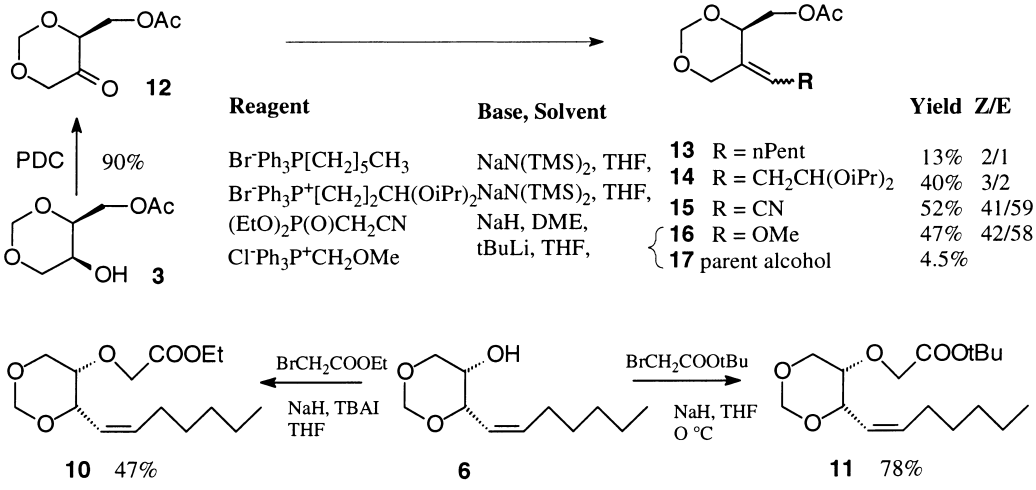


Oxidation of secondary alcohol **6** to ketone **7** proved more difficult than expected, probably due to the axial position of the hydroxy group and the subsequent hydrogen bonding to the formacetal moiety. Oxidation procedures such as, for instance, the Swern oxidation or involving a perruthenate (TPAP) or activated PCC as reagent were inefficient. Doubly activated PDC (with both molecular sieves and acetic anhydride)[20] furnished unstable ketone **7** in a reasonable 66% yield. Wittig olefination of the phosphorane derived from ethyl 4-bromobutyrate with ketone **7** failed under various conditions, but we were able to add the stabilized phosphonate ylid of ethyl bromoacetate to obtain ester **8** as a mixture of *Z* and *E* isomers in low yield (17%). Attempts to homologate ketone **7** did not meet with more success, the addition of the phosphonium salt formed from methoxymethyl bromide affording enol ether **9**, as the single *E* isomer, in 10% yield. The enantiomeric excess of **8** and **9** was not investigated. The reluctance of ketone **7** to undergo a clean Wittig addition appeared to be a consequence more of the fragility of the keto–dioxane system having a highly labile H4 than of simple hindrance of the carbonyl function.



Interest had been devoted to analogs in which a double bond had been replaced by a heteroatom, such as in some ether analogs that showed biological activity.[9] We have shown that alcohol **6** can be a precursor of chiral ether analogs by *O*-alkylation with bromoesters. Alcohol **6** added to ethyl bromoacetate with the help of phase transfer agent TBAI as the catalyst to form ether analog **10**, and to *t*-butyl bromoacetate under the classical conditions of the Williamson ether synthesis (NaH/THF), to form ether analog **11**.

Table 2
Wittig additions to 5-oxo-1,3-dioxane **12**

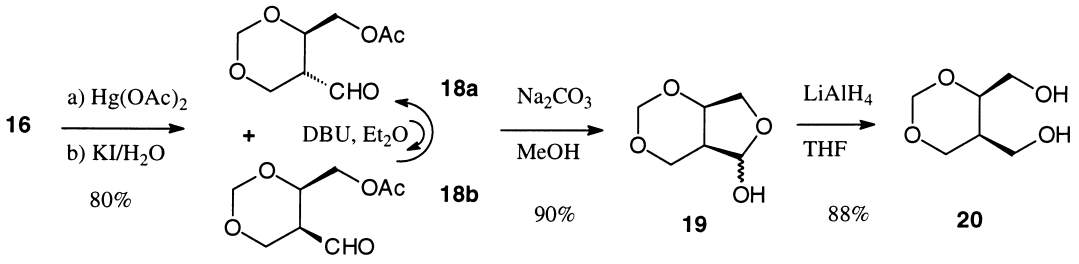


2.2. *Type A2 analogs derived from alcohol* ***3***

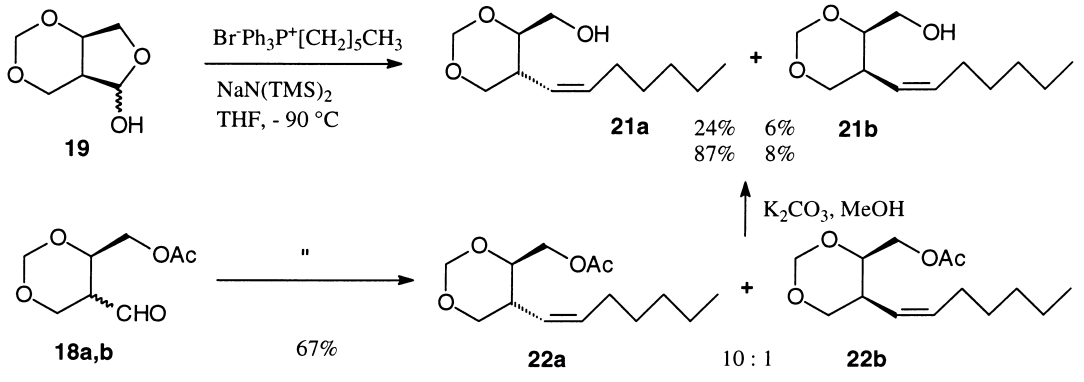
Alcohol **3** is a chiral building block complementary to **2** in the sense that the strategy to build up appendages to form arachidonic acid analogs is formally reversed.

Oxidation of alcohol **3** with doubly activated PDC cleanly afforded ketone **12** in 90% yield. Ketone **12** has one electron-withdrawing group less than ketone **7** and is much more stable than this parent compound. Ketone **12** was submitted to Wittig addition with various ylids to produce precursors of type A2 analogs (Table 2). With a C6 alkylating phosphonium salt, the reaction afforded olefin **13**, as a *Z/E* mixture, in 13% yield. With a C3 homologating agent, olefin **14** was obtained in 40% yield and, with a phosphonate agent, olefin **15** was obtained in 52% yield, both as mixtures of *Z/E* isomers. Albeit encouraging, these results were plagued with poor stereochemical control. We next turned our attention toward the addition of the ylid derived from methoxymethyl-triphenylphosphonium chloride that led to olefin **16** in 47% yield along with alcohol **17** (4.5%), the recyclable alcohol obtained by in situ saponification of the acetate group. *t*-Butyllithium must be used as the base for this reaction, since we observed a transylidation phenomenon that led to butylidene transfer onto ketone **12**, when *n*-butyllithium was used.[21] In this strategy the *Z/E* isomerism in **16** was no more damaging to the synthesis since this enol ether was hydrolyzed to homologated aldehyde **18**.

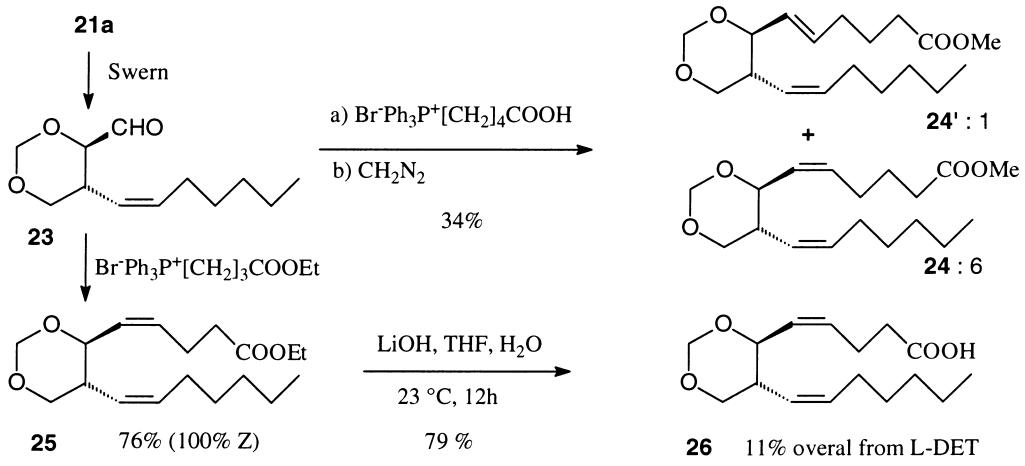
Mild acid catalyzed hydrolysis of **16** was inoperative on this oxygen rich substrate, and forced acidic conditions partially hydrolyzed the acetate and formacetal functions. Mercuric acetate allowed the hydrolysis of **16** under neutral conditions to afford aldehyde **18** as a 1:1 mixture of *erythro* (**18a**) and *threo* (**18b**) diastereomers. The *threo* isomer was converted to the more stable *erythro* form **18a** by treatment with DBU in an aprotic medium (Et_2O), providing an entry to the *erythro* analogs series. Acetoxyaldehyde **18a**,**b** was saponified to *threo* lactol **19** under basic protic conditions, an entry now to the *threo* analogs series. The *cis* fusion of the rings was determined by NMR analysis that showed only two isomers at the anomeric proton signal. This in situ eq/ax epimerization was probably driven by the greater stability of *cis* bicyclic compounds having a five-membered ring over *trans* fusion.[22] Finally, reduction of lactol **19** afforded one single isomer of diol **20**, having the *threo* arrangement as expected.



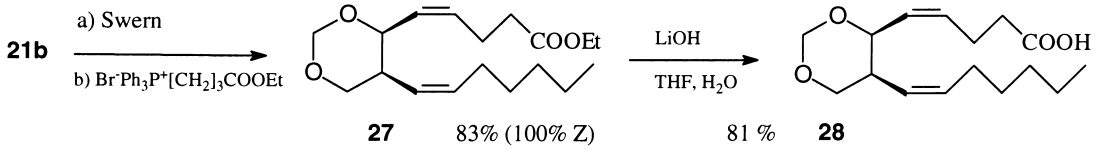
Lactols usually undergo Wittig reactions with long chain alkylidene phosphoranes.[23] Wittig addition of the ylid of hexyl-triphenylphosphonium bromide appeared disappointing and afforded isomeric alcohols **21a** and **21b**, respectively, in 24% and 6% yields. The stereochemical assignment again was made by NMR analysis (Table 1). Epimerization certainly occurred during the Wittig reaction. The *threo* aldehyde precursor of the adduct reacted much more slowly than the *erythro* diastereomer and hence, under the basic conditions of the Wittig addition, epimerized into the *erythro* isomer, thermodynamically more stable with the two equatorial substituents. This result precluded the synthesis of *threo* analogs by this route but allowed the direct treatment of aldehyde **18** to give olefin **22** as a constant 10:1 mixture of *erythro*:*threo* diastereomers, regardless of the isomeric ratio in the aldehyde. The isomers were isolated after saponification of acetate **22** to alcohols **21a** (87%) and **21b** (8%). NMR analysis determined the configuration of the major isomer, *erythro* **21a**, and conversion to the corresponding fluoroaryl lactic ester proved its enantiomeric purity.



Swern oxidation of *erythro* primary alcohol **21a** afforded unstable aldehyde **23** which was submitted as such to various Wittig reactions. Addition of the ylid of carboxybutyl-triphenylphosphonium bromide under the conditions that favor '*Z* olefination' led, in that case and after direct esterification, to a 4:1 mixture of 'C19' ester analog **24** and **24′**. The anionic ylid put in use was certainly responsible for the occurrence of minor *E* isomer **24′**. We did not use the corresponding ester because of its known propensity to cyclize under basic conditions.[24] Addition of the C4 ylid derived from ethyl bromobutyrate cleanly afforded pure *Z*-'**18**' ester analog **25** in 76% yield from **21a**. Mild saponification with LiOH in THF/H_2O at room temperature restored the acid polar group of **26**, a chiral analog of arachidonic acid *trans* bridged between the original positions 6 and 13.



The same synthetic sequence was applied to *threo* alcohol **21b** to afford pure *cis* ester analog **27** and *cis* acid **28**. Epimerization at a single atom occurring before any racemization would be easily detected by NMR, in both E and T series. No epimerization to the isomer was observed and we concluded that the analogs **24** to **28** were enantiomerically pure.



The strategies and synthetic sequences we described allow the preparation of chiral pinched analogs of fatty acids based on a 1,3-dioxane core, using chiral buiding blocks derived from diethyl tartrate. The stereochemistry of appendages on the heterocyclic ring can be *cis* or *trans* and an ether function can be introduced in the analogs. Although some yields were modest, one synthesis afforded a dienic analog built in 12 steps from L-DET with an overall yield of 11%. The synthetic chemistry herein brings new insight to the reactivity of functionalized 1,3-dioxanes such as 5-hydroxy- and 5-oxo-1,3-dioxane derivatives and affords intermediates having well assigned stereochemical features that might be of general use.[25]

3. Experimental

Infrared spectra were recorded on a Perkin–Elmer FTIR 1605 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on an AC 200 or AMX 400 Bruker instrument, in $CDCl_3$ as an internal reference for chemical shifts (7.24 and 77.1 ppm respectively) expressed as δ values in ppm and coupling constants in hertz. 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*)-1,3:2,4-Di-*O*-methylene threitol **1**, (2*S*,3*S*)-2-*O*-methoxymethyl-1,3-*O*-methylene threitol **2** and (2*S*,3*S*)-4-*O*-acetyl-1,3-*O*-methylene threitol **3** were prepared according to Dulphy et al.[16]

3.1. General procedure for the Swern oxidation of alcohols **2** and **21a** to aldehydes **4** and **23**

3.1.1. (4R,5R)-4-Formyl-5-methoxymethoxy-1,3-dioxan **4**

To a solution of oxalyl chloride (147 μl, 1.72 mmol) in CH_2Cl_2 (0.5 ml) cooled to −70°C were successively added DMSO (246 μl, 3.43 mmol) in CH_2Cl_2 (0.5 ml) and a solution of alcohol **2** (255 mg, 1.43 mmol) in CH_2Cl_2 (3 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 (995 μl, 7.15 mmol). The mixture was allowed to reach rt, diluted with petroleum ether, then filtered through Celite. The crude aldehyde **4** (215 mg, 85% yield) was used as such in the next step. IR (CCl_4), cm^{-1}: 2846, 1742, 1245, 1183, 1152, 1109, 1049. ^{1}H NMR: 9.61 (1H, s), 5.23 (1H, d, *J*=6.3), 4.81 (1H, d, *J*=6.3), 4.72 (1H, d, *J*=7.2), 4.62 (1H, d, *J*=7.2), 4.19 (1H, d, *J*=12.7), 4.14 (1H, d, *J*=2.2), 3.96 (1H, sbr), 3.75 (1H, d, *J*=12.7), 3.33 (3H, s). ^{13}C NMR: 200.1, 95.5, 93.1, 81.7, 69.7, 68.3, 55.9.

Alcohol **21a** (51 mg, 0.238 mmol) was oxidized to uncharacterized crude aldehyde **23** (49 mg).

3.2. General procedure for the PDC oxidation of alcohols **6** and **3** to ketones **7** and **12**

3.2.1. (4S)-4-Hept-1-enyl-1,3-dioxan-5-one **7**

To a mixture of heat-activated 3A molecular sieves (140 mg) and PDC (100 mg, 0.623 mmol) was successively added a solution of alcohol **6** (35 mg, 0.175 mmol) in CH_2Cl_2 (1 ml) and acetic anhydride (41 μl, 0.437 mmol). The mixture was efficiently stirred for 30 min at rt. The mixture was diluted with ether (5 ml) then filtered through a short silica gel column. Traces of pyridine and acetic acid were eliminated by three azeotropic distillations of heptane under vacuum to afford crude sensitive ketone **7** (23 mg, 66% yield). IR (CCl_4), cm^{-1}: 2928, 2857, 1743, 1697, 1259, 1170, 1110, 1049. ^{1}H NMR: 5.85 (1H, dt, *J*=10.5, 7.6), 5.47 (1H, dd, *J*=10.7, 7.1), 5.14 (1H, d, *J*=5.8), 5.02 (1H, d, *J*=5.8), 4.97 (1H, d, *J*=7.8), 4.39 (1H, d, *J*=7.4), 4.28 (1H, d, *J*=7.3), 2.09 (2H, dd, *J*=13.7, 6.9), 1.41–1.00 (6H, m), 0.86 (3H, t, *J*=6.4). ^{13}C NMR: 204.1, 138.7, 121.3, 91.0, 79.0, 72.7, 31.4, 28.9, 28.3, 22.5, 14.0.

3.2.2. (4S)-1,3-Dioxan-5-one-4-ylmethyl acetate **12**

Alcohol **3** (575 mg, 3.26 mmol) was oxidized to crude sensitive ketone **12** (509 mg, 90% yield). IR (CCl_4), cm^{-1}: 2962, 2856, 1751, 1381, 1260, 1220, 1115, 954. ^{1}H NMR: 5.15 (1H, d, *J*=6.2), 5.01 (1H, d, *J*=6.2), 4.53–4.47 (2H, m), 4.42 (1H, dd, *J*=6.6, 6.4), 4.34 (1H, s), 4.32 (1H, s), 2.07 (3H, s). ^{13}C NMR: 202.9, 170.6, 91.3, 80.3, 73.1, 62.5, 20.8.

3.2.3. (4S,5S)-(Z)-4-(Hept-1-enyl)-1,3-dioxan-5-ol **6**

Mom ether **5** (50 mg) in MeOH (1 ml) was refluxed for 8 h in the presence of acidic resin Amberlyst IR50 (5 mg). Chromatography on silica gel afforded **6** (39 mg, 97% yield). IR (film), cm^{-1}: 3454, 2926, 2774, 1657, 1463, 1237, 1175, 1148, 1050, 967, 931. ^{1}H NMR: 5.64 (1H, dt, *J*=11.3, 7.1), 5.60 (1H, dd, *J*=11.2, 7.1), 5.06 (1H, d, *J*=6.2), 4.79 (1H, d, *J*=6.2), 4.43 (1H, d, *J*=6.9), 4.05 (1H, d, *J*=11.8), 3.83 (1H, dd, *J*=11.8, 1.3), 3.41 (1H, d, *J*=9.8), 2.68 (1H, d, *J*=11.0), 2.12–1.99 (2H, m), 1.41–1.22 (6H, m), 0.87 (3H, t, *J*=6.9). ^{13}C NMR: 135.1, 125.5, 94.0, 75.9, 72.1, 67.3, 31.5, 29.2, 28.2, 22.6, 14.1. $[\alpha]_D^{20}$ +58.2 (c 20×10^{-3}, $CHCl_3$). Anal. calcd: C, 65.97; H, 10.07. Found: C, 65.84; H, 10.11.

3.2.4. tert-Butyl (4S,5S)-4-(hept-1-enyl)-1,3-dioxan-5-yloxy acetate **11**

Sodium hydride (12 mg, 0.5 mmol) was dissolved in dry THF (0.5 ml), and dry diol **6** (67 mg, 0.334 mmol) in THF (1 ml) was added at 0°C. After stirring for 15 min, *t*-butyl bromoacetate (86 mg, 0.4 mmol) was added and the reaction mixture was stirred for 10 min. The mixture was hydrolyzed with

brine and extracted with CH_2Cl_2. The solvents were distilled off under vacuum and the residue was flash chromatographed to afford ether **11** (82 mg, 78% yield). IR (film), cm^{-1}: 2926, 2856, 1752, 1660, 1206, 1177, 1111, 1032. ^1H NMR: 5.75–568 (2H, m), 5.08 (1H, d, *J*=6.2), 4.79 (1H, d, *J*=6.2), 4.49 (1H, dd, *J*=7.2, 2.0), 4.31 (1H, dd, *J*=12.3, 0.9), 4.12 (2H, d, *J*=1.4), 3.80 (1H, dd, *J*=12.3, 1.8), 3.35 (1H, d, *J*=2.0), 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), 2.10–2.06 (2H, m), 1.44 (9H, s), 1.41–1.23 (6H, m), 0.86 (3H, t, *J*=6.5). ^{13}C NMR: 169.7, 134.8, 125.3, 93.2, 81.6, 74.5, 74.3, 68.5, 68.2, 31.4, 29.1, 28.1, 22.5, 14.0 (2C). $[\alpha]_D^{21}$ +1.4 (c 15×10^{-3}, CCl_4). Anal. calcd: C, 47.19; H, 7.92. Found: C, 47.15; H, 7.94.

*3.2.5. Methyl (4*R,*5*R/S*)-5-formyl-1,3-dioxan-4-yl acetate* ***18***

Enolether **16** (50 mg, 0.247 mmol) in THF (2.5 ml) and water (0.25 ml) was stirred at rt for 24 h in the presence of mercuric acetate (237 mg, 0.742 mmol). The mixture was diluted with Et_2O (6 ml) then with a saturated aqueous KI solution (15 ml). After extraction with CH_2Cl_2 and drying over $MgSO_4$ the solvents were distilled off under vacuum and the residue was flash chromatographed to afford aldehyde **18** as a 1:1 mixture of stereomers (39 mg, 82% yield). IR (CCl_4), cm^{-1}: 2851, 1749, 1726, 1370, 1231, 1041, 797. ^1H NMR: **18** *threo*: 10.04 (1H, d, *J*=3.0), 5.19 (1H, d, *J*=6.2), 4.80 (1H, d, *J*=6.3), 4.42 (1H, d, *J*=11.8), 4.33–4.17 (2H, m), 4.11–4.02 (1H, m), 3.91 (1H, dd, *J*=11.9, 2.7), 2.27 (1H, sbr), 2.06 (3H, s). **18** *erythro*: 9.66 (1H, d, *J*=1.7), 5.06 (1H, d, *J*=6.4), 4.63 (1H, d, *J*=6.4), 4.33–4.17 (3H, m), 4.11–4.02 (1H, m), 3.69 (1H, dd, *J*=11.2, 11.0), 2.98 (1H, dtd, *J*=10.9, 6.0, 1.7), 2.08 (3H, s). ^{13}C NMR (T,E): 202.1/198.9, 170.6 (2C), 94.5/93.1, 75.6/62.5, 67.4/65.1, 64.3 (2C), 49.4/48.7, 20.7 (2C).

*3.2.6. (4*R,*5*S*)-Tetrahydrofuro(3,4-*d*)-1,3-dioxyn-5-ol* ***19***

Acetate **18** (26 mg, 0.138 mmol) in MeOH (0.41 ml) was magnetically stirred for 5 h at rt with sodium carbonate (7.3 mg, 0.07 mmol). The solution was diluted with CH_2Cl_2 (5 ml) and filtered through Celite. Chromatography afforded lactol **19** (18 mg, 90% yield). IR (film), cm^{-1}: 3411, 2930, 2781, 1175, 1102, 1049, 932. ^1H NMR: 5.75 (1H, dd, *J*=5.8, 4.2), 5.07–5.00 (1H, t, *J*=6.9), 4.72 (1H, d, *J*=6.5), 4.35 (1H, d, *J*=11.6), 4.21–3.89 (3H, m), 3.97 (1H, d, *J*=11.6), 3.47 (1H, dd, *J*=7.0), 2.07–1.95 (1H, m). Anomer: 5.44 (1H, dd, *J*=11.9, 5.9), 5.07–5.00 (1H, t, *J*=6.9), 4.66 (1H, d, *J*=6.5), 4.33 (1H, d, *J*=11.4), 4.21–3.89 (3H, m), 3.99 (1H, d, *J*=11.4), 3.47 (1H, dd, *J*=7.0), 2.07–1.95 (1H, m). ^{13}C NMR: 100.2, 92.2, 76.4, 72.9, 63.8, 46.0. Anomer: 99.9, 92.1, 75.9, 72.4, 63.7, 40.9. Anal. calcd: C, 69.67; H, 10.44. Found: C, 69.63; H, 10.45.

*3.2.7. (4*R,*5*S*)-4,5-Dihydroxymethyl-1,3-dioxan* ***20***

Lactol **19** (15 mg, 0.1 mmol) was reduced with $LiAlH_4$ (11 mg, 0.3 mmol) suspended in THF (0.6 ml) at 0°C for 30 min. Excess hydride was quenched with $Na_2SO_4\cdot10H_2O$ (11 mg) and Celite (11 mg) by stirring for 1 h. The solution was filtered, concentrated and flash chromatographed to afford diol **20** (13 mg, 88% yield). IR (film), cm^{-1}: 3580, 3450, 1095, 1064, 1025, 900. ^1H NMR: 5.06 (1H, d, *J*=6.0), 4.73 (1H, d, *J*=6.0), 4.14–4.06 (1H, m), 4.12 (1H, d, *J*=11.6), 3.90–3.66 (4H, m), 3.79 (1H, dd, *J*=11.7, 3.0), 2.83 (2H, sbr), 1.75 (1H, sbr). ^{13}C NMR: 94.4, 78.2, 69.8, 63.1, 60.5, 39.2. $[\alpha]_D^{22}$ −10.8 (c 6×10^{-3}, CH_2Cl_2).

*3.2.8. (4*R,*5*R*)-4-Hydroxymethyl-5-(hept-1-enyl)-1,3-dioxan* ***21a***

Acetate **22a**,**b** (90 mg, 0.35 mmol) in THF:MeOH (1 ml each) was stirred with K_2CO_3 (12 mg, 0.08 mmol) at rt for 2 h. The solution was filtered through silica gel and chromatographed to afford alcohol **21a** (65 mg, 87% yield) along with alcohol **21b** (6 mg, 8% yield). IR (CCl_4), cm^{-1}: 3602, 3494, 2851, 1261, 1171, 1134, 1074, 1032, 939. ^1H NMR: 5.55 (1H, dt, *J*=11.2, 7.2), 5.08 (1H, d, *J*=6.3), 4.90 (1H,

ddd, *J*=11.3, 9.8, 1.5), 4.68 (1H, d, *J*=6.2), 3.89 (1H, d, *J*=11.4, 4.8), 3.67–3.42 (3H, m), 3.35 (1H, dd, *J*=11.2, 11.1), 2.82 (1H, dtd, *J*=10.8, 10.0, 5.0), 2.09–1.91 (3H, m), 1.35–1.15 (6H, m), 0.86 (3H, t, *J*=6.4). ^{13}C NMR: 135.7, 123.7, 93.5, 81.0, 70.0, 63.7, 35.7, 31.5, 29.3, 27.9, 22.5, 14.1. $[\alpha]_D^{18}$ −6.4 (c 20×10^{-3}, CH_2Cl_2). Anal. calcd: C, 67.26; H, 10.35. Found: C, 67.24; H, 10.37.

21b: IR (CCl_4), cm^{-1}: 3602, 3494, 2851, 1261, 1171, 1134, 1074, 1032, 939. ^{1}H NMR: 5.82 (1H, dd, *J*=11.3, 10.3), 5.55 (1H, dt, *J*=11.2, 7.2), 5.12 (1H, d, *J*=6.0), 4.75 (1H, d, *J*=6.1), 3.90–3.81 (3H, m), 3.64 (1H, ddd, *J*=11.7, 8.4, 3.4), 3.40 (1H, ddd, *J*=11.7, 8.6, 3.6), 2.42 (1H, dbr, *J*=10.3), 2.00–1.90 (2H, m), 1.87–1.81 (1H, m), 1.36–1.21 (6H, m), 0.86 (3H, t, *J*=6.6). ^{13}C NMR: 132.5, 125.5, 94.0, 79.6, 72.1, 64.0, 34.8, 31.4, 29.2, 27.5, 22.4, 13.9. $[\alpha]_D^{20}$ −5.6 (c 6×10^{-3}, CH_2Cl_2).

3.3. 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 (O_2 must be excluded)[19] 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 NH_4Cl solution and water were added and the mixture was thrice extracted with Et_2O. The combined organic layers were washed with brine and dried over $MgSO_4$ for 5 min. Filtration over silica gel followed by column chromatography afforded pure olefinic adducts.

*3.3.1. (4*S*,5*S*)-(*Z*)-4-(Hept-1-enyl)-5-methoxymethoxy-1,3-dioxane **5***

Aldehyde **4** (53 mg, 0.3 mmol) led to olefin **5** (58 mg, 80% yield). IR (CCl_4), cm^{-1}: 2920, 2780, 1659, 1467, 1356, 1178, 1043. ^{1}H NMR: 5.64–5.58 (2H, m), 5.11 (1H, d, *J*=6.3), 4.81 (1H, d, *J*=6.3), 4.78 (1H, d, *J*=7.0), 4.66 (1H, d, *J*=7.0), 4.50 (1H, dd, *J*=6.6, 1.8), 4.15 (1H, d, *J*=12.3), 3.79 (1H, dd, *J*=12.3, 1.5), 3.45 (1H, d, *J*=1.5), 3.39 (3H, s), 2.07–2.02 (2H, m), 1.40–1.18 (6H, m), 0.86 (3H, t, *J*=6.8). ^{13}C NMR: 134.5, 125.8, 95.7, 93.4, 74.8, 71.4, 68.9, 55.7, 31.3, 29.0, 28.0, 22.4, 13.9. $[\alpha]_D^{20}$ +76.1 (c 24×10^{-3}, $CHCl_3$). Anal. calcd: C, 65.60; H, 9.44. Found: C, 65.58; H, 9.41.

*3.3.2. Methyl (4*S*)-4-(hept-1-enyl)-1,3-dioxan-5-ylidenacetate **8***

Ketone **7** (23 mg, 0.116 mmol crude) led to olefin **8** as a mixture of diastereomers (5 mg, 17% yield from the alcohol). IR (CCl_4), cm^{-1}: 2974, 2860, 1725, 1659, 1376, 1217, 1151, 1118, 798. ^{1}H NMR: 5.84–5.59 (2H, m), 5.52–5.40 (1H, m), 5.10 and 5.07 (1H, d, *J*=6.1), 5.04–5.00 (1H, dbr, *J*=8.3), 4.93 and 4.82 (1H, d, *J*=6.1), 4.53–4.46 (1H, dbr, *J*=13.5), 4.25–4.19 (1H, d, *J*=13.6), 3.68 and 3.67 (3H, s), 2.25 (1H, dd, *J*=14.8, 7.0), 2.06–1.96 (1H, m), 1.43–1.26 (6H, m), 0.89–0.82 (3H, dt, *J*=6.4, 6.2). ^{13}C NMR two isomers: 166.1/165.3, 152.9/152.2, 139.1/136.7, 124.8/123.3, 115.3, 92.7/88.3, 74.1/68.9, 68.0/66.1, 51.5, 31.6/31.5, 29.1/28.9, 28.2/27.9, 22.6/22.5, 14.1/14.0. Anal. calcd: C, 46.15; H, 7.75. Found: C, 46.08; H, 7.82.

*3.3.3. (4*R*)-(*Z,E*)-4-(Hept-1-enyl)-5-methoxymethyliden-1,3-dioxane **9***

Ketone **7** (32 mg, 0.162 mmol crude) led to olefin **9** (3 mg, 8% yield). IR (CCl_4), cm^{-1}: 2976, 2863, 1686, 1446, 1380, 1120, 1034, 934. ^{1}H NMR: 5.86 (1H, sbr), 5.67 (1H, dt, *J*=11.0, 7.3), 5.40 (1H, dd, *J*=11.0, 8.0), 5.10 (1H, d, *J*=6.4), 4.92 (1H, d, *J*=8.2), 4.87 (1H, d, *J*=6.4), 4.84 (1H, d, *J*=13.0), 4.05

(1H, d, *J*=12.8), 3.57 (3H, s), 2.06–1.99 (2H, m), 1.39–1.23 (6H, m), 0.89 (3H, t, *J*=6.5). ^{13}C NMR: 143.4, 135.1, 125.6, 110.6, 93.6, 73.4, 63.5, 60.0, 31.5, 29.1, 28.0, 22.6, 14.1. Anal. calcd: C, 68.06; H, 9.28. Found: C, 67.80; H, 9.45.

*3.3.4. (4*R*)-(*Z/E*)-5-Hexyliden-1,3-dioxan-4-ylmethyl acetate* ***13***

Ketone **12** (102 mg, 0.59 mmol crude) led to olefin **13** (16 mg, 13% yield). IR (film), cm^{-1}: 2957, 2857, 1744, 1597, 1458, 1232, 1174, 1126, 1035, 938. ^{1}H NMR: *E* isomer: 5.38 (1H, t, *J*=7.2), 5.08 (1H, d, *J*=6.2), 4.85 (1H, d, *J*=6.2), 4.52 (1H, d, *J*=11.9), 4.35–4.29 (1H, m), 4.18 (1H, d, *J*=11.9), 4.18 (2H, t, *J*=10.4), 2.08 (3H, s), 2.06–1.89 (2H, m), 1.39–1.24 (6H, m), 0.86 (3H, t, *J*=6.4); *Z* isomer: 5.42 (1H, t, *J*=7.0), 5.01 (1H, d, *J*=6.4), 4.89–4.84 (1H, m), 4.87 (1H, d, *J*=6.4), 4.56 (1H, d, *J*=11.8), 4.40–4.29 (2H, m), 4.03 (1H, dd, *J*=11.8, 4.2), 2.08 (3H, s), 2.06–1.89 (2H, m), 1.39–1.24 (6H, m), 0.86 (3H, t, *J*=6.4) ^{13}C NMR: *E* isomer: 171.0, 128.1, 129.7, 91.9, 75.9, 65.1, 31.4, 29.1, 26.7, 22.7, 20.9, 14.0; *Z* isomer: 170.9, 129.0, 126.9, 29.0, 88.6, 71.3, 69.6, 62.0, 31.5, 29.0, 26.8, 22.5, 20.9, 14.0. Anal. calcd: C, 68.89; H, 9.52. Found: C, 68.82; H, 9.49.

*3.3.5. (4*S*)-(*Z/E*)-5-(3,3-Diisopropoxypropyliden)-1,3-dioxan-4-ylmethyl acetate* ***14***

Ketone **12** (74 mg, 0.425 mmol crude) led to olefin **14** (53 mg, 40% yield). Chromatography afforded a sample of each isomer.

(*Z*)-**14**: IR (CCl_4), cm^{-1}: 2973, 1746, 1230, 1174, 1126, 1036. ^{1}H NMR: 5.46 (1H, t, *J*=7.4), 5.01 (1H, d, *J*=6.4), 4.90–4.84 (1H, m), 4.87 (1H, d, *J*=6.4), 4.55 (2H, ddd, *J*=10.4, 7.7, 4.2), 4.35 (1H, d, *J*=12.8), 4.18 (1H, d, *J*=12.8), 4.11 (1H, dd, *J*=11.9, 4.2), 3.81 (2H, sept, *J*=6.1), 2.34–2.25 (2H, m), 2.07 (3H, s), 1.16 (6H, d, *J*=6.2), 1.10 (6H, dd, *J*=6.1). ^{13}C NMR: 170.9, 130.4, 124.1, 98.9, 88.5, 71.5, 69.6, 68.5 (2C), 61.9, 33.5, 23.3 (2C), 22.6, 22.4, 20.9. $[\alpha]_D^{22}$ +10.4 (c 7×10^{-3}, CCl_4).

(*E*)-**14**: IR (CCl_4), cm^{-1}: 2973, 1746, 1230, 1174, 1126, 1036. ^{1}H NMR: 5.39 (1H, dd, *J*=6.4, 6.3), 5.07 (1H, d, *J*=6.2), 4.83 (1H, d, *J*=6.2), 4.51 (2H, dd, *J*=5.9, 5.4), 4.40–4.30 (3H, m), 4.24 (1H, d, *J*=13.4), 3.80 (2H, sept, *J*=6.1), 2.29 (2H, dd, *J*=6.4, 6.34), 2.07 (3H, s), 1.15 (6H, d, *J*=6.2), 1.10 (6H, dd, *J*=6.1). ^{13}C NMR: 170.9, 131.5, 121.3, 99.2, 91.9, 88.5, 75.8, 68.4, 68.3, 65.4, 63.7, 33.4, 23.3 (2C), 22.6, 22.5, 21.0, 20.9. $[\alpha]_D^{22}$ +9.4 (c 7×10^{-3}, CCl_4). Anal. calcd: C, 71.39; H, 9.59. Found: C, 71.31; H, 9.55.

*3.3.6. (4*S*)-(*Z/E*)-5-Cyanomethylen-1,3-dioxan-4-ylmethyl acetate* ***15***

Ketone **12** (60 mg, 0.345 mmol crude) led to olefin **15** (35 mg, 52% yield). IR (CCl_4), cm^{-1}: 2954, 2854, 2224, 1740, 1642, 1371, 1229, 1175, 1124, 1038, 942. ^{1}H NMR: 5.35–5.32 (1H, m), 5.11 and 5.03 (1H, dd, *J*=6.3 and 6.4), 4.48 and 4.85 (1H, dd, *J*=6.3 and 6.4), 4.60 and 4.57 (1H, dd, *J*=11.7 and 11.6), 4.52–4.28 (4H, m), 2.10 and 2.09 (3H, 2s). ^{13}C NMR: 170.5 (2C), 154.7 (2C), 114.1 (2C), 97.3/95.7, 92.2/89.1, 74.2/ 72.5, 67.7/67.2, 62.5/61.8, 20.8 (2C).

*3.3.7. (4*S*)-(*Z/E*)-5-(Methoxymethylen)-1,3-dioxan-4-ylmethyl acetate* ***16***

Ketone **12** (285 mg, 1.64 mmol crude) led to olefin **16** (150 mg, 45% yield), along with alcohol **17** (13 mg, 4.5% yield).

(*Z*)-**16**: IR (CCl_4), cm^{-1}: 2956, 2842, 1745, 1688, 1232, 1112, 1033. ^{1}H NMR: 5.98 (1H, sbr), 5.05 (1H, d, *J*=6.4), 4.86 (1H, d, *J*=6.4), 4.75 (1H, dd, *J*=12.5, 3.6), 4.50 (1H, dd, *J*=11.9, 8.7), 4.25 (1H, dd, *J*=8.6, 3.6), 4.25 (1H, d, *J*=11.9), 4.11 (1H, d, *J*=12.5), 3.60 (3H, s), 2.08 (3H, s). ^{13}C NMR: 171.0, 144.0, 106.9, 90.5, 71.1, 66.3, 62.8, 60.2, 21.0. (*Z*) $[\alpha]_D^{22}$ +10.4 (c 65×10^{-3}, CCl_4).

(*E*)-**16**: IR (CCl_4), cm^{-1}: 2956, 2842, 1745, 1688, 1232, 1112, 1033. ^{1}H NMR: 5.94 (1H, sbr), 5.09 (1H, d, *J*=6.4), 4.82 (1H, d, *J*=6.4), 4.67 (1H, d, *J*=13.0), 4.36 (1H, d, *J*=4.6), 4.28 (2H, dd, *J*=4.5, 4.4),

4.18 (1H, d, *J*=12.9), 3.60 (3H, s), 2.09 (3H, s). ^{13}C NMR: 170.9, 142.8, 108.3, 92.2, 73.1, 63.5, 62.7, 60.1, 20.9. $[\alpha]_D^{22}$ +9.4 (c 65×10^{-3}, CCl_4). Anal. calcd: C, 73.37; H, 9.64. Found: C, 73.28; H, 9.67.

Alcohol **17**: IR (CCl_4), cm^{-1}: 3423, 2939, 2849, 1685, 1233, 1168, 1109, 1022. ^{1}H NMR: 5.08 (1H, d, *J*=6.2), 4.83 (1H, d, *J*=6.2), 4.71 (1H, d, *J*=13.0), 4.23 (1H, t, *J*=5.3), 4.10 (1H, d, *J*=12.9), 3.84 (2H, m), 3.59 (3H, s), 2.06 (1H, sbr). ^{13}C NMR: 142.6, 108.4, 92.5, 75.8, 62.9, 62.3, 60.0.

*3.3.8. (4*R,*5*R*)-5-(Hept-1-enyl)-1,3-dioxa-4-ylmethyl acetate* ***22a***

Aldehyde **18a**,**b** (100 mg, 0.53 mmol crude) led to a 10:1 mixture of olefins **22a** and **22b**, from which pure olefin **22a** was isolated (91 mg, 67% yield). IR (film), cm^{-1}: 2854, 1743, 1238, 1033. ^{1}H NMR: 5.56 (1H, dt, *J*=10.9, 7.4), 5.08 (1H, d, *J*=6.4), 4.91 (1H, dd, *J*=10.9), 4.67 (1H, d, *J*=6.3), 4.22 (1H, dd, *J*=12.0, 2.2), 3.98 (1H, dd, *J*=11.8, 6.6), 3.89 (1H, dd, *J*=11.3, 4.8), 3.60 (1H, ddd, *J*=10.2, 6.6, 2.2), 3.35 (1H, t, *J*=11.1), 2.84 (1H, dtd, *J*=10.6, 10.2, 5.1), 2.06 (3H, s), 2.05–1.96 (2H, m), 1.35–1.20 (6H, m), 0.86 (3H, t, *J*=6.3). ^{13}C NMR: 170.9, 135.9, 123.3, 93.6, 78.5, 70.0, 64.9, 35.8, 31.5, 29.2, 27.9, 22.5, 20.9, 14.0. $[\alpha]_D^{18}$ −5.1 (c 12×10^{-3}, CH_2Cl_2). Anal. calcd: C, 73.37; H, 9.64. Found: C, 73.28; H, 9.67.

*3.3.9. Methyl (*Z*)-6-[(4*S,*5*R*)-(*Z*)-(5-hept-1-enyl)-1,3-dioxan-4-yl]hex-5-enoate* ***24***

Crude aldehyde **23** (0.229 mmol) led to a 4:1 mixture of esters **24** (35 mg, 34% yield) along with ester **24′** (4 mg, 5% yield).

24: IR (film), cm^{-1}: 2927, 2854, 1739, 1457, 1366, 1132, 1025, 960. ^{1}H NMR: 5.52 (1H, dt, *J*=11.0, 7.4), 5.47 (1H, dtd, *J*=10.9, 7.4, 1.1), 5.34 (1H, dd, *J*=11.0, 8.7), 5.05 (1H, d, *J*=6.6), 4.82 (1H, dd, *J*=10.9, 9.9), 4.70 (1H, d, *J*=6.4), 4.08 (1H, t, *J*=9.1), 3.90 (1H, dd, *J*=11.3, 4.9), 3.64 (3H, s), 3.38 (1H, dd, *J*=11.3, 11.2), 2.75 (1H, dtd, *J*=11.0, 8.7, 4.8), 2.29 (2H, t, *J*=7.4), 2.11 (2H, q, *J*=7.6), 2.0 (2H, q, *J*=7.1), 1.67 (2H, quint, *J*=7.6), 1.25 (6H, m), 0.85 (3H, t, *J*=6.5). ^{13}C NMR: 174.2, 135.3, 133.8, 128.9, 124.1, 93.6, 76.8, 70.5, 51.7, 40.1, 33.5, 31.7, 29.5, 28.2, 27.7, 24.8, 22.7, 14.3. $[\alpha]_D^{23}$ −5.0 (c 1.05×10^{-3}, CCl_4). Anal. calcd: C, 69.64; H, 9.74. Found: C, 69.58; H, 9.73.

24′: IR (film), cm^{-1}: 2927, 2854, 1739, 1650, 1457, 1366, 1171, 1132, 1025, 960. ^{1}H NMR: 5.67 (1H, dt, *J*=15.4, 6.9), 5.50 (1H, dt, *J*=10.9, 7.4), 5.41 (1H, dd, *J*=15.5, 6.5), 5.07 (1H, d, *J*=6.6), 4.86 (1H, dd, *J*=11.0, 9.8), 4.69 (1H, d, *J*=6.4), 3.89 (1H, dd, *J*=11.3, 4.9), 3.75 (1H, dd, *J*=9.7, 6.6), 3.64 (3H, s), 3.35 (1H, dd, *J*=11.2, 11.2), 2.72 (1H, dtd, *J*=11.0, 8.7, 4.9), 2.27 (2H, t, *J*=7.6), 2.06–1.98 (4H, m), 1.68 (2H, quint, *J*=7.5), 1.32–1.23 (6H, m), 0.86 (3H, t, *J*=6.9). ^{13}C NMR: 174.0, 134.8, 132.6, 129.1, 124.3, 93.5, 81.4, 70.4, 51.5, 40.1, 33.4, 31.7, 31.5, 29.3, 28.0, 24.2, 22.6, 14.1.

*3.3.10. Ethyl (*Z*)-5-[(4*S,*5*R*)-(*Z*)-(5-hept-1-enyl)-1,3-dioxan-4-yl]pent-4-enoate* ***25***

Crude aldehyde **23** (0.238 mmol) led to ester **25** (56 mg, 76% yield) IR (film), cm^{-1}: 2958, 2854, 1736, 1663, 1457, 1371, 1236, 1174, 1131, 1080, 933. ^{1}H NMR: 5.55–5.42 (2H, m), 5.34 (1H, dd, *J*=10.9, 8.5), 5.05 (1H, d, *J*=6.3), 4.83 (1H, dtd, *J*=9.9, 1.5), 4.71 (1H, d, *J*=6.3), 4.19–4.09 (1H, m), 4.16–4.05 (2H, q, *J*=7.1), 3.91 (1H, dd, *J*=11.3, 4.8), 3.38 (1H, dd, *J*=11.3, 10.1), 2.78 (1H, dtd, *J*=10.6, 10.1, 4.8), 2.46–2.27 (4H, m), 2.05–1.95 (2H, m), 1.59–1.12 (6H, m), 1.23 (3H, t, *J*=7.1), 0.86 (3H, t, *J*=6.5). ^{13}C NMR: 172.9, 135.1, 132.3, 129.0, 123.9, 93.3, 76.6, 70.3, 60.4, 39.8, 34.0, 31.5, 29.3, 28.0, 23.8, 22.5, 14.2, 14.0. $[\alpha]_D^{21}$ −2.7 (c 28×10^{-3}, CCl_4). Anal. calcd: C, 69.64; H, 9.74. Found: C, 69.66; H, 9.78.

*3.3.11. Ethyl (*Z*)-5-[(4*S,*5*S*)-(*Z*)-(5-hept-1-enyl)-1,3-dioxan-4-yl]pent-4-enoate* ***27***

Oxidation of alcohol **21b** to the corresponding crude aldehyde (0.187 mmol) and subsequent Wittig reaction led to ester **27** (48 mg, 83% yield).

IR (film), cm^{-1}: 2927, 2854, 1739, 1650, 1457, 1366, 1171, 1132, 1025, 960. ^{1}H NMR: 5.82 (1H, dd, *J*=11.1, 10.0), 5.59 (1H, ddd, *J*=11.1, 7.3, 7.1), 5.52–5.46 (2H, m), 5.07 (1H, d, *J*=6.2), 4.81 (1H, d,

J=6.2), 4.56 (1H, dd, *J*=6.7, 6.6), 4.10 (2H, q, *J*=7.2), 3.89 (1H, d, *J*=6.6), 3.88 (1H, d, *J*=6.0), 2.46–2.33 (5H, m), 1.93–1.86 (2H, m), 1.27–1.15 (6H, m), 1.23 (3H, t, *J*=7.2), 0.85 (3H, t, *J*=6.8). ^{13}C NMR: 172.8, 132.6, 131.0, 129.0, 125.9, 93.7, 74.9, 71.7, 60.4, 37.7, 34.0, 31.5, 29.3, 27.6, 23.5, 22.5, 14.2, 14.0. $[\alpha]_D^{21}$ −0.3 (c 48×10^{-3}, $CHCl_3$). Anal. calcd: C, 69.64; H, 9.74. Found: C, 69.66; H, 9.78.

3.4. 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 ether extracted. After drying over magnesium sulfate, the concentrated residue was filtered over silica gel.

*3.4.1. (4*S,*5*R*)-(*Z,Z*)-5-(5-Hept-1-enyl-1,3-dioxan-4-yl)pent-4-enoic acid **26***

79% yield. IR (film), cm^{-1}: 3200, 2854, 1712, 1663, 1174, 1131, 1090, 933. ^{1}H NMR: 5.60–5.46 (2H, m), 5.37 (1H, dd, *J*=11.0, 8.4), 5.06 (1H, d, *J*=6.3), 4.88 (1H, dd, *J*=10.7, 10.1), 4.71 (1H, d, *J*=6.3), 4.15 (1H, dd, *J*=9.1, 8.9), 3.92 (1H, dd, *J*=11.3, 4.8), 3.39 (1H, dd, *J*=11.3, 10.1), 2.77 (1H, dtd, *J*=10.1, 4.8), 2.40 (4H, sb), 2.03–1.95 (2H, m), 1.37–1.15 (6H, m), 0.86 (3H, t, *J*=6.6). ^{13}C NMR: 178.9, 135.3, 132.0, 129.3, 123.8, 93.3, 76.6, 70.3, 39.8, 33.8, 31.5, 29.3, 28.0, 23.5, 22.5, 14.1. $[\alpha]_D^{21}$ −2.0 (c 24×10^{-3}, $CHCl_3$). Anal. calcd: C, 68.06; H, 9.28. Found: C, 68.0; H, 9.34.

*3.4.2. (4*S,*5*S*)-(*Z,Z*)-5-(5-Hept-1-enyl-1,3-dioxan-4-yl)pent-4-enoic acid **28***

81% yield. IR (film), cm^{-1}: 3200, 2854, 1712, 1663, 1174, 1131, 1090, 933. ^{1}H NMR: 5.82 (1H, ddb, *J*=11.0, 10.3), 5.59 (1H, ddd, *J*=11.1, 7.3), 5.51–5.37 (2H, m), 5.07 (1H, d, *J*=6.2), 4.81 (1H, d, *J*=6.2), 4.56 (1H, dd, *J*=6.6, 2.8), 3.92 (1H, dd, *J*=11.0, 2.5), 3.84 (1H, dd, *J*=11.1, 2.2), 2.46–2.40 (1H, m), 2.40 (4H, sb), 1.96–1.86 (2H, m), 1.37–1.15 (6H, m), 0.85 (3H, t, *J*=6.6). ^{13}C NMR: 178.5, 132.6, 131.0, 129.1, 125.7, 93.6, 74.9, 71.7, 37.7, 34.0, 31.5, 29.3, 27.6, 23.4, 22.6, 14.1. $[\alpha]_D^{20}$ −0.42 (c 26×10^{-3}, $CHCl_3$). Anal. calcd: C, 68.06; H, 9.28. Found: C, 67.98; H, 9.38.

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