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ORIGINAL ARTICLE

Enantiospecific total synthesis of the squalene synthase inhibitors (–)-CJ-13,982 and its enantiomer from a common intermediate

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The total syntheses of both the natural and unnatural enantiomers of the alkyl citrate natural product CJ-13,982 (1) from the common D-ribose-derived acid 6 are described.
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INTRODUCTION

The alkyl citrate family of natural products contain a common 2-alkyl citrate moiety with a wide variety of side chains and oxidation levels.[1] These metabolites are inhibitors of squalene synthase, the enzyme responsible for the first pathway-specific step in cholesterol biosynthesis. Some of the simplest examples include CJ-13,982 (**1**) and CJ-13,981 (**2**) (Figure 1), which contain an unsubstituted alkyl or alkenyl group, and were isolated from an unidentified fungus CL15036 in 2001.[2] A more complex example is the alkyl citrate L-731,120 (**3**),[3] which was isolated from the same fungal species as zaragozic acid A (**4**),[4–8] a picomolar inhibitor of squalene synthase. Recently, L-731,120 (**3**) has also been identified as a key intermediate in the biosynthesis zaragozic acid A (**4**).[9] The absolute configuration at C12 in L-731,120 (**3**) is inferred from its biosynthetic relationship to **4.**

The synthesis of alkyl citrate natural products is challenging due to the high oxidation level and the need for stereocontrol of the two contiguous asymmetric centres.[1] To date, only total syntheses of the unnatural enantiomers (+)-CJ-13,982 (*ent*-**1**) and (+)-CJ12,981 (*ent*-**2**) have been reported utilising an *anti*-Evans aldol reaction followed by a stereoselective Seebach self retention of a stereocentre (SRS) alkylation as the key steps to secure the alkyl citrate fragment.[10]

DISCUSSION

We envisaged an approach to the unnatural enantiomer of CJ-13,982 (**1**) starting from the known γ-lactone **5**, which was utilised by us for the total synthesis of trachyspic acid[11,12] and the proposed structure for citrafungin A.[13] The key step in the synthesis of **5** was the Ireland–Claisen rearrangement of allyl ester **7**, synthesised from D-deoxyribose-derived acid **6** (Scheme 1). This reaction proceeds without any observed β-elimination under the standard conditions[12] shown to afford the ester **8.** The [3,3]-sigmatropic rearrangement occurs to form the new C–C bond on face of the tetrahydrofuran (THF) ring opposite the β-OPMB group in high diastereoselectivity. Ester **8** was then converted into the lactone **5** in a seven-step sequence.[11]

For the total synthesis of (+)-(2*R*, 3*R*)-CJ-13,982 (*ent*-**1**), lactone **5** was reduced with DiBALH to give a mixture of the corresponding lactol and a small amount of diol, which could be oxidised to the lactol with DMP. Wittig extension of the lactol afforded alkene **9** in 46% overall yield. Cross metathesis[14] with undecene using Grubbs second-generation catalyst provided the *E*-alkene **10** as the only stereoisomer. Hydrogenation then afforded the saturated triester **11**, which on treatment with trifluoroacetic acid (TFA) gave (+)-CJ-13,982 (*ent*-**1**), $[\alpha]_D^{25} = +14.1$ (*c* 0.35, acetone) in high yield. This material was identical to that reported by Barrett.[10]

Whilst the above route could provide the (–)-**1** using the known enantiomer of **6**,[11] it is inefficient especially with respect to constructing the contiguous asymmetric centres. Therefore, we envisaged a more convergent approach which would provide the natural enantiomer (–)-(2*S*,3*S*)-CJ-13,982 (**1**) as well as related alkyl citrate natural products.

As shown in Scheme 2, an alternative approach would be the [3,3]-sigmatropic rearrangement of the *Z*-silylketene acetal **12** (also derived from D-deoxyribose) with the correct side chain attached via the chair-like transition state shown to afford the alkene **13** with the two new stereocenters introduced in a steroselective manner in a single C–C bond-forming step. This is in analogy with our approach to the bicyclic core of the zaragozic acid C.[15] Oxidative cleavage of the alkene and degradation of the THF ring to introduce the final carboxylic acid would then secure the alkyl citrate moiety **14**.

This proposal was tested first using the ester **16** derived from a coupling between acid **6** and allylic alcohol **15** as shown in Scheme 3. Exposure of **16** to the standard conditions[11,12] (Scheme 1) gave the alkene **17** as an inseparable ~3:1 mixture of diastereoisomers as judged by ^{1}H NMR integration, presumably differing at the indicated stereocenter. Cleavage of the *t*-butyldimethylsilyl (TBS) ether induced

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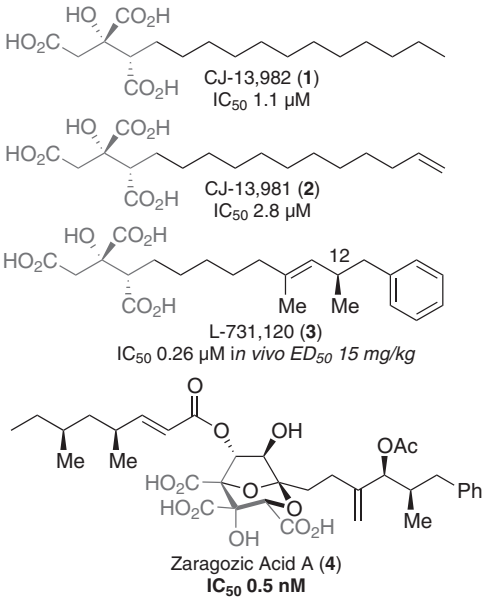
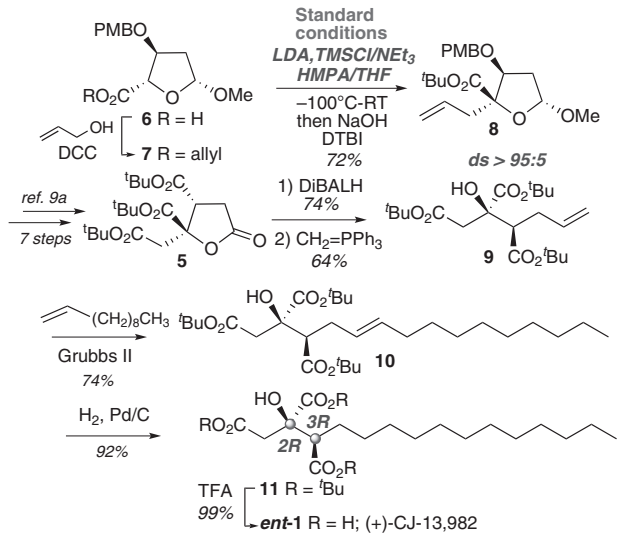
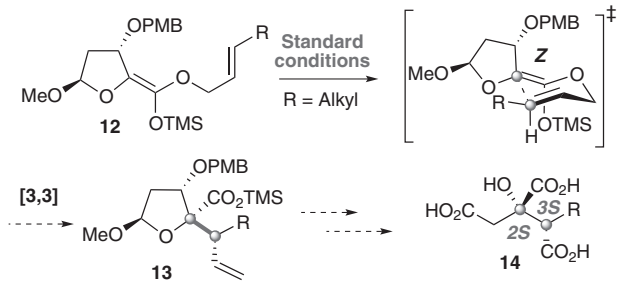


Figure 1 Alkyl citrate natural products **1–4**. A full colour version of this figure is available at the *Journal of Antibiotics* journal online.



Scheme 1 Synthesis of (+)-CJ-13,982 (*ent*-**1**). A full colour version of this scheme is available at the *Journal of Antibiotics* journal online.



Scheme 2 Convergent approach to simple alkyl citrates. A full colour version of this scheme is available at the *Journal of Antibiotics* journal online.

lactonisation and subsequent PMB group deprotection gave the spirolactones **18** and **19** in a 2.9:1 ratio. These compounds were easily separated by flash chromatography and both were crystalline. X-ray analysis of each revealed the stereochemistry was as predicted. Thus, the rearrangement proceeded via the chair-like transition state as shown in Scheme 2 to afford the desired isomer **18** as the major product. The minor diaseteroisomer **19**, with the incorrect stereochemistry at the stereocenter marked (Scheme 3) probably results from [3,3]-sigmatropic rearrangement of the corresponding *E*-silylketene acetal, which is formed as the minor geometric isomer during the enolisation/silylation reaction.[16]

The synthesis of the (–)-CJ-13,982 precursor began as shown in Scheme 4. Ester **21** was formed by dicylohexylcarbodiimide-mediated coupling of acid **6** and alcohol **20**. Ireland–Claisen rearrangement under the standard conditions[11] gave the desired isomer **22** as the major product along with the minor isomer **23** in a 2.5:1 ratio that were separable by flash chromatography. The stereochemistry of the major isomer was assigned in analogy with the initial study (Scheme 3), as well as its subsequent conversion into the target compound.

The total synthesis of (–)-CJ-13,982 (**1**) is detailed in Scheme 5 and begins with the conversion of acetal **22** into lactone **24** by hydrolysis and oxidation. Removal of the PMB ether and mesylation with concomitant elimination gave the α,β-unsaturated lactone **25** in good yield. DiBAlH reduction afforded the allylic alcohol **26**, which was protected on the tertiary alcohol via bis-silylation and desilylation of the primary alcohol to give trimethylsilyl (TMS) ether **27**. Alcohol reduction with alkene transposition using the conditions reported by Movassaghi and Ahmad[17] with the reagent *N*-isopropylidene-*N*′-2-nitrobenzenesulfonyl hydrazine (IPNBSH) gave the diene **28**. Protection of the tertiary alcohol was required for this transformation to avoid formation of a cyclic ether in the Mitsunobu reaction. Ozonolysis, oxidation and formation of the *t*-butyl esters using dicyclohexyl-*t*-butylisourea[18] gave tri-*t*-butyl ester *ent*-**11** (the TMS ether was also removed in this sequence) and a final deprotection using TFA afforded (–)-CJ-13,981 (**1**), $[\alpha]_D^{25}$ –14.1 (*c* 0.25, acetone), which was identical to the natural product.

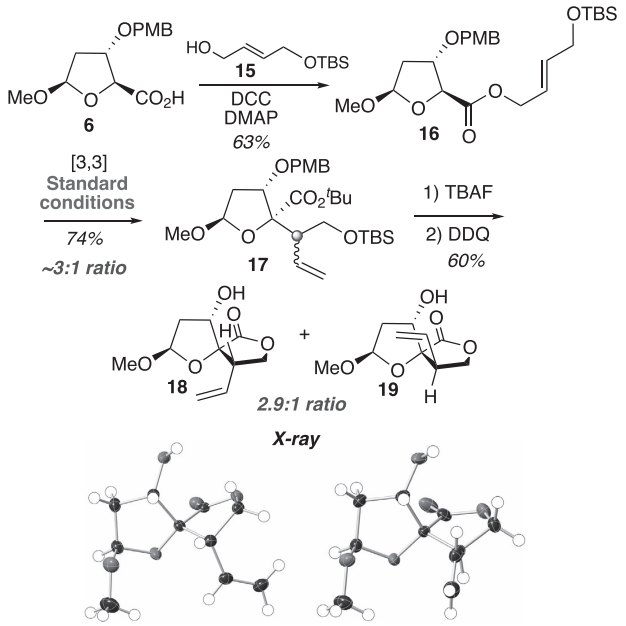
CONCLUSION

We have completed a total synthesis of (+)-CJ-13,981 (*ent*-**1**) and the first synthesis of natural (–)-CJ-13,981 (**1**) from the common acid **6**. Each approach utilised an Ireland–Claisen rearrangement in the presence of a β-leaving group. The first involved a sequential formation of the two stereocenters present in the alkyl citrate whilst the second more convergent shorter approach introduced both asymmetric centres in a single C–C bond-forming reaction with good stereocontrol for the desired configuration. This methodology could supply all the simple alkyl citrates in a highly convergent manner.

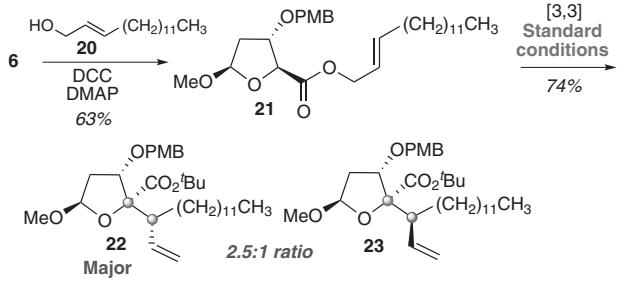
EXPERIMENTAL PROCEDURES

General

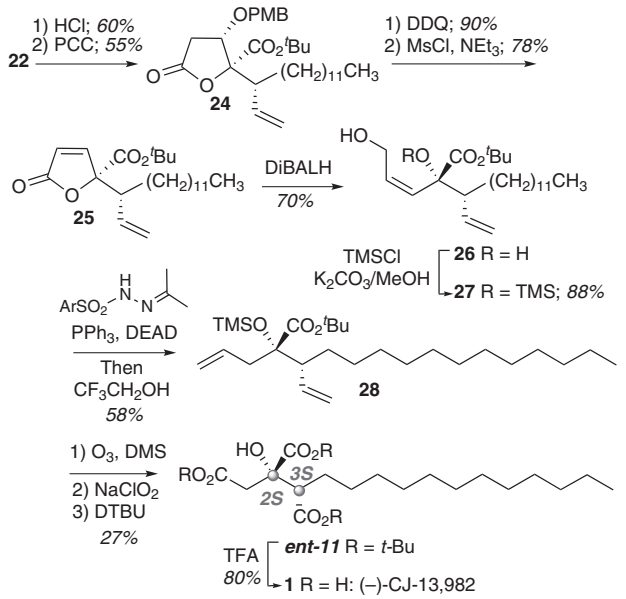
^{1}H NMR spectra (600, 500 or 400 MHz) and proton decoupled carbon NMR spectra (^{13}C NMR, 150, 125 or 100 MHz) were obtained in deuterochloroform with residual chloroform as internal standard unless otherwise noted. Chemical shifts are followed by multiplicity, coupling constant(s) (*J*, Hz), integration and assignments where possible. Flash chromatography was carried out on silica gel 60. Analytical TLC was conducted on aluminium-backed 2 mm-thick silica gel 60 GF_{254} and chromatograms were visualised with 20% w/w phosphomolybdic acid in ethanol or aq. $KMnO_4$. High-resolution MS were obtained by ionising samples via ESI. Anhydrous THF, Et_2O and CH_2Cl_2 were dried using a solvent cartridge system. Dry methanol was distilled from magnesium methoxide. All other solvents were purified by standard methods. Petrol used refers to



Scheme 3 Ireland–Claisen rearrangement of ester **16**. A full colour version of this scheme is available at the *Journal of Antibiotics* journal online.



Scheme 4 Ireland–Claisen rearrangement of ester **21**. A full colour version of this scheme is available at the *Journal of Antibiotics* journal online.



Scheme 5 Synthesis of (–)-CJ-13,982 (**1**). A full colour version of this scheme is available at the *Journal of Antibiotics* journal online.

petroleum ether 40–60 °C boiling range. All other commercially available reagents were used as received.

Tri-*tert*-butyl ester 9

A solution of DiBAlH in hexanes (0.55 ml, 1 M, 0.55 mmol) was added to lactone **5** (74 mg, 0.19 mmol) in dry THF (2 ml) at −78 °C and the resulting solution was allowed to stir at −78 °C for 5 h. The reaction was quenched with 10% HCl and water followed by the usual workup with EtOAc. Purification by flash chromatography with 20% EtOAc/petrol yielded lactol (43 mg, 58%) as a pale yellow oil. Further elution with 20% EtOAc/petrol provided diol (12 mg, 16 %) as a pale yellow oil. $[\alpha]_D^{23}$ –2.74 (*c* 1.20, CH_2Cl_2); IR (ATR) ν_{max} 3486, 2978, 1730, 1369, 1251, 1153 and 846 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H, $C(CH_3)_3$), 1.46 (s, 9H, $C(CH_3)_3$), 1.48 (s, 9H, $C(CH_3)_3$), 1.94 (m, 2H, $CH_2CHCO_2{}^tBu$), 2.79 (m, 3H, $CHCO_2{}^tBu$ and $CH_2CO_2{}^tBu$), 3.62 (m, 1H, $OHCH_AH_B$), 3.70 (dd, J = 11.25 and 5.61 Hz, 1H, $OHCH_AH_B$) and 4.19 (s, 1H, O*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 28.2, 28.2, 30.1, 42.0, 50.5, 61.0, 75.4, 81.5, 81.9, 83.1, 169.9, 171.9 and 172.6 ; HRMS (ESI): calculated for $C_{20}H_{36}O_8Na$ $[M+Na]^+$ 427.23024; found 427.23015. Diol (12 mg, 0.03 mmol) was dissolved in CH_2Cl_2 (2 ml) and treated with Dess-Martin periodinane (12.5 mg, 0.03 mmol) for 30 min. Sat. aqueous $Na_2S_2O_3$ and $NaHCO_3$ were added and the biphasic mixture stirred for 30 min followed by the usual workup with EtO_2. Column chromatography with 20% EtOAc/petrol eluent yielded further (10 mg, 83%, total of 53 mg, 72% over two steps) as a pale yellow oil.

^{t}BuOK (62 mg, 0.549 mmol) was added to methyltriphenylphosphonium bromide (209 mg, 0.585 mmol) in dry THF (5 ml) at 0 °C. The resulting solution was stirred at room temperature (RT) for 1 h before cooling to −78 °C, lactol (47 mg, 0.117 mmol) in dry THF (2 ml) was added and the reaction stirred at −78 °C for 1 h. The reaction was warmed to −10 °C and stirred for an additional 2.5 h before quenching with sat. NH_4Cl and the usual workup with Et_2O. Flash chromatography with 5% EtOAc/petrol as eluent gave alkene **9** (30 mg, 64%) as a yellow oil. $[\alpha]_D^{20}$ –4.80 (*c* 1.05, CH_2Cl_2); IR (ATR) ν_{max} 2926, 1731, 1369 and 1152 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 9H, $C(CH_3)_3$), 1.46 (s, 9H, $C(CH_3)_3$), 1.51 (s, 9H, $C(CH_3)_3$), 2.19 (m, 1H, $CH_2=CHCH_AH_B$), 2.51 (m, 1H, $CH_2=CHCH_AH_B$), 2.60 (dd J = 11.80 and 2.93 Hz, 1H, $CH_2CHCO_2{}^tBu$), 2.79 (ABq, J = 16.72 Hz, 2H, $CH_2CO_2{}^tBu$), 3.93 (s, 1H, O*H*), 5.01 (apparent d, J = 10.04 Hz, 1H, $CH_AH_B=CH$), 5.06 (ddd, J = 17.06, 3.18 and 1.42 Hz, 1H, $CH_AH_B=CH$) and 5.71 (m, 1H, $CH_2=CH$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 28.2, 28.3, 31.9, 42.6, 54.0, 75.5, 81.5, 81.6, 83.1, 117.0, 135.4, 170.1, 170.9 and 172.7; HRMS (ESI): calculated for $C_{21}H_{36}O_7Na$ $[M+Na]^+$ 423.23532; found 123.23525.

E-Alkene 10

Grubbs second-generation catalyst (3.2 mg, 0.0038 mmol) was added to a solution of triester **9** (15.4 mg, 0.038 mmol) and 1-undecene (78 µl, 0.38 mmol) in CH_2Cl_2 (2 ml). The resulting solution was refluxed for 16 h before being condensed and purified by flash chromatography with 5% EtOAc/petrol as eluent to yield alkene **10** (15 mg, 74%) as a colourless oil. $[\alpha]_D^{25}$ –5.3 (*c* 0.27, CH_2Cl_2); IR (ATR) ν_{max} 3446, 2925, 1738, 1366, 1229, 1217 and 912 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.26 Hz, 3H, $CH_3C_8H_{16}$), 1.21–1.34 (m, 14H, $CH_3C_7H_{14}CH_2$), 1.42 (s, 9H, $C(CH_3)_3$), 1.45 (s, 9H, $C(CH_3)_3$), 1.50 (s, 9H, $C(CH_3)_3$), 1.94 (q, J = 6.96 Hz, 2H, $C_8H_{17}CH_2$), 2.12 (m, 1H, $C=CHCH_AH_B$), 2.43 (m, 1H, $C=CHCH_AH_B$), 2.55 (m, 1H, CH_2CH), 2.61 (d, J = 16.5 Hz, 1H, $CH_AH_BCO_2{}^tBu$), 2.94 (d, J = 16.5 Hz, 1H, $CH_AH_BCO_2{}^tBu$), 3.90 (s, 1H, O*H*), 5.29 (m, 1H, CH=C*H*) and 5.46 (m, 1H, CH=C*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 22.8, 28.1, 28.2, 28.3, 29.4, 29.5, 29.7, 30.7, 32.1, 32.7, 42.7, 54.7, 75.6, 81.4, 81.5, 83.0, 126.4, 133.3, 170.1, 171.1 and 172.7; HRMS (ESI): calculated for $C_{30}H_{54}O_7Na$ $[M+Na]^+$ 549.37618; found 549.37633.

Tri-*tert*-butyl ester 11

A suspension of palladium on carbon (10%, 15 mg) and alkene **10** (15 mg, 0.028 mmol) in dry THF (4 ml) under a H_2 atmosphere was stirred for 5 h. The suspension was filtered through Filteraid (medium, Ajax Chemicals, Victoria, Australia) and washed with EtOAc and the filtrate was condensed and purified by flash chromatography with 5% EtOAc/petrol as eluent to give

alkane **11** (13.8 mg, 92%). $[\alpha]_D^{25}$ +3.2 (*c* 0.46, CH_2Cl_2); IR (ATR) ν_{max} 2528, 2926, 1731, 1368 and 1151 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (m, 3H, $CH_3C_{11}H_{22}$), 1.24–1.31 (m, 22H, $CH_3C_{11}H_{22}$), 1.42 (s, 9H, CCH_3), 1.47 (s, 9H, CCH_3), 1.50 (s, 9H, CCH_3), 2.50 (dd, *J* = 11.88 and 2.77 Hz, 1H, $CHCO_2{}^tBu$), 2.77 (ABq, *J* = 16.45 Hz, 2H, $CCH_2CO_2{}^tBu$), 3.89 (s, 1H, O*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 22.8, 27.4, 27.7, 28.1, 28.2, 28.3, 29.5, 29.5, 29.5, 29.7, 29.8, 29.8, 29.8, 32.1, 42.8, 54.5, 75.8, 81.3, 81.4, 82.9, 170.1, 171.8 and 172.8; HRMS (ESI): calculated for $C_{30}H_{56}O_7Na$ $[M+Na]^+$551.39183; found 551.39185

(+)-CJ-13,982 (*ent*-1)

Triester **11** (9 mg, 0.017 mmol) in CH_2Cl_2 (3 ml) was cooled to 0 °C and treated with TFA (360 µl). The reaction was stirred at 0 °C for 2 h before warming to RT and stirring for a further 16 h. The volatile organics were removed under reduced pressure to give (+)-CJ-13,982 (*ent*-**1**) (6.1 mg, 99%) as a white amorphous powder. $[\alpha]_D^{25}$ +14.1 (*c* 0.35, Acetone); lit.[10] $[\alpha]_D^{25}$ +16.6 (*c* 0.5, Acetone); IR (ATR) ν_{max} 3508, 2918, 2850, 1699, 1463, 1415, 1248, 1226 and 1116 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 0.90 (t, *J* = 6.90 Hz, 3H, $CH_3C_{11}H_{22}$), 1.17–1.39 (m, 20H, $CH_3C_{10}H_{20}CH_2$), 1.49 (m, 1H, $C_{11}H_{23}CH_AH_BCH$), 1.81 (m, 1H, $C_{11}H_{23}CH_AH_BCH$), 2.65 (dd, *J* = 11.90, 2.65 Hz, 1H, $CHCO_2H$), 2.69 (d, *J* = 16.28 Hz, 1H, $CH_AH_BCO_2H$), 3.03 (d, *J* = 6.44 Hz, 1H, $CH_AH_BCO_2H$); ^{13}C NMR (125 MHz, CD_3OD) δ 14.4, 23.7, 28.3, 28.8, 30.4, 30.5, 30.6, 30.7, 30.7, 30.7, 33.0, 43.1, 54.5, 77.0, 174.5, 177.0 and 177.5; HRMS (ESI): calculated for $C_{18}H_{32}O_7Na$ $[M+Na]^+$ 383.20412; found 383.20402.

Ester 16

DMAP (53 mg, 0.43 mmol) and (*E*)-4-(*tert*-butyldimethylsilyloxy)but-2-en-1-ol (0.68 g, 3.38 mmol) were added to a solution of acid **6** (0.78 g, 2.75 mmol) in CH_2Cl_2 (15 ml). The solution was stirred at 0 °C for 5 min before DCC (1.74 g, 8.4 mmol) was added. The resulting suspension was stirred at 0 °C for 2 h before warming to RT for a further 16 h before filtering through Celite. The condensed filtrate was purified by flash chromatography with 15% EtOAc/petrol as eluent yielded ester **16** (0.81 g, 62%) as a pale yellow oil. $[\alpha]_D^{24}$ –43.3 (*c* 1.10, CH_2Cl_2); IR (ATR) ν_{max} 2929, 1757, 1730, 1514, 1248, 1060 and 834 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.06 (s, 6H, $SiCH_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 2.07 (m, 1H, CH_AH_B), 2.23 (m, 1H, CH_AH_B), 3.38 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.18 (m, 2H, $CH=CHCH_2OTBS$), 4.52 (ABq, *J* = 39.99, 11.42 Hz, 2H, OCH_2Ar), 4.54–4.58 (m, 2H, C*H*OMe and C*H*OPMB), 4.67 (m, 2H, $OCH_2CH=CH$), 5.15 (dd, *J* = 5.12, 1.61 Hz, 1H, $CHCO_2$), 5.80–5.91 (m, 2H, $CH=CH$), 6.87 (m, 2H, Ar*H*), 7.26 (m, 2H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.2, 18.5, 26.1, 39.9, 55.4, 55.5, 62.9, 65.4, 71.9, 80.9, 82.2, 106.4, 114.0, 123.1, 129.6, 129.9, 134.9, 159.5 and 171.5; HRMS (ESI): calculated for $C_{24}H_{38}O_7SiNa$ $[M+Na]^+$ 489.22790; found 489.22760.

Spirolactones 18 and 19

A solution of ^nBuLi in hexanes (2.06 ml, 1.88 M, 3.88 mmol) was added dropwise to a solution of $^iPr_2NH$ (0.5 ml, 3.3 mmol) in THF (6 ml) at −78 °C. The resulting solution was stirred at 0 °C for 10 min before cooling to −78 °C and being added dropwise to a solution of ester **16** (0.8 g, 1.73 mmol) and the supernatant of a centrifuged mixture of freshly distilled TMSCl (1.1 ml, 8.8 mmol) and NEt_3 (1.1 ml, 7.7 mmol) in THF/HMPA (15/3 ml) at −100 °C. The resulting solution was stirred at −100 °C for 10 min before warming to RT and stirring for a further 16 h. The reaction was quenched with 1 M NaOH (5 ml) and the resulting layers separated, the aqueous layer was acidified with HCl (10%) and underwent the usual workup with Et_2O. The crude acid was dissolved in CH_2Cl_2 (7 ml) and *N,N′*-diisopropyl-*O*-*tert*-butylisourea[18] (2.7 g, 13.3 mmol) was added, the solution was allowed to stir for 18 h at RT. The resulting suspension was filtered through Celite and the filtrate condensed. Flash column chromatography with 10% EtOAc/petrol as eluent gave ester **17** (~1:3 mixture, 594 mg, 65%) as a colourless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 1.5H, $SiCH_3$), 0.04 (s, 4.5H, $SiCH_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.40 (s, 2.25H, $C(CH_3)_3$), 1.45 (s, 6.75H, $C(CH_3)_3$), 2.07 (m, 1H, CH_AH_B), 2.18 (m, 1H, CH_AH_B), 2.78 (m, 0.2H, $CHCH=CH_2$), 3.00 (td, *J* = 9.43, 3.49 Hz, 0.8H, $CHCH=CH_2$), 3.37 (s, 1.8H, OCH_3), 3.39 (s, 0.6H, OCH_3), 3.60 (t, *J* = 9.64 Hz, 0.8H, $CHCH_AH_BOTBS$), 3.74 (dd, *J* = 9.97, 3.57 Hz, 0.8H, $CHCH_AH_BOTBS$), 3.79 (s, 3H, OCH_3), 3.94 (m, 0.2H, $CHCH_AH_BOTBS$), 4.12 (dq, *J* = 7.14, 1.08 Hz, 0.2H, $CHCH_AH_BOTBS$), 4.37–4.56 (m, 3H, C*H*OPMB and OCH_2Ar), 5.13–5.25 (m, 3H,C*H*OMe and $CH=CH_2$), 5.65 (dt, *J* = 17.16 and 10.15 Hz, 0.8H, $CH=CH_2$), 5.90 (dt, *J* = 17.02 and 10.52 Hz, 0.2H, $CH=CH_2$), 6.85 (m, 2H, Ar*H*), 7.21 (d, *J* = 8.37 Hz, 2H, Ar*H*).

The ester **17** (~1:3 mixture, 0.29 g, 0.55 mmol) was dissolved in THF (30 ml) and treated with TBAF (175 mg, 0.67 mmol) for 2 days. The usual workup with EtOAc gave the crude lactones, which were dissolved in CH_2Cl_2/pH 7 buffer (20/2.5 ml), DDQ (0.2 g, 0.88 mmol) was added and the biphasic mixture was stirred for 16 h. The resulting mixture was filtered through Celite and the filtrate was concentrated and purified by flash chromatography with 20% EtOAc/petrol yielded alcohol **19** (15 mg, 13 %) as colourless needle-shaped crystals. m.p. 73–77 °C; $[\alpha]_D^{23}$ –155.0 (*c* 0.47, CH_2Cl_2); IR (ATR) ν_{max} 3473, 1771, 1079 and 922 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.12 (brd, *J* = 7.79 Hz, 1H, O*H*), 2.27 (dd, *J* = 12.56 and 7.04 Hz, 1H, CH_AH_B), 2.36 (ddd, *J* = 12.60, 9.34 and 5.20 Hz, 1H, CH_AH_B), 3.34 (s, 3H, OCH_3), 4.22 (t, *J* = 9.33 Hz, 1H, $CHCH_AH_BO$), 4.47 (dd, *J* = 8.84 and 7.83 Hz, 1H, $CHCH_AH_BO$), 4.71 (dd, *J* = 16.74 and 7.64 Hz, 1H, C*H*OMe), 5.19 (dd, *J* = 5.09 and 0.49 Hz, 1H, C*H*OH), 5.25 (dt, *J* = 17.35 and 1.21 Hz, 1H, $CH=CH_AH_B$), 5.36 (dt, *J* = 10.57 and 1.10 Hz, 1H, $CH=CH_AH_B$), 5.88 (ddd, *J* = 17.46, 10.45 and 7.11 Hz, 1H, $CH=CH_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.8, 47.8, 55.3, 68.3, 71.8, 87.2, 104.6, 120.2, 130.8 and 175.7; HRMS (ESI): calculated for $C_{10}H_{14}O_5Na$ $[M+Na]^+$ 237.07334; found 237.07318. Further elution with 20% EtOAc/petrol gave **18** (45 mg, 38 %) as colourless needle-shaped crystals. m.p. 66–69 °C; $[\alpha]_D^{24}$ –156.1° (*c* 1.20, CH_2Cl_2); IR (ATR) ν_{max} 3447, 2921, 1773, 1105 and 1056 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.28–2.43 (m, 3H, $CHCH_2CH$ and O*H*), 3.16 (q, *J* = 8.10 Hz, 1H, $CHCH=CH_2$), 3.36 (s, 3H, OCH_3), 4.23 (t, *J* = 8.71 Hz, 1H, $CHCH_AH_BO$), 4.44 (dd, *J* = 8.88, 7.44 Hz, 1H, $CHCH_AH_BO$), 4.49 (m, 1H, C*H*OMe), 5.12 (d, *J* = 5.32 Hz, 1H, C*H*OH), 5.26–5.33 (m, 2H, $CH=CH_2$), 5.83 (m, 1H, $CH=CH_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.5, 47.2, 55.7, 70.4, 73.5, 85.3, 105.1, 120.6, 130.5 and 175.1; HRMS (ESI): calculated for $C_{10}H_{14}O_5Na$ $[M+Na]^+$ 237.07334; found 237.07319. Crystallographic data have been deposited with the Cambridge Crystallographic Centre deposit codes: CCDC-1566533 and 1566534.

Allylic alcohol 20

Tridecan-1-ol (2 g, 9.98 mmol) was dissolved in CH_2Cl_2 (75 ml) and Dess-Martin periodinane (6.39 g, 14.96 mmol) was added to the solution. After stirring at RT for 45 min, sat. $NaHCO_3$, 1.5 M $Na_2S_2O_3$ and CH_2Cl_2 were added and resulting mixture stirred until both layers became clear. The normal workup with CH_2Cl_2gave a residue, which was directly used in next step. To a solution of the crude aldehyde in CH_2Cl_2 (100 ml) was added methyl 2-(triphenylphosphoranylidene)acetate (4.01 g, 12 mmol) and the resultant solution was stirred at RT for 2 h. The normal workup with Et_2O followed by purification of the crude product by flash chromatography (5% EtOAc/petrol) to give methyl ester (1.9 g, 8.65 mmol, which was dissolved in THF (86 ml) cooled to −78 °C and treated with DiBAlH (1 M in THF, 37 ml, 37 mmol). After stirring at −78 °C for 2 h, the solution was warmed to 0 °C and 10% HCl was added dropwise to quenched the reaction. The normal workup with EtOAc and flash chromatographic purification of the crude product (10% EtOAc/petrol) gave allylic alcohol **20** (1.52 g, 72%) as white solid. m.p. 27–29 °C IR (ATR) ν_{max} 3314, 2922, 2853, 1466, 1002, 968 and 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.7 Hz, 3H, $C_{10}H_{20}CH_3$), 1.19–1.42 (m, 20H, $C_{10}H_{20}CH_3$), 2.04 (dd, *J* = 13.8 and 6.7 Hz, 2H, $CH_2C_{11}H_{23}$), 4.08 (s, 1H, CH_2OH), 5.74–5.59 (m, 2H, $CH=CH$) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.10, 22.67, 29.12, 29.17, 29.34, 29.48, 29.59, 29.65, 31.91, 32.20, 63.87, 128.75 and 133.65.

Ester 21

A solution of alcohol **20** (1.0 g, 4.4 mmol) and acid **6** (1.4 g, 4.8 mmol) in CH_2Cl_2 (11 ml) was cooled to 0 °C and DMAP (58 mg, 0.48 mmol) was added. The resulting solution was stirred at 0 °C for 10 min then treated with DCC (1.85 g, 8.96 mmol) and the reaction was slowly warmed up to RT and further stirred for 36 h. The suspension was filtered through Celite and evaporation of

the solvent followed by purification by flash chromatography (20% Et_2O/petrol) gave the ester **21** (1.7 g, 63%) as a colourless oil. $[\alpha]_D^{24}$–39.9 (*c* 1.00, CH_2Cl_2); IR (ATR) ν_{max} 2924, 2857, 1758, 1729, 1614, 1514, 1465, 1110, 1065 and 971 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, $J=7.0$ Hz, 3H, $C_{11}H_{22}CH_3$), 1.26 (m, 18H, $C_9H_{18}CH_3$), 1.36 (m, 2H, $CH_2C_{10}H_{21}$), 2.07 (m, 3H, CH=CHCH_2 and $CH_3OCHCH_AH_B$), 2.22 (ddd, $J=13.27$, 6.58 and 1.58 Hz, 1H, $CH_3OCHCH_AH_B$), 3.39 (s, 3H, OCH_3), 3.80 (s, 3H, $ArOCH_3$), 4.48 (d, $J=11.45$ Hz, 1H, OCH_AH_BAr), 4.59 (m, 5H, OCH_AH_BAr, $CO_2CH_2CH=$, CHOCH_2Ar and CHCO_2), 5.15 (dd, $J=5.10$ and 1.59 Hz, 1H, CHOCH_3), 5.58 (dtt, $J=5.10$, 6.68 and 1.54 Hz, 1H, $CH=CHC_{12}H_{25}$), 5.80 (dtt, $J=5.10$, 6.68 and 1.54 Hz, 1H, $CH=CHC_{12}H_{25}$), 6.87 (m, 2H, ArH), 7.26 (m, 2H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) 14.1, 22.7, 28.9, 29.2, 29.3, 29.5, 29.6, 29.6, 29.7, 29.7, 31.9, 32.3, 39.7, 55.3, 55.3, 66.0, 71.7, 80.7, 82.1, 106.2, 113.8, 123.8, 123.2, 129.4, 129.7, 137.3, 159.3 and 171.4; HRMS (ESI): calculated for $C_{29}H_{46}O_6Na$ $[M+Na]^+$ 513.3180; found 513.3181.

Esters 22 and 23

To a solution of the ester **21** (1.1 g, 2.3 mmol) in THF/HMPA (20 ml, 5:1) was added the supernatant of a centrifuged mixture of freshly distilled TMSCl (1.25 g, 11.24 mmol, 1.47 ml) and NEt_3 (0.97 g, 10.39 mmol, 1.45 ml) via cannula. The resulting solution was cooled to 100 °C and a freshly prepared solution of LDA (4.5 mmol, 0.3 M in THF, 15 ml) was added dropwise. After stirring at −100 °C for 10 min, the reaction was slowly warmed to RT over 16 h. The resulting solution was extracted with 1 M NaOH three time and the aqueous layer was acidified with 10% HCl and a normal workup with EtOAc gave the crude acid, which was dissolved in CH_2Cl_2 and *N,N′*-diisopropyl-*O*-tert-butylisourea (5 ml, 21 mmol) was added. After stirring for 24 h, the suspension was filtered through Celite and rinsed with CH_2Cl_2. Rotary evaporation and flash chromatography (5% EtOAc/petrol) purified the resulting residue and gave ester **22** (670 mg, 53%) as a colourless oil. $[\alpha]_D^{24}$ –61.7 (*c* 1.19, CH_2Cl_2); IR (ATR) ν_{max} 2926, 2854, 1735, 1615, 1515, 1466, 1249, 1104 and 1037 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, $J=6.99$ Hz, 3H, $C_{11}H_{22}CH_3$), 1.25 (m, 20H, $C_{10}H_{20}CH_3$), 1.38 (m, 2H, $CH_2C_{11}H_{23}$), 1.45 (s, 9H, $C(CH_3)_3$), 2.09 (ddd, $J=12.86$, 7.10 and 1.64 Hz, 1H, CH_ACH_B), 2.22 (ddd, $J=12.86$, 8.87 and 5.56 Hz, 1H, CH_ACH_B), 2.71 (td, $J=9.69$ and 2.76 Hz, 1H, CHC$H=CH_2$), 3.39 (s, 3H, OCH_3), 3.80 (s, 3H, $ArOCH_3$), 4.30 (dd, $J=8.87$ and 7.09 Hz, 1H, CHOCH_2Ar), 4.39 (d, $J=11.47$ Hz,1H, OCH_AH_BAr), 4.54 (d, $J=11.47$ Hz,1H, OCH_AH_BAr), 5.04 (dd, $J=17.26$ and 2.15 Hz, 1H, $CH=CH_AH_B$), 5.16–5.18 (m, 2H, CHOCH_3 and $CH=CH_AH_B$), 5.56 (dt, $J=17.24$ and 10.14 Hz, 1H, $CH=CH_2$), 6.85 (m, 2H, ArH) and 7.21 (m, 2H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) 14.1, 22.7, 27.7, 28.0, 29.3, 29.5, 29.6, 29.6, 29.6, 29.7, 30.7, 31.9, 37.9, 49.3, 55.2, 55.3, 71.9, 80.3, 81.5, 91.2, 104.1, 113.6, 118.4, 129.0, 130.2, 137.9, 159.1 and 171.0; HRMS (ESI): calculated for $C_{33}H_{54}O_6Na$ $[M+Na]^+$ 569.38043; found 569.38043. Further elution with 10% EtOAc/petrol gave **23** (265 mg, 21%) as a colourless oil. $[\alpha]_D^{25}$ –29.4 (*c* 1.21, CH_2Cl_2); IR (ATR) ν_{max} 2925, 2854, 1735, 1614, 1515, 1466, 1249, 1103 and 1037 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, $J=6.99$ Hz, 3H, $C_{11}H_{22}CH_3$), 1.32–1.19 (m, 20H, $C_{10}H_{20}CH_3$), 1.42 (s, 9H, C $(CH_3)_3$), 1.63–1.71 (m, 2H, $CH_2C_{11}H_{23}$), 2.06 (ddd, $J=13.27$, 6.36 and 2.50 z, 1H, CH_ACH_B), 2.22 (ddd, $J=13.27$, 6.36 and 2.50 Hz, 1H, CH_ACH_B), 2.34 (td, $J=10.36$ and 2.56 Hz, 1H, CHC$H=CH_2$), 3.38 (s, 3H, OCH_3), 3.80 (s, 3H, $ArOCH_3$), 4.30 (t, $J=6.33$ Hz, 1H, CHOCH_2Ar), 4.42 (ABq, $J=14.95$ Hz, 2H, OCH_2Ar), 5.03 (dd, $J=17.17$ and 2.22 Hz, 1H, $CH=CH_AH_B$), 5.09 (dd, $J=10.17$ and 2.25 Hz, 1H, $CH=CH_AH_B$), 5.22 (dd, $J=5.59$ and 2.50 Hz, 1H, CHOCH_3), 5.91 (dt, $J=17.16$ and 10.07 Hz, 1H, $CH=CH_2$), 6.84 (m, 2H, ArH), 7.21 (m, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) 14.1, 22.7, 27.6, 28.1, 29.3, 29.4, 29.6, 29.6, 29.6, 29.7, 30.7, 31.9, 38.2, 52.1, 55.2, 55.4, 71.7, 81.4, 81.4, 91.2, 104.8, 113.6, 117.3, 129.2, 130.1, 139.1, 159.1 and 169.5.

Lactone 24

The solution of ester **22** (600 mg, 1.09 mmol) in THF (22 ml) was treated with 10% HCl (20 ml) at RT and the solution was stirred for 5 days. Sat. $NaHCO_3$ was added followed by a normal workup with EtOAc and purification of the residue with 15% EtOAc/petrol gave the lactols (348 mg, 60%). The mixture lactols was dissolved in dry CH_2Cl_2 (12 ml) and cooled to 0 °C and 4 Å molecular sieves (370 mg) and PCC (280 mg, 1.30 mmol) were added. The dark brown suspension was stirred at 0 °C for 2 h before warming to RT over 16 h. The solution was filtered through fluorosil, washed with Et_2O and concentrated. Purification of the crude product by flash chromatography with 5% EtOAc/petrol yielded lactone **24** (318 mg, 55%) as a pale yellow oil. $[\alpha]_D^{25}$ +0.55 (*c* 1.59, CH_2Cl_2); IR (ATR) ν_{max} 2925, 2854, 1794, 1734, 1614, 1515, 1466, 1369, 1247, 1156 and 1035 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, $J=6.98$ Hz, 3H, $C_{11}H_{22}CH_3$), 1.15–1.44 (m, 22H, $C_{11}H_{22}CH_3$), 1.46 (s, 9H, $C(CH_3)_3$), 2.59 (dd, $J=17.89$ and 6.29 Hz, 1H, CH_ACH_B), 2.68 (dd, $J=17.89$ and 7.83 Hz, 1H, CH_ACH_B), 2.75 (td, $J=9.87$ and 3.36 Hz, 1H, CHC$H=CH_2$), 3.81 (s, 3H, $ArOCH_3$), 4.29 (t, $J=7.82$ and 6.29 Hz, 1H, CHOCH_2Ar), 4.42 (d, $J=11.40$ Hz, 1H, OCH_AH_BAr), 4.51 (d, $J=11.58$ Hz, 1H, OCH_AH_BAr), 5.11 (dd, $J=17.16$ and 1.78 Hz, 1H, $CH=CH_AH_B$), 5.22 (dd, $J=10.20$ and 1.87 Hz, 1H, $CH=CH_AH_B$), 5.43 (dd, $J=17.1$ and 10.1 Hz, 1H, $CH=CH_2$), 6.86 (m, 2H, ArH) and 7.21 (m, 2H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.1, 22.7, 27.3, 27.9, 29.2, 29.3, 29.4, 29.6, 29.6, 29.7, 31.9, 35.1, 49.1, 55.3, 72.3, 83.1, 91.9, 113.8, 120.4, 129.0, 129.4, 135.8, 159.5, 167.5 and 173.9; HRMS (ESI): calculated for $C_{32}H_{50}O_6Na$ $[M+Na]^+$ 553.3505; found 553.3503.

α,β-Unsaturated lactone 25

To a biphasic solution of lactone **24** (150 mg, 0.28 mmol) in CH_2Cl_2 and pH 7 buffer solution (2.7/0.4 ml) was added DDQ (130 mg, 0.57 mmol) and the mixture was allowed to stir for 16 h before being filtered through Celite and the was filtrate concentrated. Flash chromatography (10% EtOAc/petrol) of the resulting residue and gave alcohol (103mg, 90%), which was dissolved in pyridine (1 ml) and cooled to 0 °C and MsCl (60 µl, 0.77 mmol) was added and the solution was stirred at 0 °C for 2 h before warming to RT and stirring for an additional 16 h. Water and Et_2O were added and the combined organic extracts were washed with sat. $CuSO_4$, water and dried over $MgSO_4$ and concentrated. Purification by flash chromatography with 10% EtOAc/petrol as eluent gave α, β-unsaturated lactone **25** (86 mg, 78%) as a colourless oil. $[\alpha]_D^{25}$ +50.0 (*c* 1.45, CH_2Cl_2); IR (ATR) ν_{max} 2924, 2854, 1789, 1728, 1370, 1252, 1139, 921 and 825 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, $J=6.96$ Hz, 3H, $C_{11}H_{22}CH_3$), 1.24–1.30 (m, 20H, $C_{10}H_{20}CH_3$), 1.45 (m, 2H, $CH_2C_{11}H_{23}$), 1.48 (s, 9H, $C(CH_3)_3$), 2.84 (td, $J=9.97$ and 3.40 Hz, 1H, CHC$H=CH_2$), 5.09 (d, $J=17.10$ Hz, 1H, $CH=CH_AH_B$), 5.15 (d, $J=10.19$ Hz, 1H, $CH=CH_AH_B$), 5.35 (dt, $J=17.18$ and 9.76 Hz, 1H, $CH=CH_2$), 6.07 (d, $J=5.56$ Hz, 1H, COCH=C*H*), 7.29 (d, $J=5.59$ Hz, 1H, COC*H*=CH) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.1, 22.7, 27.0, 27.9, 28.9, 29.2, 29.3, 29.4, 29.6, 29.6, 31.9, 48.7, 84.0, 92.4, 120.0, 121.7, 134.1, 155.0, 166.3 and 171.9; HRMS (ESI): calculated for $C_{24}H_{40}O_4$ Na $[M+Na]^+$ 415.2822; found 415.2818.

Allylic alcohol 26

A solution of DiBAlH in CH_2Cl_2 (0.9 ml, 1 M, 0.9 mmol) was added to a solution of the lactone **25** (70 mg, 0.18 mmol) in dry CH_2Cl_2 (1 ml) at −78 °C and the resulting solution was allowed to stir at −78 °C for 30 min. The reaction was quenched with 10% HCl and water and the usual workup with EtOAc followed by purification of the crude product by flash chromatography with 15% EtOAc/petrol as eluent yielded diol **26** (50 mg, 70%) as a pale yellow oil. $[\alpha]_D^{25}$ +32.1 (*c* 0.85, CH_2Cl_2); IR (ATR) ν_{max} 3500, 2925, 2854, 1718, 1458, 1370, 1254, 1139 and 1032 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, $J=7.06$ Hz, 3H, $C_{11}H_{22}CH_3$), 1.13–1.36 (m, 22H, $C_{11}H_{22}CH_3$), 1.49 (s, 9H, $C(CH_3)_3$), 2.33 (td, $J=9.29$ and 2.43 Hz, 1H, CHC$H=CH_2$), 2.40 (brs, 1H, CH_2OH), 3.82 (s, 1H, CO*H*), 4.14 (dt, $J=12.83$ and 6.08 Hz, 1H, CH_AH_BOH), 4.31 (dt, $J=13.64$ and 6.19 Hz, 1H, CH_AH_BOH), 5.05 (dd, $J=17.20$ and 1.41 Hz, 1H, $CH=CH_AH_B$), 5.17 (dd, $J=10.20$ and 1.81 Hz, 1H, $CH=CH_AH_B$), 5.51 (d, $J=12.00$ Hz, 1H, $CH_2CH=CH$), 5.59 (dt, $J=17.14$ and 9.94 Hz, 1H, $CH=CH_2$), 5.75 (dt, $J=12.01$ and 6.36 Hz, 1H, $CH_2CH=$ CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.1, 22.7, 27.2, 27.9, 28.2, 29.3, 29.4, 29.5, 29.6, 29.6, 31.9, 52.4, 58.8, 80.2, 83.3, 118.4, 131.8, 132.2, 136.6 and 174.0; HRMS (ESI): calculated for $C_{24}H_{44}O_4Na$ $[M+Na]^+$ 419.3126; found 419.3127.

Diene 28

To a solution of diol **26** (25 mg, 0.063 mmol) in CH_2Cl_2 (1.6 ml) was added 2,6-lutidine (87 mg, 1.27 mmol) and freshly distilled TMSCl (163 µl, 1.27 mmol) and the resulting suspension was stirred at RT for further 24 h.

Sat. $NaHCO_3$ was added to adjust pH then followed by normal workup with Et_2O. The crude bis-silyl ether was directly dissolved in anhydrous methanol (0.5 ml) at 0 °C. A catalytic amount of K_2CO_3 (~10 mg) then was added to the solution and this was stirred for 45 min and a small amount of sat. NH_4Cl was added to adjust pH and followed by normal workup with EtOAc. Purification by flash chromatography with 15% EtOAc/petrol as eluent yielded the allylic alcohol **27** (26 mg, 88%) as a colourless oil, which was dissolved in THF/1-hexene (10:1, 2 ml), and PPh_3 (57 mg, 0.22 mmol) and IPNBSH (58 mg, 0.22 mmol) were added. The reaction was cooled to 0 °C and diethyl azodicarboxylate (35 µl, 0.22 mmol) was added dropwise to the solution. After stirring at 0 °C for 1 h, a solution of TFE in water (650 µl, 1:1) was added and the reaction was warmed up to RT and stirred further 16 h. The usual workup with Et_2O and purification by flash chromatography (100% petrol) yield diene **28** (16 mg, 58%) as a colourless oil. $[\alpha]_D^{25}$ −19.5 (*c* 0.60, CH_2Cl_2); IR (ATR) ν_{max} 2925, 2854, 1738, 1458, 1368, 1258, 1155, 1096 and 840 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.12 (s, 9H, $Si(CH_3)_3$), 0.87 (t, $J=7.1$ Hz, 3H, $C_{11}H_{22}CH_3$), 1.30–1.22 (m, 22H, $C_{11}H_{22}CH_3$), 1.44 (s, 9H, $C(CH_3)$), 2.23 (td, $J=10.6$ and 2.3 Hz, 1H, $CHCH=CH_AH_B$), 2.33 (ddd, $J=21.6$, 14.0 and 7.2 Hz, 2H, $CH_2CH=CH_2$), 5.03–4.95 (m, 3H, $CH_2CH=CH_2$ and $CHCH=CH_AH_B$), 5.11 (dd, $J=10.2$ and 2.3 Hz, 1H, $CHCH=CH_AH_B$), 5.56 (dt, $J=17.3$ and 10.0 Hz, 1H, $CHCH=CH_2$), 5.77–5.65 (m, 1H, $CH_2CH=CH_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 2.9, 14.1, 22.7, 27.2, 28.1, 29.3, 29.4, 29.6, 29.6, 29.6, 29.6, 31.9, 44.3, 52.4, 81.1, 82.9, 117.5, 117.5, 133.9, 138.2 and 173.2; HRMS (ESI): calculated for $C_{27}H_{52}O_3SiNa$ $[M+Na]^+$ 453.3750; found 453.3757.

Tri-*t*-butyl ester *ent*-11

A solution of the diene **28** (40 mg, 0.09 mmol) in CH_2Cl_2 (2 ml) and MeOH (17 µl) was cooled to − 78 °C and ozone was bubbled through the solution until a blue colour persisted. Me_2S (105 mg, 1.7 mmol) was added and the solution allowed to warm to RT for 30 min and then concentrated under reduced pressure. The crude dialdehyde was dissolved in ^{t}BuOH (2.1 ml) and 2-methyl-2-butene (420 µl) and a solution of 80% $NaClO_2$ (150 mg, 1.65 mmol) and NaH_2PO_4 (91 mg, 0.75 mmol) in water (0.7 ml) was added and the biphasic solution was stirred for 16 h. Water and EtOAc were added and the phases were separated and the aqueous phase was adjusted to pH 2 with HCl and further extracted with EtOAc. The combined organic extracts were washed with brine, dried and concentrated and the crude diacid was dissolved in CH_2Cl_2 (1.5 ml) and treated with *N,N′*-diisopropyl-*O-tert*-butylisourea (400 mg, 0.5 ml) for 16 h. The resulting suspension was filtered through a pad of Celite and the filtrate was concentrated and the crude product was purified by flash chromatography (5% EtOAc/petrol) to give triester *ent*-**11** (13 mg, 27%) as a colourless oil. $[\alpha]_D^{25}$ −3.2 (*c* 0.42, CH_2Cl_2); the IR and NMR spectra were identical to those for the (+)-enantiomer; HRMS (ESI): calculated for $C_{30}H_{56}O_7Na$ $[M+Na]^+$ 551.39183; found 551.39178.

(–)-CJ-13,982 (1)

A solution of triester *ent*-**11** (8 mg, 0.015 mmol) in CH_2Cl_2 (3 ml) was cooled to 0 °C and treated with TFA (340 µl) then was stirred at 0 °C for 2 h before warming to RT and stirring for a further 16 h. The volatile organics were removed under reduced pressure gave (–)-CJ-13,982 (**1**) (6 mg, 80%) as a white amorphous powder. $[\alpha]_D^{25}$ −14.1 (*c* 0.25, acetone); lit.[2] $[\alpha]_D^{25}$ −18.3 (*c* 2.6, acetone). The IR and NMR spectra were identical to those for the (+)-enantiomer. HRMS (ESI): calculated for $C_{30}H_{56}O_7Na$ $[M+Na]^+$ 383.2041; found 383.2041.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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