Pergamon

Tetrahedron 56 (2000) 9289–9295

TETRAHEDRON

A Novel Stereoselective Access to Substituted L-2-Deoxypentono-1,4-lactones and L-2-Deoxypentoses

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Received 10 July 2000; accepted 19 September 2000

Abstract—A stereoselective method to L-2-deoxypentose or L-2-deoxy-pentono-1,4-lactone units was developed employing the (*S*)-Hydroxynitrile lyase from *Hevea brasiliensis*. Additionally a diastereoselective reduction using either (D)- or (L)-tartaric acid in conjuction with sodium borohydride had been applied to control the ultimate stereochemistry of the bioactive compounds.

Introduction

Methods for gaining access to L-nucleosides and sugars represent motivating and promising areas of research. As routes to both enantiomeric series of nucleosides have emerged, the therapeutic advantages of the L-series (compared to their corresponding D-counterparts) are becoming increasingly recognised.[1] For example, as their tendency towards enzymatic metabolism is reduced, an increase in bio-availability and hence increased potency of the corresponding drug is observed. This is exemplified by the treatment of the human immunodeficiency virus (HIV) with the L-nucleoside analogues L-ddC[1c–h] and L-3TC.[1i,2] Indeed, an L-isomer (e.g. (−)-3TC) can also prove less cytotoxic than its enantiomer.[2]

The synthesis of the L-nucleosides can be achieved by established procedures, the difference being that the L-sugar is employed instead of the more normal D-form. Although in theory this may appear straightforward, the problem remains that the L-ribose unit (or its derivatives) is not readily available and must be synthesised from alternative asymmetric precursors, such as L-xylose[3], L-arabinose[4] or D-glutamic acid.[5] This challenge has continued to stimulate efforts in this area, resulting in methods such as that of Trost et al.[6] which elegantly employs a palladium catalysed asymmetric desymmetrization of *cis*-2,5-diacyloxy-2,5-dihydrofurans. With this in mind we set about developing a synthetic strategy which would allow access to useful substituted L-2-deoxypentose or L-2-deoxy-pentono-1,4-lactone units. One of our current research efforts is the synthetic exploitation of chiral cyanohydrins prepared via the (*S*)-Hydroxynitrile lyase from *Hevea brasiliensis*. With the development of efficient production processes[7] these compounds are now establishing themselves as preparatively useful chiral building blocks in synthesis.[8]

Results and Discussion

The chiral cyanohydrin from octenal was chosen as the starting point for our synthesis, as it is available in optically pure form and is a versatile chiral material[9] in synthesis. Also in our laboratories it has proven to be the best substrate from a series of unsaturated aldehydes.[7] The silyl protected cyanohydrin **1** was prepared as previously reported (99% e.e.),[7,10] and then coupled to methyl bromoacetate, in a zinc mediated reaction,[11] to give the γ-silyoxy-β-keto ester **2**† in good yield (76%). Stereocontrolled reduction of the ketone functionality was achieved employing the method of Yatagai et al. for prochiral ketones.[12]

Treatment of **2** with a mixture of L-tartaric acid and $NaBH_4$ yielded the *syn* compound **4** in 92% d.e. Alternatively, treatment with D-tartaric acid and $NaBH_4$ yielded the corresponding *anti* compound **3**, also in 92% d.e.

Interestingly, both reductions yielded products with a 92% d.e., which suggests that the pre-existing chirality of the substrate (i.e. **2**) does not influence the stereochemical outcome of the reduction. To our knowledge[13] this aspect has not been previously observed with this reducing system.

In connection with these results a number of reductions with

Keywords: hydroxynitrile lyase; tartaric acid; cyanohydrin; L-2-deoxypentoses.

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† The ^1H and ^{13}C NMR of compound **2** contained approximately 6% of the corresponding enol tautomer.

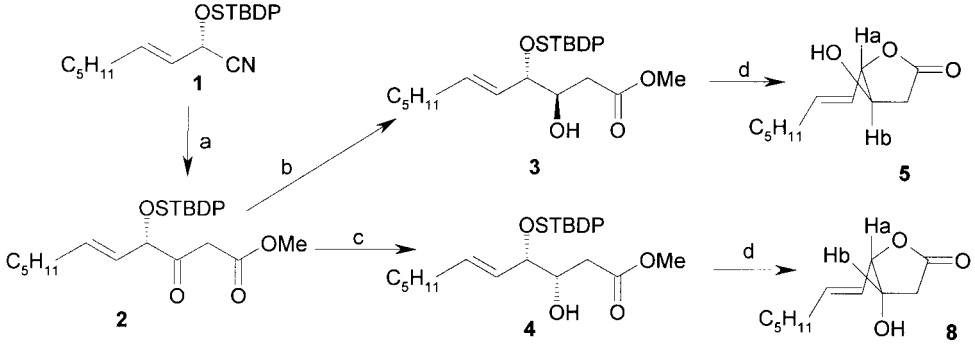
0040–4020/00/$ - see front matter
PII: S0040-4020(00)00871-1

Table 1. The reductions of silylester **2** (ratios determined using chiral HPLC (conditions: Chiralcel OD-H, 99.75:0.25 heptane: 2-propanol, 0.6 mL/min, 254 nm)).

Reducing reagent	Ratio 3:4
$NaBH_4$-D-Tartaric acid diethyl ester	59:41
$NaBH_4$-L-Tartaric acid diethyl ester	64:36
$NaBH_4$-(2*R*, 3*R*)-2,3-butanediol	50:50
$NaBH_4$	64:36
$NaBH_4$-Et_2BOMe	75:24
Bakers' Yeast	No reduction

which support the integrity of the structural assignments of the lactones, i.e. in compound **8**, Ha showed an NOE to Hb (and vice versa) which was not observed in compound **5** (Scheme 1).

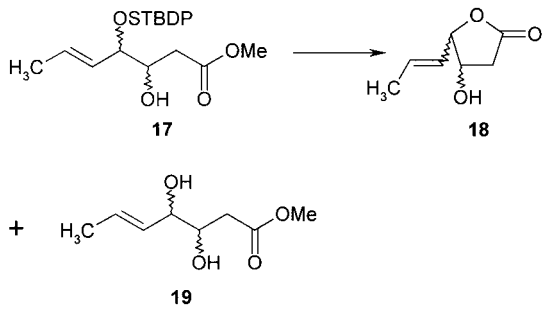
Conversion of lactone **3** to its corresponding myristoyl ester **6** proceeded in good yield (85%). Cleavage of the exocyclic alkene to the corresponding alcohol was achieved in one-pot reaction, employing low temperature ozonolysis followed by reductive work-up (BH_3Me_2S) to yield **7**. Compound **7** is the most active of the conformationally restrained analogues of diacylglycerol which were recently reported



Scheme 1. *Reagents:* (a) Methyl bromoacetate, Zn, TMS-Cl, THF, 76%. (b) D-tartaric acid-$NaBH_4$, THF, 93%. (c) L-tartaric acid-$NaBH_4$, THF, 89%. (d) tetrabutylammonium fluoride, THF, 85%.

structurally related chiral reagents, no chiral reagent or a biocatalyst were also made (Table 1). The lack of selectivity achieved when diethyl D-tartrate (as compared to D-tartaric acid) or diethyl L-tartrate (as compared to L-tartaric acid) was employed would appear to indicate that the free hydroxyl group and carboxylic acid group (in the chiral auxilliary) are important for stereoselective reduction of the substrate. It can be speculated that hydrogen bonding between the chiral reagent and the corresponding β-keto ester substrate (i.e. **2**) is important for selectivity in this reaction.

One pot deprotection and cyclisation of **3** (96:4 ratio of alcohols) using TBAF afforded the *threo*-lactone **5** and *erythro*-lactone **8** as the major and minor components respectively, which were separable by preparative chromatography.[14‡] Analogous lactonisation of compound **4** yielded *erythro*-lactone **8** and *threo*-lactone **5** as the major and minor components. NOE Experiments provided data



‡ A model study with compound **17** showed that under the conditions employed (THF, 2.2 equiv. TBAF) only lactone **18** was obtained. In the case where toluene was chosen as solvent, or where less TBAF was employed (1.1 equiv.) a mixture of the lactone **18** and the diol **19** was obtained.

by Teng et al.[15]and exhibits micromolar (2.5 μM) competitive inhibition of phorbol-12,13-dibutyrate binding to Protein Kinase C (PKC). This enzyme plays a crucial role in many cellular processes including cell differentiation and tumour growth, and has therefore been suggested as a target enzyme for anticancer therapy.[16] This synthesis (7 steps, 32% overall yield) compares favourable to that previously reported (14 steps, 8% overall yield)[16] and represents a novel stereocontrolled method for the production of L-ribonolactones (or of L-xylonolactones when diol **4** is applied).

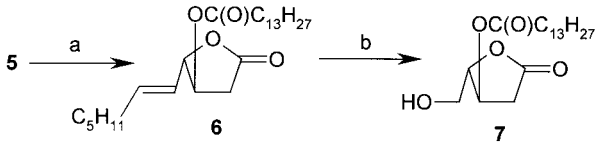
Next we turned our attention to the synthesis of compounds useful for the preparation of L-nucleosides. Lactone **8** was converted to its corresponding silyl ether **9** under standard conditions.[17] DIBALH Reduction followed by acetylation of the crude lactol yielded **10** as a single diastereomer. Desilylation (**10** to **11**) proceeded in moderate yield (60%), and subsequent conversion of the alcohol to its corresponding triflate ester facilitate azide introduction (NaN_3/DMF) with inversion to yield **12**.

Alkene cleavage was achieved using a three step method (i) conversion to the diol using osmium tetraoxide/NMO (ii) cleavage of the diol with sodium metaperiodate (iii) reduction[18] of the resultant aldehyde with $NaCNBH_3$ to yield the azidoalcohol **13** which is the required precursor[19] for the preparation of L-AZT.

β-L-FMAU is one of the more interesting fluorinated L-nucleosides[20](2′-fluoro-5-methyl-β-L-arabinofuranosyl-uracil)[21] as it shows anti-viral activity against Hepatitis B virus (HBV) and Epstein–Barr virus, but does not interfere with the host system.[22] Indeed, β-L-FMAU was confirmed

Table 2. Conditions for the optimal fluorination of lactone **14**

N-Fluorodibenzene-sulfonimide (mmole equiv.)	LiHMDS (mmole equiv.)	Time (mins)	**14** (% recovered yield)	**15** (% yield)
1.00	1.2	270	70	7
1.5	1.8	270	35	20
2.00	2.4	80	30	49
2.00	2.4	270	0	33



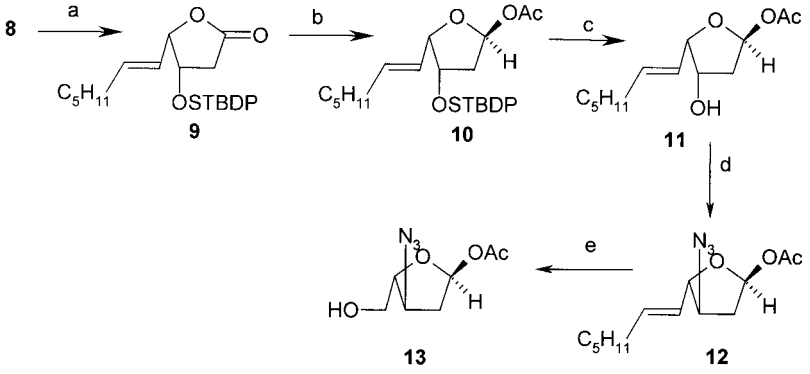
Scheme 2. *Reagents:* (a) $C_{13}H_{27}C(O)Cl$, pyridine, CH_2Cl_2, 85%. (b) O_3/CH_2Cl_2 then BH_3DMS, 40%.

to be the most potent of a series of compounds with anti-HBV acitvity.[23] In contrast the D-enantiomer causes liver tover toxicity, amongst other side effects.[24]

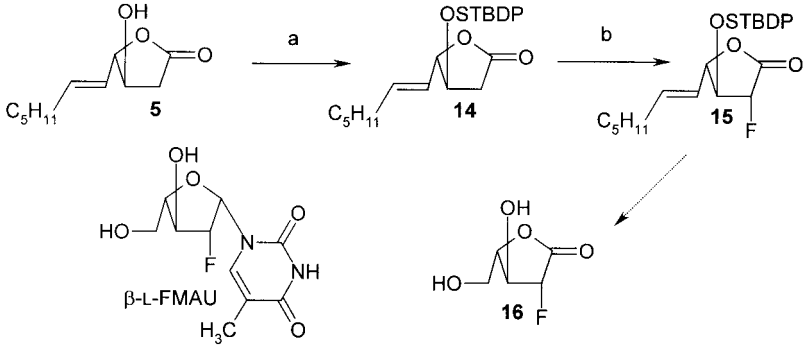
We envisaged an access to the ribono-portion (i.e. L-2-deoxy-2-fluoroarabino-pentono-1,4-lactone, **16**) of β-L-FMAU from lactone **5**. Protection of the alcohol **5** yielded silyl ether **14**. When 2-fluorination was attempted under the conditions of McAtee et al.[25], a moderate yield of **15** was obtained (Table 2, entry 1). However, increasing the amount of base and fluorinating reagent agent (i.e. *N*-fluorodibenzenesulfonimide), (Table 2, entries 2 and 4) whilst retaining a relatively short reaction time (Table 2, entry 3) allowed an optimum yield of **15** to be obtained. Employing analogous oxidative cleavage conditions to those outlined in Schemes 2 and 3, followed by desilyation, **15** would easily furnish the desired lactone **16** (Scheme 4).

Conclusion

In conclusion we have developed a general access to substituted L-2-deoxypentose or L-2-deoxy-pentono-1,4-lactone units, in which the stereochemistry at C-4 is developed by employing the (*S*)-Hydroxynitrile lyase from *Hevea brasiliensis*. Additionally the stereochemistry at C-3 can be selectively controlled by employing $NaBH_4$ and (D)- or (L)-tartaric acid. This general chemoenzymatic approach to these compounds has not previously been reported and



Scheme 3. *Reagents:* (a) *tert*-butyldiphenylsilyl chloride, imidazole, DMF, 77%. (b) DIBAL, THF, then acetic anhydride, DMAP, CH_2Cl_2, 66%. (c) tetrabutylammonium fluoride, THF, 60%. (d) trifluoroacetic acid anhydride, CH_2Cl_2, pyridine, then NaN_3, DMF, 49% and 29% recovered starting material. (e) OsO_4/*N*-methyl-*N*-morpholineoxide, acetone/pH 6.8 phosphate buffer, then $NaIO_4$, acetone/water, then $NaCNBH_3$, pH 3.68 acetate buffer, 38%.



Scheme 4. *Reagents:* (a) *tert*-butyldiphenylsilyl chloride, imidazole, DMF, 74%. (b) LiHMDS, *N*-fluorodibenzenesulfonimide, THF, 49 % and 30% recovered starting material.

provides a rapid stereocontrolled access to L-2-deoxy-pentose or L-2-deoxy-pentono-1,4-lactone building blocks.

Experimental

General

^{1}H NMR and ^{13}C NMR were recorded on Varian Gemini 200 MHz and Bruker MSL 300 MHz instruments in $CDCl_3$. Chemical shifts are relative to TMS with $CHCl_3$ as internal standard [*d* 7.23 (^{1}H) and *d* 76.90 (^{13}C)]. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Optical rotations were measured using a Perkin Elmer 341 instrument. Tetrahydrofuran was distilled from potassium benzophenone ketyl, toluene from sodium, DMF from dibutyltin dilaurate and desmopur-15 (150 mg of each/100 mL DMF) and dichloromethane from calcium hydride. All organic layers were dried using anhydrous sodium sulphate. All products were purified by silica gel column chromatography using Merck Kieselgel 60 (230–400 mesh). TLC plates were run on silica gel gel Merck 60 F_{254}, compounds were visualised by spraying with Mo-reagent [$(NH_4)_6Mo_7O_{24}4H_2O$ (100 g/L), $Ce(SO_4)_24H_2O$ (4 g/L) in H_2SO_4 (10% v/v) or $KMnO_4$ reagent [$KMnO_4$ (2.5 g/L), Na_2CO_3 (20 g/L) in H_2O. All reagents were obtained from Sigma–Aldrich and were used as purchased. Petroleum ether refers to the fraction of boiling point 60–80°C. Elemental analysis was made on EA 1108 CHN-analyser. HPLC enantiomeric separations were performed using a Jasco 880-PU pump and a Jasco 875 UV/VIS detector connected to a CHIRACEL OD-H chiral HPLC column (25 cm×0.46 cm).

(−)-(*E*,4*S*)-Methyl 3-oxo-4-*tert*-butylsilyloxyundec-5-enoate (2). To a suspension of zinc (7.08 g, 108 mmol) in dry THF (90 mL) was added trimethylsilyl chloride (1.27 mL, 10.06 mmol). After 20 min (+)-(2*S*,3*E*)-2-(*tert*-butyldiphenylsilyloxy)non-3-enenitrile (**1**) (15.14 g, 38.72 mmol) was added and the mixture heated to reflux. Methyl bromoacetate (120.03 mmol) was then added dropwise over 50 min and reflux continued for a further 70 min thereafter. The mixture was cooled to 5°C, 1 M HCl (175 mL) was added and then stirred at rt for 2.5 h. The reaction mixture was poured into sat. $NaHCO_3$ (350 mL), an emulsion formed which could be broken by the addition of water (300 mL). The aqueous phase was extracted with ethyl acetate (2×75 mL), the organic layers combined, dried, filtered and concentrated in vacuo. The crude residue was purified by column chromatography (92:8 to 98:2, petroleum ether:-ethyl acetate) to yield the title compound as a colourless oil (13.60 g, 29.18 mmol, 76%) and unreacted **1** (1.30 g, 3.32 mmol, 8.6%). $[\alpha]_D^{20}=-29.0$ (*c* 0.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 0.88 (t, 3H, *J*=7.32 Hz), 1.12 (s, 9H), 1.18–1.37 (m, 6H), 1.88–1.95 (m, 2H), 3.59 (s, 2H), 3.68 (s, 3H), 4.60 (d, 1H, *J*=6.3 Hz), 5.39 (dd, 1H, *J*=15.33, 6.3 Hz), 5.67 (dt, 1H, *J*=15.38, 7.57 Hz), 7.30–7.55 (m, 6H), 7.59–7.70 (m, 4H), ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm), 14.06, 19.33, 22.51, 26.95, 28.41, 31.29, 32.20, 43.88, 52.22, 80.63, 125.74, 127.66, 127.87, 130.12, 132.72, 133.02, 135.85, 135.99, 136.33, 167.79, 202.52.

(+)-(*E*,3*R*,4*S*)-Methyl 3-hydroxy-4-*tert*-butylsilyloxyundec-5-enoate (3). To a solution of (D)-tartaric acid (9.60 g, 64.0 mmol) in dry THF (150 mL) was added sodium borohydride (2.42 g, 64.0 mmol) portionwise and the suspension was heated at reflux for 2.5 h before being cooled to −20°C. A solution of (4*S*)-methyl 3-oxo-4-*tert*-butylsilyloxyundec-5-enoate (7.54 g, 16.00 mmol) in dry THF (75 mL) was added dropwise and the temperature maintained −20°C. After 40 h hydrochloric acid (1 M, 150 mL) was added and stirring continued for 15 min at rt. Ethyl acetate (500 mL) was added followed by solid sodium chloride to the point of saturation. The aqueous phase was separated and further extracted with ethyl acetate (200 mL). The organic phases were combined, washed with saturated sodium bicarbonate solution (2×150 mL) then saturated sodium chloride solution (100 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (90:10 to 90:20, petroleum ether:ethyl acetate) to yield the title compound as a colourless oil (6.97 g, 14.70 mmol, 93%). $[\alpha]_D^{20}=+46.3$ (*c* 1.05, $CHCl_3$); d.e.=92% (as determined by chiral HPLC, OD-H, 99.75:0.25 heptane:2-propanol, 0.6 mL/min, 254 nm); ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 0.88 (t, 3H), 1.07 (s, 9H), 1.13–1.30 (m, 6H), 1.77–1.86 (m, 2H), 2.44 (d, 1H, *J*=2.38 Hz), 2.47 (s, 1H), 2.62 (d, 1H, *J*=3.47 Hz), 3.67 (s, 3H), 4.01–4.12 (m, 2H), 5.14–5.44 (m, 2H), 7.30–7.49 (m, 6H), 7.62–7.73 (m, 4H), ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm), 14.06, 19.41, 22.51, 27.11, 28.45, 31.37, 32.14, 37.07, 51.76, 71.67, 77.61, 127.43, 127.69, 129.66, 129.84, 133.57, 133.81, 135.71, 135.95, 136.08, 172.59.

(+)-(*E*,3*S*,4*S*) Methyl 3-hydroxy-4-*tert*-butylsilyloxyundec-5-enoate (4). To a solution of (L)-tartaric acid (8.06 g, 53.72 mmol) in dry THF (125 mL) was added sodium borohydride (2.03 g, 53.72 mmol) portionwise and the suspension was heated at reflux for 2.75 h before being cooled to −20°C. A solution of (4*S*)-methyl-3-oxo-4-*tert*-butylsilyloxy-undec-5-enoate (5.38 g, 11.55 mmole) in dry THF (75 mL) was added dropwise and the temperature maintained at −20°C. After 43 h hydrochloric acid (1 M, 125 mL) was added and stirring continued for 15 min at rt. Ethyl acetate (500 mL) was added, followed by solid sodium chloride to the point of saturation. The aqueous phase was separated and further extracted with ethyl acetate (200 mL). The organic phases were combined, washed with saturated sodium bicarbonate solution (2×150 mL) then saturated sodium chloride solution (100 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (90:10 to 90:20, petroleum ether:ethyl acetate) to yield the title compound as a colourless oil (4.77 g, 10.20 mmol, 89%). $[\alpha]_D^{20}=+16.0$ (*c* 1.01, $CHCl_3$); d.e.=92% (as determined by chiral HPLC, OD-H, 99.75:0.25 heptane:2-propanol, 0.6 mL/min, 254 nm); ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 0.88 (t, 3H), 1.07 (s, 9H), 1.13–1.30 (m, 6H), 1.77–1.86 (m, 2H), 2.36 (dd, 1H, *J*=15.63, 8.60 Hz), 2.53 (dd, 1H, *J*=15.87, 3.23 Hz), 2.76 (d, 1H, *J*=3.85 Hz), 3.68 (s, 3H), 3.97–4.08 (m, 2H), 5.16–5.41 (m, 2H), 7.31–7.49 (m, 6H), 7.63–7.71 (m, 4H), ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm), 14.06, 19.43, 22.51, 27.11, 28.37, 31.37, 32.14, 37.39, 51.78, 71.74, 77.71,

127.43, 127.71, 129.67, 129.85, 133.51, 133.70, 135.81, 135.92, 136.07, 172.66.

(−)-(4*R*,5*S*)-4-Hydroxy-5-((*E*)-hept-1-enyl)tetrahydrofuran-2-one (5). To a cooled (5°C) solution of (5*E*,3*R*,4*S*)-methyl 3-hydroxy-4-*tert*-butylsilyloxyundec-5-enoate (6.47 g, 13.83 mmol) in THF (165 mL) was added TBAF dropwise (0.691 M in acetonitrile, 30.0 mL, 20.74 mmol). After 48 h at rt, ethyl acetate (300 mL) was added and the organic phase was washed with brine (3×25 mL), then dried, filtered and concentrated in vacuo. The crude residue was purified by column chromatography (70:30 to 50:50, petroleum ether:ethyl acetate) to yield the title compound **5** as a colourless oil (2.23 g, 11.8 mmol, 85%) and lactone **8** (175 mg, 6%). $[\alpha]_D^{20}=-67.1$ (*c* 1.21, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 0.86 (t, 3H, *J*=7.08 Hz), 1.21–1.43 (m, 6H), 2.04 (q, 2H, *J*=6.84, 6.54 Hz), 2.47 (dd, 1H, *J*=17.82, 3.66 Hz), 2.78 (dd, 1H, *J*=17.77, 6.16 Hz), 3.12 (bs, 1H), 4.30 (m, 1H), 4.79 (dd, 1H, *J*=6.34, 2.44 Hz), 5.42 (dd, 1H, *J*=15.38, 6.57 Hz), 5.83 (dt, 1H, *J*=15.38, 7.56 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm), 14.04, 22.48, 28.43, 31.34, 32.23, 37.02, 72.21, 87.98, 124.34, 136.34, 172.59.

(−)-(4*R*,5*S*)-4-Tetradecanoyl-5-((*E*)-hept-1-enyl)tetrahydrofuran-2-one (6). To a solution of (4*R*,5*S*)-4-hydroxy-5-(*E*-hept-1-enyl)-tetrahydro-furan-2-one (150 mg, 0.75 mmol) in CH_2Cl_2 (1 mL) was added a mixture of pyridine (90 mg, 1.13 mmol) and myristoyl chloride (224 mg, 0.90 mmol) in CH_2Cl_2 (2 mL) and stirring continued for 20 h at rt. A mixture of CH_2Cl_2/H_2O (15 mL of each) was then added and organic phase washed with H_2O (2×10 mL), $CuSO_4$ (3% w/v, 10 mL) then brine (10 mL). The organic phase was separated, dried, filtered and concentrated in vacuo. The crude residue was purified by column chromatography (95:5, petroleum ether:ethyl acetate) to yield the title compound **6** as a white solid (249 mg, 0.51 mmol, 85%). $[\alpha]_D^{20}=-16.0$ (*c* 1.08, $CHCl_3$); Mp 28–29°C; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 0.86 (t, 3H, *J*=7.08 Hz), 1.18–1.45 (m and overlapping s, 26H), 1.53–1.70 (m, 2H), 2.04 (q, 2H, *J*=7.82, 6.10 Hz), 2.33 (t, 2H, *J*=7.33 Hz), 2.52 (dd, 1H, *J*=18.31, 1.76 Hz), 2.90 (dd, 1H, *J*=18.31, 6.54 Hz), 4.91 (d, 1H, *J*=5.56 Hz), 5.12 (dt, 1H, *J*=6.40, 1.71 Hz), 5.46 (ddt, 1H, *J*=15.52, 5.70, 1.33 Hz), 5.83 (dt, 1H, *J*=15.44, 6.72 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm), 14.04, 14.17, 22.49, 22.74, 28.39, 29.10, 29.26, 29.40, 29.47, 29.63, 29.68, 31.33, 31.96, 32.18, 33.74, 34.12, 73.62, 84.76, 123.67, 135.98, 172.97, 174.13. Anal. calcd for $C_{25}H_{44}O_4$: C, 73.48; H, 10.85; O, 15.66; Found: C, 73.60; H, 10.87.

(+)-(4*R*,5*S*)-4-Tetradecanoyl-5-hydroxymethyltetrahydrofuran-2-one (7). Through a solution of (4*R*,5*S*)-4-tetradecanoyl-5-((*E*)-hept-1-enyl)-tetrahydrofuran-2-one (75 mg, 0.18 mmol) in CH_2Cl_2 (9 mL) at −78°C was passed ozone for 1 h. The solution was warmed to rt, stirred for 15 min and then under an argon atmopshere BH_3Me_2S (1 M in CH_2Cl_2, 0.75 mL, 0.75 mmol) was added dropwise over 25 min. After 20 h, MeOH (0.5 mL) was added and stirring continued for 2 h. The mixture was concentrated in vacuo and the crude residue was purified by column chromatography (90:10 to 65:35, petroleum ether:ethyl acetate) to yield the title compound **7** as a white solid (25 mg, 0.07 mmol, 40%). $[\alpha]_D^{20}=+19.0$ (*c* 1.01, $CHCl_3$) (Lit.17 $[\alpha]_D^{20}=+19.40$ (*c* 1.16, $CHCl_3$)); Mp 60–61°C (Lit.[17] 61–62°C); ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 0.88 (t, 3H, *J*=7.08 Hz), 1.23 (s, 20H), 1.55–1.68 (m, 2H), 2.33 (t, 2H, *J*=7.32 Hz), 2.55 (dd, 1H, *J*=18.58, 1.90 Hz), 3.07 (dd, 1H, *J*=18.60, 7.54 Hz), 3.93 (m, 2H), 4.50 (m, 1H), 5.36 (dt, 1H, *J*=7.43, 1.71 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm), 14.36, 22.94, 24.98, 29.32, 29.46, 29.59, 29.67, 29.88, 32.17, 34.32, 35.68, 62.54, 71.75, 85.73, 173.74, 175.38.

(−)-(4*S*,5*S*)-4-Hydroxy-5-(*E*-hept-1-enyl)tetrahydrofuran-2-one (8). The title compound was prepared using the method described for lactone **5**, employing (5*E*,3*S*,4*S*)-methyl-3-hydroxy-4-*tert*-butylsilyloxy-undec-5-enoate (4.67 g, 9.97 mmol), TBAF (0.691 M in acetonitrile, 21.6 mL, 14.95 mmol), THF (118 mL) and a reaction time of 20 h. The crude residue was purified by column chromatography (60:40 to 40:60, petroleum ether:ethyl acetate) to yield the title compound **8** as a white solid (1.78 g, 8.98 mmol, 90%). $[\alpha]_D^{20}=-56.2$ (*c* 1.21, $CHCl_3$); Mp 42–43°C; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 0.88 (t, 3H, *J*=7.08 Hz), 1.23–1.53 (m, 6H), 2.04 (q, 2H, *J*=6.83, 6.73 Hz), 2.27 (bs, 1H), 2.59 (dd, 1H, *J*=17.63, 1.41 Hz), 2.78 (dd, 1H, *J*=17.57, 5.12 Hz), 4.46 (m, 1H), 4.86 (dd, 1H, *J*=6.84, 3.18 Hz), 5.58 (dd, 1H, *J*=15.49, 6.89 Hz), 5.97 (dt, 1H, *J*=15.49, 6.73 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm), 14.06, 22.51, 28.48, 31.39, 32.49, 38.77, 69.77, 84.88, 121.35, 139.03, 175.58. Anal. calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15; O, 24.21; Found: C, 66.71; H, 9.13.

(−)-(4*S*,5*S*)-4-*tert*-Butyldiphenylsilyloxy-5-((*E*)-hept-1-enyl)tetrahydrofuran-2-one (9). To a cooled solution (5°C) of imidazole (825 mg, 12.12 mmol) in DMF (0.5 mL) was added *tert*-butyldiphenylchlorosilane (2.49 g, 9.09 mmol). After 15 min the alcohol **8** (1.20 g, 6.06 mmol) was added dropwise and the solution warmed to rt, at which it was stirred for 4 h. Water (100 mL) was then added and the aqueous phase extracted with CH_2Cl_2 (3×75 mL). The organic extracts were combined, dried, filtered and concentrated in vacuo. The crude residue was purified by column chromatography (90:10 to 85:15, petroleum ether:ethyl acetate) to yield the title compound **9** as a white solid (2.04 g, 4.67 mmol, 77%). $[\alpha]_D^{20}=-57.6$ (*c* 1.07, $CHCl_3$); Mp 37–38°C; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 0.90 (t, 3H, *J*=6.51 Hz), 1.08 (s, 9H), 1.22–1.46 (m, 6H), 2.07–2.16 (m, 2H), 2.29–2.51 (m, 2H), 4.50–4.54 (m, 1H), 4.67–4.72 (m, 1H), 5.82–5.86 (m, 2H), 7.34–7.49 (m, 6H), 7.59–7.65 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm), 14.08, 19.27, 22.58, 26.85, 28.41, 31.50, 32.48, 38.88, 71.63, 85.63, 123.39, 127.85, 127.98, 130.12, 130.22, 132.58, 133.08, 135.78, 135.89, 138.11, 175.25. Anal. calcd for $C_{27}H_{36}SiO_3$: C, 74.26; H, 8.31; O, 10.99; Found: C, 74.12; H, 8.39.

(−)-(1*S*,3*S*,4*S*)-1-Acetoxy-3-*tert*-butyldiphenylsilyloxy-4-((*E*)-hept-1-enyl)tetrahydrofuran (10). To a solution of (4*S*,5*S*)-4-*tert*-butyldiphenylsilyloxy-5-(*E*-hept-1-enyl)-tetrahydro-furan-2-one (1.69 g, 3.87 mmol) at −78° under argon was added DIBAL (1.0 M in hexane, 11.6 mL, 11.6 mmol) dropwise over 15 min. After 1.5 h water (2 mL) was added and stirring continued for a further 15 min at −78° before the mixture was allowed to warm to rt, at which it was stirred for 1.5 h. The mixture was diluted with Et_2O

(100 mL) and poured into a saturated solution of disodium tartrate (110 mL) and stirring continued. After 1 h the aqueous layer was extracted with Et_2O (3×100 mL) and the organic extracts were combined, dried, filtered and concentrated in vacuo. The crude residue was redissolved in CH_2Cl_2 (30 mL), cooled to 5°C and a solution containing acetic anhydride (2.46 mL, 26.13 mmol) and DMAP (47 mg, 0.387 mmol) was added. The mixture was stirred for 3.5 h, allowed to warm to rt and then poured into saturated $NaHCO_3$ solution (40 mL). The aqueous layer was extracted with Et_2O (4×40 mL) and the organic phases combined, dried, filtered and concentrated in vacuo. The crude residue was purified by column chromatography (90:10 to 85:15, petroleum ether:Et_2O) to yield the title compound **10** as a colourless oil (1.22 g, 2.54 mmol, 66%). $[\alpha]_D^{20}=-76.7$ (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 0.89 (t, 3H, *J*=6.59 Hz), 1.07 (s, 9H), 1.25–1.49 (m, 6H), 1.88–2.24 (m and overlapping s, 7H), 4.37–4.43 (m, 1H), 4.45–4.52 (m, 1H), 5.74–5.77 (m, 2H), 6.37 (dd, 2H, *J*=5.67, 2.96 Hz), 7.34–7.49 (m, 6H), 7.59–7.65 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm), 14.07, 19.28, 21.31, 26.90, 28.56, 31.58, 32.51, 42.33, 74.04, 84.54, 97.66, 125.30, 127.76, 127.67, 129.82, 129.89, 133.27, 133.92, 135.84, 135.96, 136.41, 170.36.

(−)-(1*S*,3*S*,4*S*)-1-Acetoxy-4-((*E*)-hept-1-enyl)-3-hydroxy-tetrahydrofuran (11). To a cooled solution (5°C) of (2*S*,4*S*,5*S*)-5-acetoxy-3-*tert*-butyldiphenylsilyloxy-2-(*E*-hept-1-enyl)-oxolane (140 mg, 0.296 mmol) in THF (4 mL) was added TBAF (1.0 M in THF, 0.30 mL, 0.30 mmol) over 10 min. After stirring at rt for 1.5 h, the mixture was poured into ethyl acetate/water (10 mL/5mL) and the aqueous layer extracted with ethyl acetate (2×10 mL). The organic layers were combined, dried, filtered and concentrated in vacuo. The crude residue was purified by column chromatography (80:20 to 75:25, petroleum ether:EtOAc) to yield the title compound **11** as a colourless oil (42 mg, 0.174 mmol, 60%). $[\alpha]_D^{20}=-65.2$ (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 0.85 (t, 3H, *J*=6.59 Hz), 1.22–1.50 (m, 6H), 1.81 (bs, 1H), 2.00–2.14 (m and overlapping s, 5H), 2.35 (ddq, 2H, *J*=12.51, 5.86, 2.19 Hz), 4.30–4.36 (m, 1H), 4.55 (dd, 1H, *J*=6.35, 2.69 Hz), 5.51 (ddt, 1H, *J*=15.63, 6.60, 1.41 Hz), 5.91 (dt, 1H, *J*=15.57, 6.59 Hz), 6.42 (dd, 1H, *J*=5.86, 2.25 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm), 14.03, 21.32, 22.51, 28.64, 31.43, 32.54, 41.98, 72.42, 83.62, 97.64, 122.93, 137.43, 170.38.

(−)-(1*S*,3*R*,4*S*)-1-Acetoxy-3-azido-4-((*E*)-hept-1-enyl)-tetrahydrofuran (12). To a cooled (−50°C) solution of (2*S*,4*S*,5*S*)-5-Acetoxy-2-(*E*-hept-1-enyl)-3-hydroxy-oxolane (42 mg, 0.176 mmol) in CH_2Cl_2 (0.5 mL) was added pyridine (42 mg, 0.530 mmol) followed by triflic anhydride (74 mg, 0.352 mmol) in one portion and stirring continued for 45 min. Sodium azide (114 mg, 1.76 mmol) followed by DMF (1 mL) was added and the mixture allowed to warm to rt, at which it was stirred overnight. After the addition of CH_2Cl_2 (10 mL), the organic phase was washed with water (3×5 mL), dried, filtered and concentrated in vacuo. The crude residue was purified by column chromatography (90:10 to 70:30, petroleum ether:EtOAc) to yield the title compound **12** as a colourless oil (24 mg, 0.085 mmol, 49%) and recovered starting material **11** (10 mg, 0.041 mmol, 24%). $[\alpha]_D^{20}=-90.9$ (*c* 2.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 0.89 (t, 3H, *J*=6.59 Hz), 1.20–1.49 (m, 6H), 2.00–2.18 (m and overlapping s, 6H), 2.60 (ddd, 1H, *J*=14.5, 8.6, 5.7 Hz), 3.73 (dt, 1H, *J*=8.6, 5.4, 5.1 Hz), 4.47 (t, 1H, *J*=6.6 Hz), 5.40 (dd, 1H, *J*=15.5, 7.41 Hz), 5.86 (dt, 1H, *J*=15.38, 6.64 Hz), 6.32 (dd, 1H, *J*=5.69, 1.81 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm), 14.06, 21.32, 22.52, 28.45, 31.36, 32.26, 37.71, 63.64, 84.75, 97.06, 126.12, 136.80, 170.29.

(−)-(1*S*,3*R*,4*R*)-1-Acetoxy-3-azido-4-hydroxymethyltetrahydrofuran (13). The compound **12** (24 mg, 0.085 mmol) was suspended in buffer/acetone mixture (0.5 M, pH 6.8 phosphate, 0.140 mL/1.42 mL), to which was added NMO (19.9 mg, 0.17 mmol) followed by osmium tertroxide (2 crystals). After 6 h at rt, sodium sulfite was added and stirring continued for a further 1.5 h. Ethyl acetate (10 mL) was added and the organic layer washed with water (2×1 mL) then brine solution (1 mL). The organic layer was dried, filtered and concentrated in vacuo. The crude diol was resuspended in acetone/H_2O (1.5 mL/0.62 mL), sodium metaperiodate (30 mg, 0.141 mmol) was added and after 6 h the mixture filtered, diluted with CH_2Cl_2 (8 mL) and washed with brine solution (2×3 mL). The combined aqueous layers were back extracted with CH_2Cl_2 (5 mL) and thereafter the organic layers combined, dried, filtered and concentrated in vacuo. The crude aldehyde was resuspended in THF (1.2 mL), cooled to 0°C and $NaBH_3CN$ added in one portion followed by buffer (pH 3.68, NaOAc/HOAc) and the mixture allowed to warm to rt. After 3.5 h acetone (3 mL) was added to consumed excess $NaBH_3CN$ followed by, after 30 min, ethyl acetate (10 mL). The organic layer was washed with H_2O (2×3 mL), dried filtered and concentrated in vacuo. The crude residue was purified by column chromatography (70:30 to 60:40, petroleum ether:EtOAc) to yield the title compound **13** as a colourless oil (6 mg, 0.030 mmol, 38%). $[\alpha]_D^{20}=-117.8$ (*c* 0.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 2.11 (s, 3H), 2.19 (ddd, 1H, *J*=14.64, 4.57, 3.17 Hz), 2.57 (ddd, *J*=14.63, 8.66, 5.47 Hz), 3.70 (bd, 1H, *J*=12.22 Hz), 3.89 (dd, 1H, *J*=12.33, 2.83 Hz), 4.10 (m, 1H), 4.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 21.41, 38.50, 59.66, 62.29, 84.94, 97.06, 170.49.

(−)-(4*R*,5*S*)-4-*tert*-butyldiphenylsilyloxy-5-((*E*)-hept-1-enyl)tetrahydrofuran-2-one (14). To a cooled solution (5°C) of imidazole (343 mg, 5.05 mmol) in DMF (0.2 mL) was added *tert*-butyldiphenylchlorosilane (1.04 g, 3.78 mmol). After 15 min the alcohol **5** (0.50 g, 2.52 mmol) was added dropwise and the solution warmed to rt, at which it was stirred for 2 h. Water (10 mL) was then added and the aqueous phase extracted with CH_2Cl_2 (4×10 mL). The organic extracts were combined, dried, filtered and concentrated in vacuo. The crude residue was purified by column chromatography (95:5 to 90:10, petroleum ether:ethyl acetate) to yield the title compound **14** as a white solid (891 mg, 1.86 mmol, 74%). $[\alpha]_D^{20}=-8.10$ (*c* 0.67, $CHCl_3$); Mp 47–48°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.87 (t, 3H, *J*=6.35 Hz), 1.08 (s, 9H), 1.20–1.39 (m, 6H), 1.88–2.02 (m, 2H), 2.40–2.62 (m, 2H), 4.19–4.25 (m, 1H), 4.72 (dd, *J*=6.59, 2.01 Hz, 1H), 5.10 (ddt, 1H, *J*=15.38, 6.68, 1.38 Hz), 5.59 (ddt, 1H, *J*=15.38, 8.11, 1.03 Hz), 7.35–7.50 (m, 6H), 7.60–7.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ (ppm), 14.05, 19.07, 22.51,

26.82, 28.38, 31.33, 32.16, 37.38, 73.71, 87.90, 124.45, 127.96, 128.01, 130.24, 132.83, 135.71, 135.80, 136.08, 175.11. Anal. calcd for $C_{27}H_{36}SiO_3$: C, 74.26; H, 8.31; O, 10.99; Found: C, 74.25; H, 8.37.

(−)-(2*R*,4*R*,5*S*)-4-*tert*-butyldiphenylsilyloxy-2-fluoro-5-((*E*)-hept-1-enyl)tetrahydrofuran-2-one (15). A solution of lactone **14** (280 mg, 0.583 mmol) and *N*-fluorodibenzenesulfonimide (367 mg, 1.16 mmol) in THF (2.8 mL) was cooled to −78°C, to which was added LiHMDS (3.4 mL, 0.41 M in THF, 1.4 mmol) dropwise over 50 min. The mixture was stirred for a further 30 min, afterwhich saturated ammonium chloride was added (9 mL) and the cooling bath removed. After 30 min at rt, the mixture was diluted with ethyl acetate (60 mL) and the organic phase washed with saturated sodium bicarbonate (2×10 mL). The organic phase was dried, filtered and concentrated in vacuo and the mixture purified by column chromatography (toluene as eluent). Recrystallisation from petroleum ether yielded the title compound as a colourless oil (132 mg, 2.65 mmol, 49%) and recovered lactone **15** (84 mg, 0.175 mmol, 30%). $[\alpha]_D^{20}=-90.9$ (*c* 2.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 0.88 (t, 3H, *J*=6.55 Hz), 1.08 (s, 9H), 1.20–1.33 (m, 6H), 1.86–1.93 (m, 2H), 4.24 (dt, 1H, *J*=17.0, 7.71 Hz), 4.57 (t, 1H, *J*=7.84 Hz), 5.00 (dd, 1H, *J*=15.38, 8.35 Hz) 5.21 (d, 1H, *J*=51.4, 7.81 Hz), 5.82 (dt, 1H, *J*=15.14, 6.81 Hz), 7.34–7.51 (m, 6H), 7.52–7.65 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm), 14.01, 19.28, 22.49, 26.82, 28.02, 31.35, 32.18, 77.76 (d, *J*=19.4 Hz), 81.60 (d, *J*=11.0 Hz), 91.4 (d, *J*=200 Hz), 123.39, 127.81, 127.91, 130.40, 131.86, 132.21, 135.92, 135.80, 140.39, 168.44 (*J*=22.1 Hz).

Acknowledgements

The authors wish to thank Carina Illaszewicz, Hansjörg Weber and Lothar Brecker for measuring the NMR spectra. The authors would like to thank DSM-Chemie Linz and the European Union (Project No: ERBBIO4CT960112) for financial support.

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