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Synthesis and Biological Testings as Inhibitors of HMGCoA Reductase of the Seco-acid of Tuckolide and its C-7 Epimer

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Abstract—The seco-acid of the natural macrolactone, tuckolide (decarestrictin D) and the C-7 epimer have been prepared in enantiomerically pure form from D-gluconolactone and poly(3-hydroxy butyric acid). The key steps are Horner–Emmons olefination and stereoselective reduction of the resulting enone to provide both epimers at C-7. None of the seco-acids inhibit microsomal HMGCoA reductase of pea or rat liver. It may be concluded that the cholesterol biosynthesis inhibiting effect of tuckolide is unlikely to proceed via HMGCoA reductase inhibition.

Introduction

The control of cholesterol blood level is of considerable interest for the control of coronary diseases which are responsible for about 40% of morbidity in developed countries. Efficient drugs are now on the market and most of these compounds, known as statines or mevinic acids, are more or less related to a family of lactonic compounds derived from the lead compounds compactin and mevinolin.[1,2] They are inhibitors of the rate-limiting enzyme of cholesterol biosynthesis, 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMGR), which is responsible for the double reduction of 3-hydroxy-3-methyl-glutaryl coenzyme A into mevalonic acid. It is known that the control of this enzyme is efficient in the lowering of plasma cholesterol (Fig. 1).[3]

The biologically active form of mevinic acids is the open chain hydroxy-acid which mimics the natural substrate 3-hydroxy-3-methyl-glutaryl coenzyme A. At the molecular level the key feature of mevinic acids is the presence of a dihydroxy-acid moiety associated with a lipophilic part which is quite intricate in the natural inhibitors such as compactin, mevinolin and pravastatin. The search for more simple compounds resulted in the preparation of aromatic derivatives associated with the hydroxy-acid part.[2]

Decarestrictin D, a macrolactone recently isolated from *Penicillium corylophilum* and *P. simplicissimum*,[4a] and tuckolide, the same compound isolated from the fungi *Polyporus tuberaster*,[4b] proved to be inhibitors of cholesterol biosynthesis in vitro in the HEP-G2 cells assay.[5] These data were confirmed in vivo with an activity at 10 mg/kg in rats equivalent to clofibrate at 100 mg/kg. Moreover no antibacterial and antifungal activities were detected.

Tuckolide/decarestrictin D should be an interesting lead compound for the discovery of new cholesterol lowering agents. This interest was recently reinforced by the disclosure by Andrus and Shih of a total synthesis of this compound in optically active form using Sharpless dihydroxylation as the key step.[6,7] In this paper the suggestion that tuckolide would be an inhibitor of HMGR on the basis of structural similarities between tuckolide and mevinolin attracted our attention. These similarities rely on the presence of a lactone moiety and the presence of an hydroxy group in β position of the carbonyl group. However the lipophilic part, present in mevinolin, which is essential for inhibition cannot be found in tuckolide. The lactone function of 'mevinic acids' is formed upon isolation and it is well known that the *free acid* is the biologically active form.[8–10] This suggested that the seco-acid of tuckolide might be the real inhibitor of HMGR. In that case the open-chain acid of tuckolide would be a lead compound en route to a new class of 'hydrophilic' inhibitors with a rather simple structure.[11] On this basis we decided to prepare the seco-acid of tuckolide and to evaluate its biological properties as inhibitor of HMGR.

Key words: Cholestereol biosynthesis; HMGCoA reductase; inhibition; tuckolide; synthesis.

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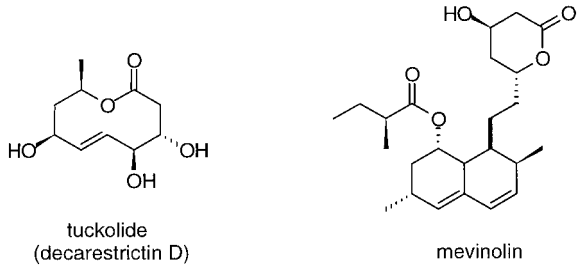


Figure 1.

Results

Our retrosynthetic analysis of hydroxy-acid **24** is based on an olefinic coupling between two enantiomerically pure building blocks. The phosphonate moiety **I** could be obtained by condensation of a phosphonate anion on a suitable derivative of 3-hydroxy butyric acid. The aldehydic part **II** could be obviously prepared from D-gluconic acid 1,5-lactone, a cheap and readily available starting material.

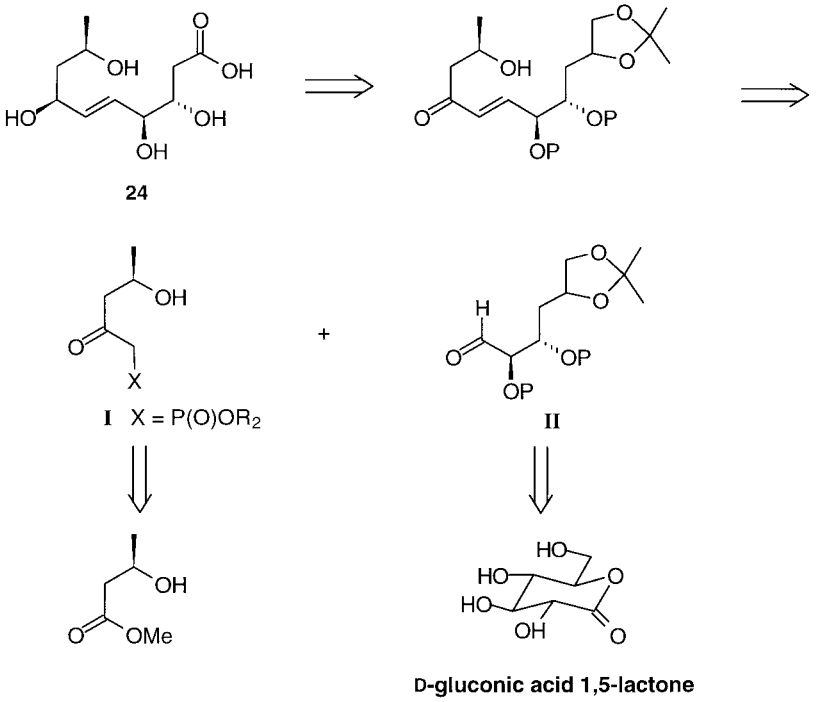
Synthesis of the phosphonate moiety

Poly [(*R*) 3-hydroxy butyric acid] **1** was depolymerized according to Seebach procedure to provide ester **2** in 71% yield.[12] The hydroxyl group of **2** was protected as a silyl ether using conventionnal procedure to provide ester **3** in 95% yield. The next crucial step was the homologation of ester **3** to the ketophosphonate **5**. Although the direct condensation of lithiophosphonates on esters is possible, Weinreb amide was preferred.[13] Ester **3** was transformed into amide **4** using an efficient, recently reported, procedure.[14] Treatment of **3** with the magnesium salt of *N,O*-dimethylhydroxylamine in THF at −10 °C led to amide **4** (86%), which was condensed with lithiotrimethylphosphonate at low temperature to prevent any epimerisation. This led reproducibly to the expected phosphonate **5**.[15–18] At this stage the extent of epimerisation, if any, cannot be determined. However, in the subsequent step, no detectable formation of diastereoisomers which may be formed from the *S*-epimer of **5** was observed.

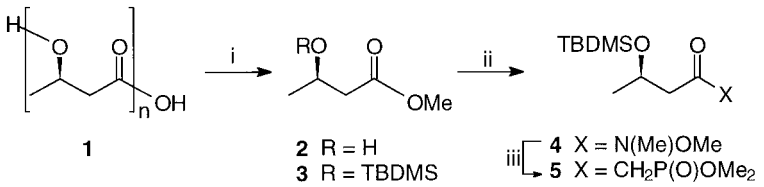
Synthesis of the aldehydic moiety

The presence in D-glucono-1,5-lactone of all the chiral centers needed in synthon **II** made it an ideal precursor provided that the carboxylic acid could be efficiently transformed into an aldehyde. We started from the known ester **6** prepared in a single step from D-gluconolactone in 50% yield.[19] The alcohol group of **6** was efficiently removed under radical conditions by formation of a phenylthiocarbonate or better by use of imidazolyl thionocarbonate **7** followed by treatment with tributyltin hydride. The deoxy compound **8** was obtained routinely in 60–65% for the two steps.[19]

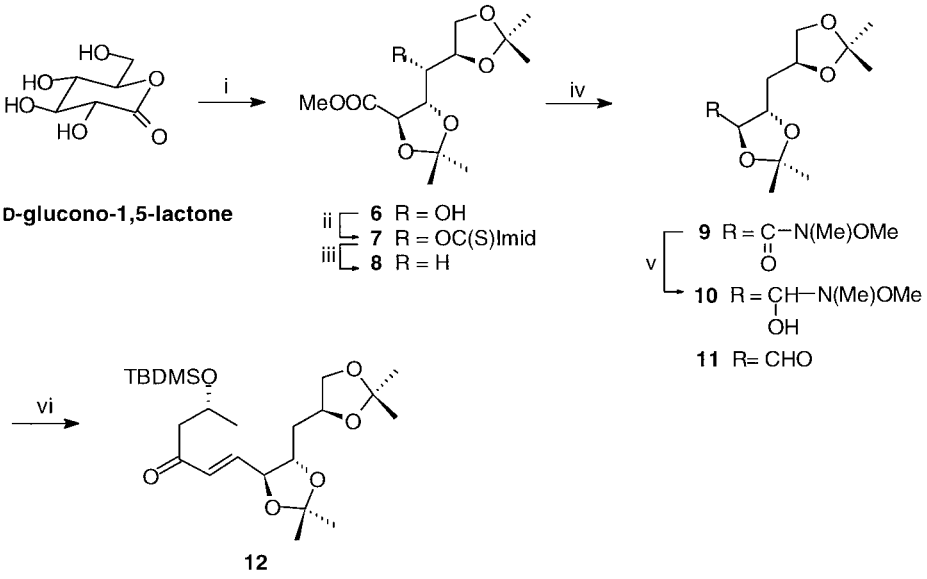
In order to achieve the reduction of the ester group into the required aldehyde function, we turned once again to Weinreb amide, the reduction of which is well documented and provide almost pure aldehyde upon treatment with lithium aluminium hydride. Treatment of ester **8** with the magnesium salt of *N,O*-dimethylhydroxylamine led to the amide **9** in 70% yield, together with a small amount of the corresponding isopropyl ketone (25%) because of the competing reaction of **8** or **9** with isopropyl magnesium chloride. The amide **9** was then subjected to lithium aluminium hydride reduction. Total consumption of the starting material was evident from TLC analysis, but to our surprise, hydrolysis of the



Scheme 1. Retrosynthetic analysis of tuckolide-seco-acid **24**.



Scheme 2. Reagents: (i) H_2SO_4, 1,2-dichlorethane:MeOH, reflux, 72 h; (ii) TBDMSCl, CH_2Cl_2, NEt_3, DMAP; (iii) $LiCH_2P(O)OMe_2$, THF, −100 °C.



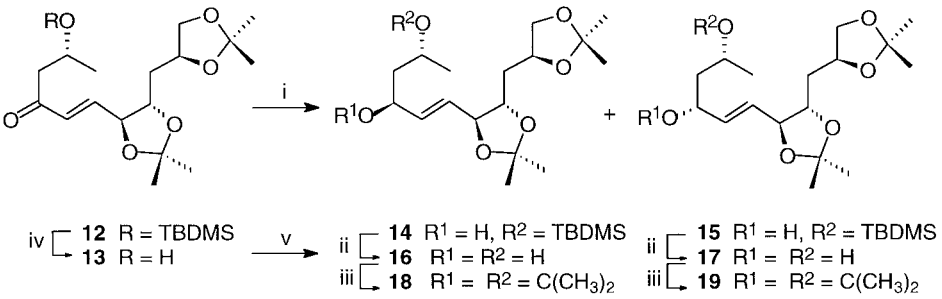
Scheme 3. Reagents: (i) DMP, Acetone, PTSA; (ii) $(Imid)_2CS$, 2 equiv, pyridine/CH_2Cl_2, rt, 18 h; (iii) Bu_3SnH, 1.2 equiv, AIBN, degased toluene, 6 h, 60–65%; (iv) MeNH(OMe)·HCl 1.6 equiv THF then *i*-PrMgCl, 3.2 equiv, −20 °C; (v) $LiAlH_4$, 1.2 equiv THF, 0 °C, 89%; (vi) **5**, 1.5 equiv, Et_2O, $LiOH·H_2O$, 2.6 equiv then **10**, Et_2O, 82.

reaction mixture led to only small amounts of the expected aldehyde **11**. The main compound was isolated and identified as the hemi-aminal resulting from simple reduction of the carbonyl group. This was evident from spectral data which showed the presence of an hydroxyl and the *N,O*-dimethyl groups and the presence of two diastereoisomers at the newly created chiral center. This stability can be explained by a possible hydrogen bond formation between the OH group and the neighboring groups which preclude the decomposition of the adduct in neutral medium. Assuming that the hemi-aminal **10** should decompose easily in slightly basic medium, we attempted the Horner–Emmons olefination between **5** and **10**. To our delight, using Blackwell conditions ($LiOH-H_2O$, ether),[20] a clean reaction occurred giving only the *trans* olefin in 82% yield.

Stereoselective reduction of the carbonyl group

The last key step of the synthesis was the reduction of the carbonyl group at C-8 of enone **12**. In a first series of experiments this enone was reduced stereo-randomly using Luche conditions. A 1:1 mixture of the two C-8 epimers **14** and **15** was obtained in 85–90%. The two compounds were easily separated by column chromatography. In order to determine the absolute configuration at C-8 of **14** and **15**, each of them was separately desilylated (TBAF, THF, rt) and the resulting diols were treated with dimethoxypropane and *p*-toluenesulfonic acid in acetone to give the corresponding acetonides **18** or **19** in 95% yield. The absolute configuration at C-8 of each acetonide was determined using the ^{13}C NMR method developed by Rychnovsky.[21] The difference of chemical shifts of the methyl groups of the acetonide are characteristic of the *anti* or *syn* configuration. Accordingly we were able to attribute the *anti* configuration to diol **14** and the *syn* configuration to diol **15**.

We also explored the stereoselective reduction, taking advantage of the presence of the hydroxy group at C-10 to direct the reduction at C-8. Such stereoselective reductions of β-hydroxy-ketones have ample precedents in the literature, however the reduction of a β-hydroxy-enone under such conditions is by far less documented. In order to direct the reduction of the carbonyl group at C-8, the hydroxyl group at C-10 must be desilylated to ensure complexation to the boron reagent. However all attempts to effect conventional desilylation (TBAF, THF, rt) failed to give the expected alcohol probably due to undesired reaction of the enone in basic medium. We turned to acid hydrolysis and found that under carefully controlled conditions (AcOH, THF, H_2O, rt, 4 days), it was possible to isolate the desired hydroxy-



Scheme 4. Reagents: (i) $NaBH_4$, $CeCl_3$, MeOH, 90%; (ii) TBAF, 1.1 equiv, THF; (iii) DMP, Acetone, PTSA cat., 95% 2 steps; (iv) AcOH:H_2O:THF, 3:7:20, 4 days, rt; (v) $Me_4NBH(OAc)_3$, 5 equiv, CH_3CN:AcOH, 1:1.

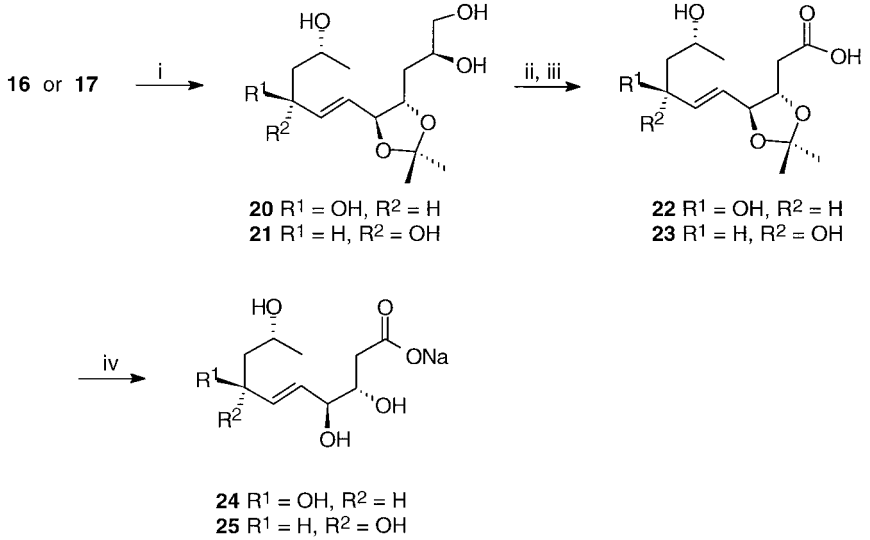
ketone **13** in fair yield together with some starting material. The formation of a saturated product resulting probably from 1,4-addition on the enone system was also observed but was not further investigated. Evans method was chosen to reduce the carbonyl group to obtain the *anti* configuration as in the natural product.[22] Treatment of ketone **13** with tetramethylammonium triacetoxy borohydride in acetonitrile provided a 9:1 mixture of the diols **16** and **17**. The *anti* configuration of compound **16** was confirmed by transformation into the acetonide **18** previously prepared. The observed stereoselectivity of the reagent for the *anti* configuration was in agreement with literature data.[23] It is interesting to note that no double bond reduction is observed. Due to the difficulty to remove the silyl protecting group to achieve chelation controlled reduction, no attempts were made to prepare the *syn* isomer by a similar route. We preferred to use the non-stereoselective reduction and subsequent chromatographic separation of the diastereoisomers.

Diol cleavage and final deprotection

The last steps of the synthesis were performed on compounds **14** and **15**. Desilylation under standard conditions led to diols **16** and **17**, respectively. The remainder of the synthesis consisted in selective removal of one isopropylidene group and oxidative cleavage of the resulting 1,2-diol. All attempts to use Wu's method (H_5IO_6, ether)[24] to perform both reactions in a single step failed. A stepwise procedure was explored. We found that careful acid hydrolysis (AcOH:H_2O:THF, 9:1:5, 55 °C) led to the tetrols **20** and **21**, respectively, in about 80% yield and fully deprotected material in about 10% yield. Each diol was then successively treated with sodium periodate to carry out the diol cleavage and the resulting aldehyde was oxidized without purification ($NaClO_2$, *t*BuOH, 2-methyl-2-butene) to provide the corresponding carboxylic acids **22** (88%) and **23** (68%), respectively. The final step was the removal of the last protecting group by acid hydrolysis (AcOH:H_2O:THF, 1:1:2, 60 °C) followed by treatment with sodium hydroxide to yield the target compounds **24** and **25**.

Biological evaluation

As was previously mentioned, in animal and plant cells HMGR is a highly regulated control point in the biosynthesis of a vast array of isoprenoids and prenyllipids. In plants the isoprenoid pathway has additional branches that lead to photosynthetic pigments, growth regulators (abscisic acid, gibberellins, and some cytokinins) and phytoalexins. Therefore, inhibition of HMGR-linked isoprenoid biosynthesis would have wide



Scheme 5. Reagents: (i) AcOH:H_2O:THF, 9:1:5, 55 °C, 80%; (ii) $NaIO_4$, 1.5 equiv, MeOH:H_2O; 2-methyl-2-butene, *t*BuOH then $NaClO_2$, 6 equiv, NaH_2PO_4, 4.5 equiv in H_2O; (iv) AcOH:H_2O:THF, 1:1:2, 60 °C, 20 h then NaOH.

Table 1. Lemna and HMGR inhibition by **24** and **25**

	Lemna I_{50} (ppm)[a]	HMGR I_{50}[a]	
		Rat	Pea
Mevastatin	0.1	1.1×10^{-6} M	4×10^{-7} M
24	> 50[b]	$>7.5\times10^{-4}$ M[b]	$>7.5\times10^{-4}$ M[b]
25	> 50[b]	$>7.5\times10^{-4}$ M[b]	$>7.5\times10^{-4}$ M[b]

[a]I_{50} concentration which causes 50% inhibition of the control values.
[b]No inhibition at the specified concentration.

ranging effects on plant growth and development. Mevastatin was a potent inhibitor of pea and rat liver microsomal HMGR activity. **24** and **25** did not inhibit either the plant or mammalian enzymes. These results correlated with biological activity where mevastatin was a potent inhibitor of *Lemna* growth (GR_{50} 0.1 ppm). However, **24** and **25** were not active on *Lemna*.

Conclusion

The present work has provided two new compounds corresponding to the open form of the macrolactone tuckolide and its C-6 epimer starting from two enantiomerically pure natural products. The key feature of these syntheses are the efficient and highly stereocontrolled Horner–Emmons coupling between a phosphonate and an hemi-aminal resulting from the reduction of a Weinreb amide. Subsequent reduction of the resulting β-hydroxy-enone is possible with high stereocontrol using Evans conditions without reduction of the double bond. None of the final products have shown interesting inhibitory activity toward HMGR. Because it has been postulated that the tight binding of HMGR inhibitors is the result of the compounds ability to simultaneously interact with the HMGR binding domain of the enzyme and an adjacent hydrophobic pocket, which does not appear to be utilized in substrate binding, it is not surprising that the absence of a lipophilic moiety, such as the decalin ring present on mevinic acids, on **24** and **25** likely limits the binding of these compounds to HMGR. Our results show that the reported inhibition of cholesterol biosynthesis by tuckolide is likely not related to the inhibition of HMGR by the open-chain hydroxy-acid but is probably related to a subsequent step of the biosynthesis.

Experimental

^{1}H NMR spectra were recorded with a Bruker AC 250 operating at 250 MHz and 63 MHz for the ^{13}C, using deuteriochloroform as solvent. Assignments were confirmed by double irradiation or two dimensional spectroscopy. Chemical shifts are reported relative to internal $SiMe_4$. TLC was performed on silica gel plates (Merck $60F_{254}$). Column chromatography used silica gel (Merck 60 70–23 mesh). Preparative high pressure liquid chromatography was performed on 40 mm diameter stainless steel column (Prochrom, Champigneulles, France) using silica gel (Merck 60 40–60 μ). Optical rotations were measured on a Perkin–Elmer 141 polarimeter at 20 °C. Melting points were measured in capillary tubes and are uncorrected. The elementary analyses were performed by the Service Central de Microanalyses du CNRS at Vernaison, France. Mass spectra were obtained on a Nermag R10-10C in the EI mode or VG Plattform in the ES mode. Tetrahydrofuran was distilled prior to use from sodium-benzophenone.

(*R*)-Methyl 3-*O*-(*tert*-butyldimethylsilyl)-butanoate (3). To a stirred solution of **2**[12] (10.8 g, 91.2 mmol) in CH_2Cl_2 (300 mL) under a nitrogen atmosphere were added successively *tert*-butylchlorodimethylsilane (13.7 g, 91.2 mmol), Et_3N (20 mL), DMAP (1.10 g, 9.1 mmol) and Et_3N (18 mL). The reaction mixture was stirred at room temperature for two days and then washed successively with 3 N HCl (90 mL) and water. The organic layer was dried ($MgSO_4$) and evaporated under vacuum. Flash chromatography on silica gel afforded the silyl ether **3** (20.1 g, 95%) which can be used in the next step. R_f 0.74 (hexane:ethyl acetate, 8:2); ^{1}H NMR: δ 0.05 (s, 3H, SiCH_3), 0.07 (s, 3H, SiCH_3), 0.87 (s, 9H, SiC(CH_3)$_3$), 1.21 (d, 3H, H_3C-CHOTBDMS, J = 6 Hz), 2.38 (dd, 1H, CH_2COOCH$_3$, J = 3, J_{gem} = 9 Hz), 3.68 (s, 3H, COOCH_3), 4.28 (m, 1H, C*H*OTBDMS).

(*R*)-3-*O*-(*tert*-Butyldimethylsilyl)-*N*-methoxy-*N*-methylbutanamide (4). The ester **3** (5.0 g, 21 mmol) and *N*-methoxy-*N*-methylamine hydrochloride (2.92 g, 30 mmol) were suspended in 40 mL of THF cooled to −10 °C under nitrogen atmosphere. A solution of isopropyl magnesium chloride in THF (25 mL, 2.4 M) was added dropwise below −10 °C. The mixture was stirred for 2 h at −10 °C, quenched with saturated aqueous NH_4Cl and diluted with ether. The organic layer was washed with water, dried over $MgSO_4$ and concentrated. Purification on silica gel afforded the amide **4** as a clear oil (5.5 g, 86%). R_f 0.25 (hexane:ethyl acetate, 9:1). ^{1}H NMR: δ 0.02 (s, 3H, SiCH_3), 0.07 (s, 3H, SiC*H*3), 0.88 (s, 9H, SiC(CH_3)$_3$), 1.20 (d, 3H, H_4, $J_{3,4}$ = 6 Hz), 2.35 (dd, 1H, H_2, J_{gem} = 14, $J_{2,3}$ = 5.5 Hz), 2.77 (dd, 1H, H_2', $J_{2',3}$ = 7 Hz), 3.18 (s, 3H, NCH_3), 3.70 (s, 3H, OCH_3), 4.35 (ddd, 1H, H_3); MS (*m*/*z*): 246 $(M-15)^+$. Anal. calcd for $C_{12}H_{27}NO_3Si$: C, 55.14; H, 10.42; N, 5.36. Found: C, 55.56; H, 10.11; N, 5.30.

(*R*)-4-*O*-(*tert*-Butyldimethylsilyl)-1-(dimethoxyphosphinyl)-pentan-2-one (5). A 100-mL round-bottomed flask equipped with a rubber septum was charged with *n*-BuLi (10.9 mL, 1.25 M in hexane) under an argon atmosphere and cooled to −80 °C. Dimethyl methylphosphonate (1.5 mL, 13.9 mmol) was added dropwise by syringe. During addition, a mixture of THF (2 mL) and Et_2O (2 mL) was added to aid in stirring. The reaction mixture was stirred 15 min after the completion of the addition and cooled to −110 °C, a solution of **4** (2.81 g, 10.8 mmol) in a mixture of THF (1 mL) and Et_2O (1 mL) was added. The mixture was stirred at −110 °C for 15 min and allowed to warm slowly to −70 °C over 20 min. The reaction was quenched with a mixture of 1 M H_3PO_4 (20 mL) and Et_2O (60 mL). The

layers were separated and the aqueous layer was extracted twice with EtOAc (100 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$, brine and dried over $MgSO_4$. The crude product was chromatographed on silica gel to afford **5** as a clear oil (2.70 g, 77%). R_f 0.51 (ethyl acetate); $[\alpha]_D$ −30.5° (*c* 0.91, $CHCl_3$); IR: 1715 cm^{-1}; ^1H NMR: δ 0.01 (s, 3H, $SiCH_3$), 0.045 (s, 3H, $SiCH_3$), 0.85 (s, 9H, $SiC(CH_3)_3$), 1.15 (d, 3H, H_5, $J = 6$ Hz), 2.61 (dd, 1H, H_3, $J_{gem} = 15.5$, $J_{3,4} = 5$ Hz), 2.78 (dd, 1H, $H_{3'}$, $J_{3',4} = 7$ Hz), 3.05 (d, 1H, $H_{1'}$), 3.14 (d, 1H, H_1, $J_{gem} = 3$ Hz), 3.73 (d, OCH_3, $J = 1$ Hz), 3.78 (s, 3H, OCH_3), 4.26 (m, H_4); ^{13}C NMR: δ 4.99–4.55 ($Si(CH_3)_2$), 18.00 ($SiC(CH_3)_3$), 23.88 (C_5), 25.76 (3C, $SiC(C)H_3)_3$), 41.57, 43.61, 53.30; ^{31}P NMR: δ 23.57 ($PO(OCH_3)_2$).

4-Deoxy-2,3:5,6-di-*O*-isopropylidene-D-xylo-*N*-methoxymethylhexonamide (9). To a solution of ester **8**[19] (5.2 g, 18.9 mmol) and *N*-methoxy-*N*-methylamine hydrochloride (2.95 g, 30 mmol) in anhydrous THF (50 mL) under nitrogen at −20 °C was added slowly over 1 h a solution of isopropyl magnesium chloride (30 mL, 2 M in Et_2O, 60 mmol). The reaction was monitored by TLC (hexane:ethyl acetate, 7:3) and after 1 h, was quenched by saturated aqueous NH_4Cl (8 mL). The aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel (hexane:ethyl acetate, 7:3) to provide the expected amide **9** (3.91 g, 12.9 mmol, 68%). R_f 0.80 (hexane:ethyl acetate, 7:3); $[\alpha]_D$ −1.6° (*c* 1.6, $CHCl_3$); IR: 1670, 1457, 1380 cm^{-1}; ^1H NMR: δ 1.27 (s, 3H, $C(CH_3)$), 1.34 (s, 3H, $C(CH_3)$), 1.40 (s, 6H, $C(CH_3)$), 1.82 (ddd, 1H, H_4, $J_{gem} = 14$, $J_{4,5} = 5$, $J_{3,4} = 7$ Hz), 1.93 (ddd, 1H, $H_{4'}$, $J_{4',5} = 7$, $J_{3,4'} = 5$ Hz), 3.18 (s, 3H, NCH_3), 3.51 (dd, 1H, H_6, $J_{gem} = 8.5$ Hz, $J_{5,6} = 6.5$ Hz), 3.70 (s, 3H, OCH_3), 4.03 (dd, 1H, $H_{6'}$, $J_{5,6'} = 6$ Hz), 4.12 (m, 1H, H_5), 4.40–4.51 (m, 2H, H_2, H_3); ^{13}C NMR δ 25.60, 25.95, 26.82, 27.29 (4C, $C(CH_3)_2$), 37.41 (C_4), 61.47, 66.67 (OCH_3, NCH_3), 69.33, 69.64, 73.31, 77.46 (4C, C_2, C_3, C_5, C_6), 108.58, 110.38 ($C(CH_3)_2$), 169.98 (C_1).

4-Deoxy-2,3:5,6-di-*O*-isopropylidene-D-xylo-hexose (11). To a solution of Weinreb amide **9** (3.75 g, 12.4 mmol) in anhydrous THF (120 mL) at 0 °C under nitrogen was added lithium aluminium hydride (0.635 g, 15 mmol) in 3 portions over 10 min. After stirring for 5 min, hydrolysis was carefully carried out by adding water (0.7 mL), 30% aqueous solution of NaOH (1.4 mL) and finally water (15 mL). The aqueous layer was extracted with 2×40 mL of Et_2O. The combined organic layers were dried over $MgSO_4$ and solvents were evaporated. Purification by column chromatography on silica gel (hexane:ethyl acetate, 5:5) gave the hemi-aminal **10** (3.39 g, 11.1 mmol, 89%) as a diastereoisomeric mixture that was used in coupling with phosphonate **5** without further purification.

(2*S*,4*S*,5*S*,6*E*,10*R*)-10-*O*-(*tert*-Butyldimethylsilyl)-1,2:4,5-di-(isopropylidenedioxy)-6-undecen-8-one (12). A solution of phosphonate **5** (7.10 g, 21.9 mmol) and lithium hydroxide monohydrate (0.93 g, 38.7 mmol) in anhydrous Et_2O (65 mL) was stirred under nitrogen at room temperature during 0.5 h. A solution of compound **10** (4.5 g, 14.7 mmol) in Et_2O (25 mL) was then added dropwise over 15 min. After stirring during 0.5 h, this mixture was hydrolysed with satured aqueous NH_4Cl (10 mL). The organic layer was washed with water (2×10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography (hexane:ethyl acetate, 9:1) afforded **12** (5.39 g, 17.7 mmol, 82%). R_f 0.55 (hexane:ethyl acetate, 8:2); $[\alpha]_D$ −21.3° (*c* 1.1, $CHCl_3$); IR: 1674, 1634, 1472, 1371 cm^{-1}; ^1H NMR: δ 0.04 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$), 0.82 (s, 9H, $SiC(CH_3)_3$), 1.15 (d, 3H, H_{11}, $J_{10,11} = 6$ Hz), 1.32 (s, 3H, $C(CH_3)_2$), 1.36 (s, 3H, $C(CH_3)_2$), 1.38 (s, 3H, $C(CH_3)_2$), 1.39 (s, 3H, $C(CH_3)_2$), 1.73 (ddd, 1H, H_3, $J_{gem} = 15.5$, $J_{3,4} = 8.5$, $J_{4a,5} = 5$ Hz), 1.86 (ddd, 1H, H_{10}, $J_{3',4} = 8$, $J_{2,3'} = 4$ Hz), 2.49 (dd, 1H, H_9, $J_{gem} = 15.5$, $J_{9,10} = 5$ Hz), 2.79 (dd, 1H, $H_{9'}$, $J_{9',10} = 7$ Hz), 3.54 (dd, 1H, H_1, $J_{gem} = 8.5$, $J_{1,2} = 6.5$ Hz), 3.83 (ddd, 1H, H_4, $J_{3,4} = 3.5$ Hz), 4.05 (dd, 1H, $H_{1'}$, $J_{1',2} = 6$ Hz), 4.10–4.22 (m, 2H, H_2, H_5), 4.30 (m, 1H, $H_{3'}$), 6.34 (dd, 1H, H_7, $J_{trans} = 16$, $J_{5,7} = 1.5$ Hz), 6.73 (dd, 1H, H_6, $J_{5,6} = 5.5$ Hz); ^{13}C NMR: δ −4.53, −4.88 ($Si(CH_3)_2$), 18.19 ($SiC(CH_3)_3$), 24.21 (C_{11}), 25.77 (3C, $SiC(CH_3)_3$), 26.75 ($C(CH_3)_2$), 27.03, 27.26 ($C(CH_3)_2$), 37.75 (C_3), 50.17 (C_9), 65.73 (C_{10}), 69.78 (C_1), 73.39 (C_2), 77.49 (C_4) 80.67 (C_5), 108.95, 109.71 ($C(CH_3)_2$), 131.46 (C_7), 141.70 (C_6), 198.75 (C_8), MS (*m*/*z*): 427 $(M-15)^+$. Anal. calcd for $C_{23}H_{42}O_6Si$: C, 62.40; H, 9.60. Found: C, 62.06; H, 9.61.

(2*S*,4*S*,5*S*,6*E*,10*R*)-10-Hydroxy-1,2:4,5-di-(isopropylidenedioxy)-6-undecen-8-one (13). To a stirred solution of the silyl ether **12** (0.52 g, 1.17 mmol) in THF (20 mL) was added a mixture of water (7 mL) and acetic acid (3 mL). After being stirred for 4 days at room temperature, the solution was neutralised with solid sodium carbonate. The aqueous layer was extracted with EtOAc and combined organic layers were washed with saturated aqueous NaCl, dried over Na_2SO_4 and the solvent evaporated under vacuum. Purification by HPLC (hexane:ethyl acetate gradient from 90:10 to 50:50) afforded the β-hydroxyketone **13** (0.191 g, 0.58 mmol, 50%) accompanied with some starting material (0.103 g, 0.23 mmol, 20%). R_f 0.34 (hexane:ethyl acetate, 5:5); $[\alpha]_D$ 33.8° (*c* 2.06, $CHCl_3$); ^1H NMR: δ 1.18 (d, 1H, H_{11}, $J_{10,11} = 6$ Hz), 1.33 (s, 3H, $C(CH_3)_2$), 1.38 (s, 3H, $C(CH_3)_2$), 1.40 (s, 3H, $C(CH_3)_2$), 1.42 (s, 3H, $C(CH_3)_2$), 1.78 (ddd, 1H, H_3, $J_{gem} = 13$, $J = 5$ Hz, $J = 8.5$ Hz), 1.86 (ddd, 1H, $H_{3'}$, $J = 4$, $J = 7$ Hz), 2.55–2.80 (m, 2H, H_9, $H_{9'}$), 3.55 (dd, 1H, H_1, $J_{gem} = 8$, $J_{1,2} = 7$ Hz), 3.86 (ddd, 1H, H_4, $J = 8.5$ Hz), 4.07 (dd, 1H, $H_{1'}$, $J_{1',2} = 6$ Hz), 4.12–4.31 (m, 4H, H_2, H_5, H_8, H_{10}), 6.35 (dd, 1H, H_7, $J_{trans} = 16$, $J_{5,7} = 1$ Hz), 6.80 (dd, 1H, H_6, $J_{5,6} = 5$ Hz); ^{13}C NMR: δ 22.34 (C_{11}), 25.67, 26.65, 26.96, 27.17 (4C, $C(CH_3)_2$), 36.76 (C_3), 48.25 (C_9), 63.82 (C_{10}), 69.70 (C_1), 73.35 (C_2), 77.97 (C_4), 80.55 (C_5), 108.98, 109.80 ($C(CH_3)_2$), 130.55 (C_7), 142.58 (C_6), 200.33 (C_8).

Compounds 14 and 15. To a solution of ketone **12** (1.50 g, 3.39 mmol) and $CeCl_3 \cdot 7H_2O$ (1.26 g, 3.39 mmol) in 30 mL of MeOH at 0 °C was added $NaBH_4$ (0.128 g, 3.39 mmol) in one portion. A vigorous gas evolution took place. Stirring was continued for a few minutes

before the pH was adjusted to **7** with diluted aqueous HCl. MeOH was evaporated under vacuum and the yellow residue was diluted with Et_2O and washed with H_2O and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by preparative high pressure liquid chromatography (hexane:ethyl acetate, 85:15) to give **15** (0.78 g, 1.77 mol, 52%) and **14** (0.56 g, 1.28 mmol, 38%).

(2*S*,4*S*,5*S*,8*S*,10*R*)-10-*O*-(*tert*-Butyldimethylsilyl)-8-hydroxy-1,2:4,5-di-(isopropylidenedioxy)-6-undecene (14). R_f 0.55 (hexane:ethyl acetate, 7:3); $[\alpha]_D$ −8.6° (*c* 1.33, $CHCl_3$); ^{1}H NMR: δ 0.08 (s, 6H, Si(CH_3)$_2$)), 0.90 (s, 9H, SiC(CH_3)$_3$)), 1.23 (d, 3H, H_{11}, $J_{10,11}$ = 6.5 Hz), 1.34 (s, 3H, C(CH_3)$_2$)), 1.38 (s, 9H, C(CH_3)$_2$)), 1.52–1.73 (m, 3H, H_3, H_9, $H_{9'}$), 1.90 (ddd, 1H, $H_{3'}$, J_{gem} = 14, $J_{2,3'}$ = 7, $J_{3',4}$ = 2.5 Hz), 3.37 (d, 1H, O*H*, $J_{8,OH}$ = 2 Hz), 3.58 (dd, 1H, H_1, J_{gem} = 8.5, $J_{1,2}$ = 7 Hz), 3.79 (ddd, 1H, H_4, $J_{3,4}$ = 10, $J_{4,5}$ = 9.5 Hz), 3.98 (dd, 1H, H_5, $J_{5,6}$ = 6.5 Hz), 4.08 (dd, 1H, $H_{1'}$, $J_{1',2}$ = 5.5 Hz), 4.21 (m, 1H, H_2), 4.50 (m, 1H, H_8), 5.68 (ddd, 1H, H_6, J_{trans} = 15.5, $J_{6,8}$ = 1 Hz), 5.84 (dd, 1H, H_7, $J_{7,8}$ = 5 Hz); ^{13}C NMR: δ −5.01, −4.43 (Si(*C*H$_3$)$_2$), 22.85 (C_{11}), 25.74 (1C, C(*C*H$_3$)$_2$), 25.77 (3C, C′*C*H$_3$)$_2$), 26.99 (C(*C*H$_3$)$_2$), 27.27 (1C, C(*C*H$_3$)$_2$), 36.31 (C_3), 44.18 (C_9), 67.26, 68.39 (C_8, C_{10}), 69.85 (C_1), 73.77 (C_2), 77.80 (C_4), 82.19 (*C*5), 108.76, 108.87 (*C*(CH$_3$)$_2$), 125.97 (C_6), 138.36 (C_7). MS (*m*/*z*): 329 (M−15)$^+$. Anal. calcd for $C_{23}H_{44}O_6Si$: C, 62.12; H, 9.97. Found: C, 62.39; H, 10.04.

(2*S*,4*S*,5*S*,8*R*,10*R*)-10-*O*-(*tert*-Butyldimethylsilyl)-8-hydroxy-1,2:4,5-di-(isopropylidenedioxy)-6-undecene (15). R_f 0.48 (hexane:ethyl acetate, 7:3). $[\alpha]_D$ −19.7° (*c* 0.28, $CHCl_3$).

(2*S*,4*S*,5*S*,8*S*,10*R*)-8,10-Dihydroxy-1,2:4,5-di-(isopropylidenedioxy)-6-undecene (16). Compound **14** (1.87 g, 4.21 mmol) was dissolved in 20 mL of anhydrous THF under nitrogen at room temperature. Tetrabutylammonium fluoride (1 M solution in THF, 4.3 mL, 4.3 mmol) was added. After stirring for 5 min, the solution was quickly washed with water, dried with sodium sulfate and concentrated under reduced pressure. Rapid column chromatography (hexane:ethyl acetate, 5:5) gave the pure product **16** (1.37 g, 4.1 mmol, 98%). R_f 0.85 (dichloromethane:methanol, 9:1); $[\alpha]_D$ 10.6° (*c* 1.6, $CHCl_3$); ^{1}H NMR: δ 1.13 (d, 3H, H_{11}, $J_{10,11}$ = 5.5 Hz), 1.26 (s, 3H, C(CH_3)$_2$), 1.30 (s, 6H, C(CH_3)$_2$), 1.33 (s, 3H, C(CH_3)$_2$), 1.42−1.75 (m, 3H, H_9, $H_{9'}$, H_3), 1.80 (ddd, 1H, $H_{3'}$, J_{gem} = 12.5, $J_{2,3'}$ = 7, $J_{3',4}$ = 3 Hz), 3.50 (dd, 1H, H_1, J_{gem} = 9, $J_{1,2}$ = 6.5 Hz), 3.74 (ddd, 1H, H_4, $J_{3,4}$ = 10, $J_{4,5}$ = 7 Hz), 3.88 (dd, 1H, H_5, $J_{5,6}$ = 7.5 Hz), 3.80−4.03 (m, 1H, H_{10}), 4.02 (dd, 1H, $H_{1'}$, $J_{1',2}$ = 5.5 Hz), 4.15 (m, 1H, $H_{2'}$), 3.50−4.40 (2H, 2O*H*), 4.20 (m, 1H, H_8), 5.54 (dd, 1H, H_6, J_{trans} = 15.5, $J_{5,6}$ = 7.5 Hz), 5.77 (dd, 1H, H_7, $J_{7,8}$ = 5.5 Hz); ^{13}C NMR: δ 24.28 (C_1), 25.93 (C(*C*H$_3$)$_2$), 27.08 (C(*C*H$_3$)$_2$), 27.37 (C(*C*H$_3$)$_2$), 36.68 (C_3), 44.74 (C_9), 68.12 (C_{10}), 70.53 (C_1), 74.24 (C_2), 75.10 (C_8) 78.36 (C_4), 82.20 (C_5), 108.95, 109.42 (*C*(CH$_3$)$_2$), 126.84 (C_6), 138.10 (C_7). MS (*m*/*z*): 315 (M−15)$^+$. Anal. calcd for $C_{17}H_{30}O_6$: C, 61.8; H, 9.2. Found: C, 61.42; H, 9.30.

(2*S*,4*S*,5*S*,8*R*,10*R*)-8,10-Dihydroxy-1,2:4,5-di-(isopropylidenedioxy)-6-undecene (17). Compound **17** was prepared in quantitative yield from **15** according to the above mentioned procedure. R_f 0.15 (hexane:ethyl acetate, 5:5); $[\alpha]_D$ 7.2° (*c* 0.9, $CHCl_3$); IR: 3396, 1457, 1370 cm^{-1}; ^{1}H NMR δ 1.10 (d, 3H, H_{11}, $J_{10,11}$ = 6 Hz), 1.29 (s, 3H, C(CH_3)$_2$), 1.32 (ls, 9H, C(CH_3)$_2$), 1.44−1.69 (m, 3H, H_9, $H_{9'}$, H_3), 1.79 (ddd, 1H, $H_{3'}$, J_{gem} = 12.5, $J_{2,3'}$ = 7.5, $J_{3',4}$ = 2.5 Hz), 3.51 (dd, 1H, H_1, J_{gem} = 9, $J_{1,2}$ = 7 Hz), 3.70 (ddd, 1H, H_4, $J_{3,4}$ = 10.5, $J_{4,5}$ = 7.5 Hz), 3.91 (dd, 1H, H_5, $J_{5,6}$ = 7.5 Hz), 3.85−4.05 (m, 1H, H_{10}), 4.02 (dd, 1H, $H_{1'}$, $J_{1',2}$ = 6 Hz), 4.15 (dddd, 1H, H_2, $J_{2,3}$ = 5.5 Hz), 3.60−4.20 (2H, 2O*H*), 4.29 (ddd, 1H, H_8, $J_{7,8}$ = 5.5, $J_{8,9}$ $J_{8,9'}$ = 12 Hz), 5.58 (dd, 1H, H_6, J_{trans} = 15, $J_{5,6}$ = 7.5 Hz), 5.76 (dd, 1H, H_7, $J_{7,8}$ = 5.5 Hz); ^{13}C NMR: δ 23.88 (C_1), 25.73 (C(*C*H$_3$)$_2$), 26.98 (C(*C*H$_3$)$_2$), 27.27 (C(*C*H$_3$)$_2$), 36.28 (C_3), 44.54 (C_9), 67.98 (C_{10}), 69.78 (C_1), 72.03 (C_8), 73.78 (C_2), 77.74 (C_4), 82.00 (C_5), 108.72, 109.02 (*C*(CH$_3$)$_2$), 126.36 (C_6), 137.88 (C_7). MS (*m*/*z*): 315 (M−15)$^+$. Anal. calcd for $C_{17}H_{30}O_6$: C, 61.8; H, 9.2. Found: C, 61.38; H, 9.22.

(2*S*,4*S*,5*S*,8*S*,10*R*)-1,2:4,5:8,10-Tri-(isopropylidenedioxy)-6-undecene (18). To a stirred solution of **14** (0.172 g, 0.38 mmol) in THF was added TBAF (0.40 mmol, 1M solution in THF) at room temperature. After being stirred for 1 h, the mixture was diluted with Et_2O, washed successively with saturated aqueous NH_4Cl, NaCl, dried ($MgSO_4$) and the solvent removed in vacuo. Without further purification the resulting oil was dissolved in a mixture of acetone (5 mL) and 2,2-dimethoxypropane (0.5 mL) and a catalytic amount of APTS was added. After a few minutes the reaction was finished and the mixture was neutralised with solid sodium carbonate, filtered through a pad of Celite and evaporated under vacuum. The residue was purified by chromatography on silica to afford compound **18** in 95% yield. R_f 0.11 (hexane:ethyl acetate 5:5); $[\alpha]_D$ −30.9° (*c* 0.5, $CHCl_3$); ^{1}H NMR: δ 1.18 (d, 1H, H_{11}, $J_{10,11}$ 6.5 Hz), 1.33 (s, 6H, C(CH_3)$_2$), 1.35 (s, 3H, C(CH_3)$_2$), 1.39 (s, 9H, C(CH_3)$_2$), 1.54−1.80 (m, 3H, H_9, $H_{9'}$, H_3), 1.91 (ddd, 1H, $H_{3'}$, J_{gem} = 14.0, $J_{3',4}$ 3.0, $J_{2,3'}$ = 6.5 Hz), 3.58 (dd, 1H, H_1, J_{gem} = 9, $J_{1,2}$ = 6.5 Hz), 3.77 (ddd, 1H, H_4, J = 8, J' = 10 Hz), 3.90−4.10 (m, 2H, H_5, H_{10}), 4.07 (dd, 1H, $H_{1'}$, $J_{1',2}$ = 5 Hz), 4.20 (m, 1H, H_2, $J_{2,3}$ = 8 Hz) , 4.36 (m, 1H, H_8, $J_{7,8}$ = 5 Hz), 5.61 (dd, 1H, H_6, J_{trans} = 15, $J_{5,6}$ = 7.0, $J_{6,8}$ = 1.0 Hz), 5.85 (dd, 1H, H_7); ^{13}C NMR: δ 21.68, 24.92 (2C), 25.70 (2C), 26.94, 27.21 (7C, C_{11}, C(*C*H$_3$)$_2$), 36.31, 39.11 (C_3, C_9), 62.44, 66.65, 69.81, 73.82, 77.71, 82.18 (6C, C_1, C_2, C_4, C_5, C_8, C_{10}), 100.17, 108.62, 108.87 (3C, *C*(CH$_3$)$_2$), 126.50, 136.05 (C_6, C_7).

(2*S*,4*S*,5*S*,8*R*,10*R*)-1,2:4,5:8,10-Tri-(isopropylidenedioxy)-6-undecene (19). Compound **19** was prepared from **17** in 95% yield according to the procedure described for the synthesis of **18**. R_f 0.25 (hexane:ethyl acetate 3:7); $[\alpha]_D$ +5.7° (*c* 1.2, $CHCl_3$); ^{1}H NMR: δ 1.18 (d, 1H, H_{11}, $J_{10,11}$ = 7 Hz), 1.35 (s, 3H, C(CH_3)$_2$), 1.37 (s, 3H, C(CH_3)$_2$), 1.39 (s, 6H, C(CH_3)$_2$), 1.41 (s, 3H, C(CH_3)$_2$), 1.46 (s, 3H, C(CH_3)$_2$), 1.48−1.70 (m, 3H, H_9, $H_{9'}$, H_3), 1.89 (ddd, 1H, $H_{3'}$, J_{gem} = 14, $J_{3,4}$ = 3, $J_{2,3'}$ = 6.5 Hz), 3.58 (dd, 1H, H_1, J_{gem} = 8, $J_{1,2}$ = 7.5 Hz), 3.76 (ddd, 1H,

H_4, $J_{3',4}=9$, $J_{4,5}=9$ Hz), 3.92–4.05 (m, 2H, H_5, H_{10}), 4.08 (dd, 1H, $H_{1'}$, $J_{1',2}=6$ Hz), 4.21 (m, 1H, H_2, $J_{2,3}=5.5$ Hz), 4.36 (ddd, 1H, H_8, $J_{7,8}=5$, $J_{8,9}=2$, $J_{8,9'}=12$ Hz), 5.65 (dd, 1H, H_6, $J_{trans}=15.5$, $J_{5,6}=7.5$ Hz), 5.79 (dd, 1H, H_7); ^{13}C NMR: δ 20.08, 22.48, 26.09, 27.36 (2C), 27.58, 30.54 (7C, C_{11}, C(CH_3)$_2$), 36.73, 38.93 (C_3, C_9), 70.22 (C_1), 65.14, 69.11, 74.20, 78.11, 82.38 (5C, C_2, C_4, C_5, C_8, C_{10}), 98.94, 108.95, 109.21 (3C, C(CH_3)$_2$), 127.06, 135.93 (C_6, C_7); MS (*m*/*z*): 355 $(M-15)^+$. Anal. calcd for $C_{20}H_{34}O_6$: C, 64.74; H, 9.20. Found: C, 64.47; H, 9.36.

(2*S*,4*S*,5*S*,8*S*,10*R*)-1,2,8,10-Tetrahydroxy-4,5-(isopropylidenedioxy)-6-undecene (20). The diol **16** (1.36 g, 4.12 mmol) was dissolved in THF (5 mL) and a mixture of water (1 mL) and acetic acid (9 mL) was added. The solution was heated at 55 °C and the reaction monitored by thin layer chromatography. To avoid total deprotection of **16**, reaction was stopped after 5 h. Solvents were evaporated under reduced pressure and the residue was co-evaporated with toluene. Column chromatography on silica gel (dichloromethane:methanol 95:5) afforded the expected product **20** (0.95 g, 1.87 mmol, 80%) together with totally deprotected compound (0.127 g, 0.4 mmol, 10%). R_f 0.14 (dichloromethane:methanol 9:1); IR: 3357, 1654 cm^{-1}, ^{1}H NMR: δ 1.16 (d, 3H, H_{11}, $J_{10,11}=6$ Hz), 1.40 (s, 6H, C(CH_3)$_2$), 1.52–1.73 (m, 4H, H_3, $H_{3'}$, H_9, $H_{9'}$), 3.42 (dd, 1H, H_1, $J_{gem}=11.5$, $J_{1,2}=6.5$ Hz), 3.53 (dd, 1H, $H_{1'}$, $J_{1',2}=3.5$ Hz), 3.72–4.50 (4H, 4 O*H*), 3.70–3.85 (m, 1H, H_4), 3.85–4.03 (m, 2H, H_2, H_5), 4.05–4.18 (m, 1H, H_{10}), 4.29 (ddd, 1H, H_8, J J' $J''=6$ Hz), 5.65 (dd, 1H, H_6, $J_{trans}=15.5$, $J_{5,6}=9$ Hz), 5.89 (dd, 1H, H_7, $J_{7,8}=6$ Hz); ^{13}C NMR: δ 23.76 (C_{11}), 27.20, 27.45 (C(CH_3)$_2$), 35.38 (C_3), 44.33 (C_9), 64.89, 69.21, 69.50 (3C, C_2, C_8, C_{10}), 66.79 (C_1), 77.68 (C_8), 82.08 (C_5), 109.06 (C(CH_3)$_2$), 126.78 (C_6), 138.24 (C_7).

(2*S*,4*S*,5*S*,8*R*,10*R*)-1,2,8,10-Tetrahydroxy-4,5-(isopropylidenedioxy)-6-undecene (21). Compound **21** was prepared in 78% yield from **17** according to the above mentioned procedure. R_f 0.13 (dichloromethane:methanol 9:1); IR: 3415, 1651, 1374 cm^{-1}; ^{1}H NMR: δ 1.17 (d, 3H, H_{11}, $J_{10,11}=6.5$ Hz), 1.38 (s, 6H, C(CH_3)$_2$), 1.56–1.82 (m, 4H, H_3, $H_{3'}$, H_9, $H_{9'}$), 3.42 (dd, 1H, H_1, $J_{gem}=12$, $J_{1,2}=7.5$ Hz), 3.64 (dd, 1H, $H_{1'}$, $J_{1',2}=3.5$ Hz), 3.70–4.75 (4H, 4 O*H*), 3.82–4.08 (m, 4H, H_2, H_4, H_5, H_{10}), 4.29 (ddd, 1H, H_8, $J_{7,8}=5$, $J_{8,9}$ $J_{8,9'}=6$ Hz), 5.69 (dd, 1H, H_6, $J_{trans}=15.5$, $J_{5,6}=7.5$ Hz), 5.87 (dd, 1H, H_7); ^{13}C NMR: δ 24.05 (C_{11}), 27.27, 27.52 (C(CH_3)$_2$), 35.26 (C_3), 44.73 (C_9), 66.87 (C_1), 67.70, 69.51, 71.34 (3C, C_2, C_8, C_{10}), 77.75 (C_8), 81.85 (C_5), 109.13 (C(CH_3)$_2$), 126.39 (C_6), 137.82 (C_7).

(3*S*,4*S*,7*R*,9*R*)-7,9-Dihydroxy-3,4-(isopropylidenedioxy)-5-decenoic acid (23). To a solution of *syn* diol **21** (0.527 g, 1.82 mmol) in dry methanol (14 mL) was added at room temperature a solution of sodium periodate (0.584 g, 2.73 mmol) in water (4 mL). The solution turned cloudy. After being stirred for 10 min, the white suspension was filtered and rinsed with methanol. Solvents were removed under reduced pressure and the expected crude aldehyde was used in the next step without further purification. The crude aldehyde (0.46 g, 1.78 mmol) was dissolved in a mixture of *tert*-butanol (26 mL) and 2-methyl-2-butene (6.5 mL). A solution of sodium chlorite (1 g, 11 mmol) and sodium dihydrogenophosphate (1 g, 8.5 mmol) in water (10 mL) was added dropwise over 10 min at room temperature. Reaction was monitored by TLC (dichloromethane: methanol 85:15) and after stirring for 20 min, the solvents were removed under reduced pressure. The crude mixture was diluted with CH_2Cl_2 (30 mL) and ethanol (10 mL). The salts were filtered off under reduced pressure and carefully rinsed with ethanol. Flash column chromatography on silica gel (dichloromethane:methanol 85:15) afforded acid **23** (0.43 g, 1.57 mmol, 88%). R_f 0.20 (dichloromethane:methanol 85:15); IR: 1646, 1719 cm^{-1}; ^{1}H NMR: δ 1.18 (d, 3H, H_{10}, $J_{9,10}=6$ Hz), 1.41 (s, 3H, C(CH_3)$_2$), 1.42 (s, 3H, C(CH_3)$_2$), 1.55–1.68 (m, 2H, H_8, $H_{8'}$), 2.52 (dd, 1H, H_2, $J_{gem}=15.5$, $J_{2,3}=4.5$ Hz), 2.66 (dd, 1H, $H_{2'}$, $J_{2',3}=5$ Hz), 3.95–4.13 (m, 3H, H_3, H_4, H_9), 4.38 (dd, H_7, $J_{6,7}=4.5$, $J_{7,8}=13$ Hz), 5.68 (dd, 1H, H_5, $J_{gem}=16$, $J_{4,5}=6.5$ Hz), 5.88 (dd, 1H, H_6); ^{13}C NMR: δ 23.88 (C_{10}), 26.94, 27.07 (C(CH_3)$_2$), 44.13 (C*8*), 58.81 (C_2), 68.16 (C_9), 71.65 (C_7), 79.92, 81.50 (C_3, C_4), 109.01 (C(CH_3)$_2$), 125.87 (C_6), 137.97 (C_5), 173.59 (C_1).

(3*S*,4*S*,7*S*,9*R*)-7,9-Dihydroxy-3,4-(isopropylidenedioxy)-5-decenoic acid (22). Compound **22** was prepared in 68% yield from **20** according to the procedure mentioned above: R_f 0.15 (dichloromethane:methanol 85:15); IR: 3416, 1719, 1649 cm^{-1}; ^{1}H NMR: (400 MHz, C_3D_6O): δ 1.16 (d, 3H, H_{10}, $J_{9,10}=6$ Hz), 1.35 (s, 3H, C(CH_3)$_2$), 1.36 (s, 3H, C(CH_3)$_2$), 1.55 (ddd, 1H, H_8, $J_{gem}=14$, $J'=4$, $J''=8$ Hz), 1.61 (ddd, 1H, $H_{8'}$, $J'=4$, $J''=8$ Hz), 2.50 (dd, 1H, H_2, $J_{gem}=15.5$, $J_{2,3}=8.5$ Hz), 2.60 (dd, 1H, $H_{2'}$, $J_{2',3}=3.5$ Hz), 2.81–2.95 (m, 2H, 2O*H*), 4.00–4.10 (m, 1H, H_9), 4.05 (ddd, 1H, H_3, $J_{3,4}=8.5$ Hz), 4.16 (dd, 1H, H_4, $J_{4,5}=7$ Hz), 4.20 (m, 1H, H_7), 5.72 (ddd, 1H, H_5, $J_{5,7}=1.5$, $J_{5,6}=14.5$ Hz, $J_{4,5}=8$ Hz), 5.93 (dd, 1H, H_6, $J_{6,7}=6$ Hz); ^{13}C NMR: δ 24.75, 27.70 (C(CH_3)$_2$), 27.80 (C_{10}), 37.59 (C_2), 46.78 (C_8), 65.14 (C_9), 69.53 (C_7), 78.53, 82.80 (C_3, C_4), 109.63 (C(CH_3)$_2$), 126.71 (C_6), 140.21 (C_5), 172.22 (C_1). Anal. calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08. Found: C, 55.75; H, 7.88.

(3*S*,4*S*,7*R*,9*R*)-3,4,7,9-Tetrahydroxy-5-decenoic acid, sodium salt (25). To a solution of carboxylic acid **23** (0.051 g, 0.18 mmol) in THF (2 mL) was added 2 mL of aqueous acetic acid (1:1 v/v). The solution was heated at 60 °C for 36 h. Thin layer chromatography monitoring (toluene 10:AcOEt 35:iPrOH 55:AcOH 2N 20) showed the presence of less polar compounds resulting from lactonisations. Solvents were removed under reduced pressure. The crude mixture was diluted with 2 mL of water and aqueous 1N NaOH was added to adjust the pH to 7–8. After lactonic compounds were no longer present the solution was filtered. Lyophilisation afforded 0.019 g of the carboxylate **25** (0.07 mmol, 38%). ^{1}H NMR: (250 MHz, D_2O): δ 1.21 (d, 3H, H_{10}, $J_{9,10}=6.5$ Hz), 1.59–1.85 (m, 2H, H_8, $H_{8'}$), 2.29 (dd, 1H, H_2, $J_{gem}=15.5$, $J_{2,3}=8.5$ Hz), 2.45 (dd, 1H, $H_{2'}$, $J_{2',3}=4.5$ Hz), 3.86–3.99 (m, 2H, H_3, H_9), 4.07 (dd, 1H, H_4, $J_{3,4}=6$, $J_{4,5}=6$ Hz), 4.31 (dd, 1H, H_7, $J_{7,8}=13$, $J_{6,7}=5.5$ Hz), 5.74 (dd, 1H, H_5, $J_{trans}=15.5$ Hz), 5.83 (dd, 1H, H_6);

^{13}C NMR: δ 25.30 (C_{10}), 43.45 (C_2), 47.56 (C_8), 68.35 (C_9), 72.73 (C_7), 74.88 (C_3), 77.82 (C_4), 132.76 (C_5), 138.35 (C_6), 184.33 (C_1); MS (m/z): ES negative mode: 233 (M−23); ES positive mode: 279 $(M+Na)^+$, 257 $(M+H)^+$, 242.

(3*S*,4*S*,7*S*,9*R*)-3,4,7,9-Tetrahydroxy-5-decenoic acid, sodium salt (24). Compound **24** was prepared from **22** (0.1 g, 0.36 mmol) in 22% yield (0.02 g, 0.08 mmol) according to the above mentioned procedure. IR: 3346, 1664, 1579, 1443 cm^{-1}; ^{1}H NMR: (250 MHz, D_2O): δ 1.22 (d, 3H, H_{10}, $J_{9,10}=7$ Hz), 1.69 (dd, 2H, H_8, $H_{8'}$, $J\,J'=6.5$ Hz), 2.28 (dd, 1H, H_2, $J_{gem}=15.5$, $J_{2,3}=9$ Hz), 2.45 (dd, 1H, $H_{2'}$, $J_{2',3}=4.5$ Hz), 3.86–3.99 (m, 2H, H_3, H_9), 4.05 (dd, 1H, H_4, $J_{3,4}=12.5$, $J_{4,5}=6.5$ Hz), 4.32 (dd, 1H, H_7, $J_{7,8}=12.5$, $J_{6,7}=6$ Hz), 5.72 (dd, 1H, H_5, $J_{trans}=16$ Hz), 5.84 (dd, 1H, H_6); ^{13}C NMR: δ 25.27 (C_{10}), 43.63 (C_2), 47.55 (C_8), 67.23 (C_9), 71.42 (C_7), 74.74 (C_3), 77.63 (C_4), 131.74 (C_5), 138.63 (C_6), 182.86 (C_1); MS (m/z): ES negative mode: 233 (M−23); ES positive mode: 279 $(M+Na)^+$, 257 $(M+H)^+$, 242.

Biological evaluation of compounds 24 and 25

Lemna assay. Vegetative stock cultures of *Lemna minor* were propagated mixotrophically in a 1:1 mixture of 1/4 strength Gamborg B5 (Sigma G-5768) and ammonium-free MS (Sigma M-8280) salts containing 1% sucrose. *Lemna* was subcultured axenically at 7 days in 125-mL Erlenmeyer flasks containing 50 mL of medium in a growth chamber at 26 °C under continuous fluorescent and incandescent light sources providing 300 μE m^{-2} s^{-1}. Test compounds were dissolved in methanol:DMSO (9:1) and a 50 mL aliquot combined with 2 mL of culture medium in a multi-well plate (Falcon, model 3043). A single colony consisting of 4 fronds was added to each well. Culture dishes were incubated for 7 days at which time visual injury ratings were obtained. By 7 days approximately 8 small colonies completely cover the medium surface in the untreated wells. Growth inhibition was calculated as a percentage of the control.

Isolation of microsomes: etiolated pea seedlings

Microsomes were prepared from 8 day old etiolated pea (*Pisum sativum*) seedlings. Four hundred grams of tissue was combined with 800 mL of homogenization buffer containing 0.1 M potassium phosphate (pH 7.0), 4 mM $MgCl_2$ and 5 mM dithiothreitol. The tissue was homogenized in a Wareing blender for 20 s, filtered, and centrifuged at 10,000×g for 15 min in an SLA-1500 rotor. The supernatant was centrifuged at 100,000×g for 1 h in a Ti 45 rotor. The resulting pellet was washed, suspended in homogenization buffer, and stored at −80 °C until use. **Rat liver**. Rat liver S9 was diluted in 0.1 M potassium phosphate (pH 7.0) and microsomes were obtained by ultracentrifugation, as described above.

HMGR assay

HMGR assays were conducted in a 300 μL volume containing 0.1 M potassium phosphate (pH 7.0), 3.3 mM EDTA, 10 mM DTT, 10 mM glucose-6-phosphate, 0.15 U glucose-6-phosphate dehydrogenase, 2 mM NADPH, test compounds in DMSO (3.3% final concentration) and 5–25 μg microsomal protein. After a 10 min incubation at 30 °C, the reaction was initiated by the addition of 0.45 μCi DL-3-[glutaryl-3-^{14}C]-HMG CoA (DuPont-NEN, NEC-642) and conducted for 20 min. The assay was stopped by the addition of 30 μL of 6 N HCl and vials were centrifuged to pellet protein. ^{14}C-Mevalonic acid and ^{14}C-mevalonolactone were separated from the substrate, ^{14}C-HMG-CoA, by HPLC on an Alltech Lichrosphere C18 column (5 u, 4.6×250) using 75% water containing 0.5% phosphoric acid and 25% methanol containing 0.5% phosphoric acid. Radioactive peaks were detected using an INUS B-Ram detector.

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