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Studies towards the total synthesis of (−)-callystatin A

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ABSTRACT

The synthesis of C_1–C_{12} and C_{13}–C_{22} fragments of (−)-callystatin A is accomplished employing desymmetrization strategy for the creation of five chiral centers of the polypropionate fragment and application of cross-metathesis (CM) reaction for the first time for this molecule.

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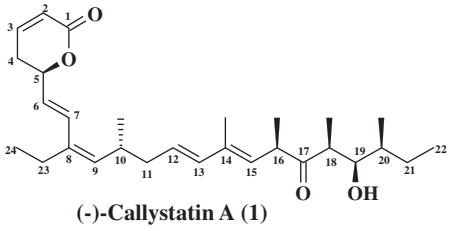
In 1997, Kobayashi et al. isolated the potent antitumor polyketide (−)-callystatin A (**1**) (Fig. 1) from the marine sponge *Callyspongia truncata.*[1] This unique natural product shows remarkable high activity (IC_{50} = 10 pg/mL) against KB tumor cell lines and IC_{50} = 20 pg/mL against L1210 cells. Kobayashi group determined the absolute configuration of the (−)-callystatin A via partial[2] and total synthesis[3] by preparing several structural analogues, which led to further insight on structure–activity relationships.[4] The structure of (−)-callystatin A contains a polypropionate chain and a lactone ring connected to each other by two conjugated diene systems separated by two sp^3 hybridised carbon atoms. Since callystatin A was isolated in very small amounts (1 mg from 100 kg of sponge), attracted more attention to provide material for extensive biological evaluation, along with access to promising novel analogues, led to considerable interest in (−)-callystatin A as a synthetic target. This resulted in several total syntheses[5] and fragment syntheses[6] of the molecule. Based on its intriguing structure and potent cytotoxicity led us to take-up the synthesis of (−)-callystatin A.

Retrosynthetically, disconnecting the carbon backbone at C (6–7) *E*-alkene and C (12–13) *E*-alkene thus dividing the target into three key subunits **3**–**5** (Scheme 1). The subunit **5** could be accessible from (*S*)-Roche ester **6** and the subunit **3** could be made from a bicyclic olefin **8** using desymmetrization strategy. The fragment **2** could be made by a cross-metathesis reaction between a known vinyl lactone **4** and the subunit **5**.

Synthetic strategy for C_7–C_{12} fragment (**5**): synthesis of C_7–C_{12} fragment **5** began with the protection of (*S*)-(+)-Roche ester **6** as its PMB ether followed by reduction of ester group using $LiBH_4$ in THF furnished alcohol **9** in 90% yield. The alcohol **9** was oxidized to aldehyde followed by homologation with (methylene)triphenyl phosphorane in dry THF using *n*-BuLi (1.6 M) to afford alkene **10** in 60% yield. The hydroboration of alkene **10** using $BH_3{\cdot}Me_2S$ complex in dry THF afforded primary alcohol, which was protected as its TBDPS ether **11** in 92% yield using TBDPSCl, imidazole in dry CH_2Cl_2. The oxidative deprotection of PMB group of compound **11** was accomplished using DDQ[7] in CH_2Cl_2:H_2O (9:1) to afford the alcohol **12** in 85% yield. The oxidation of alcohol **12** using IBX in DMSO and CH_2Cl_2 furnished aldehyde, which was then subjected to Still's modification of Horner-Wadsworth–Emmons[8] reaction using NaH and phosphonate salt **S-I** in dry THF at −78 °C to afford the *cis* α,β-unsaturated ester **13** as a major isomer in 88% yield along with the traces of *trans* isomer, that could be separated by column chromatography. The ester group in compound **13** was converted in to alcohol using DIBAL-H to afford the allyl alcohol **14** in 90% yield (Scheme 2). The alcohol **14** was oxidized to aldehyde using IBX and one carbon extension was achieved by homologation of aldehyde with (methylene)triphenyl phosphorane in dry



(-)-Callystatin A (1)

Figure 1.

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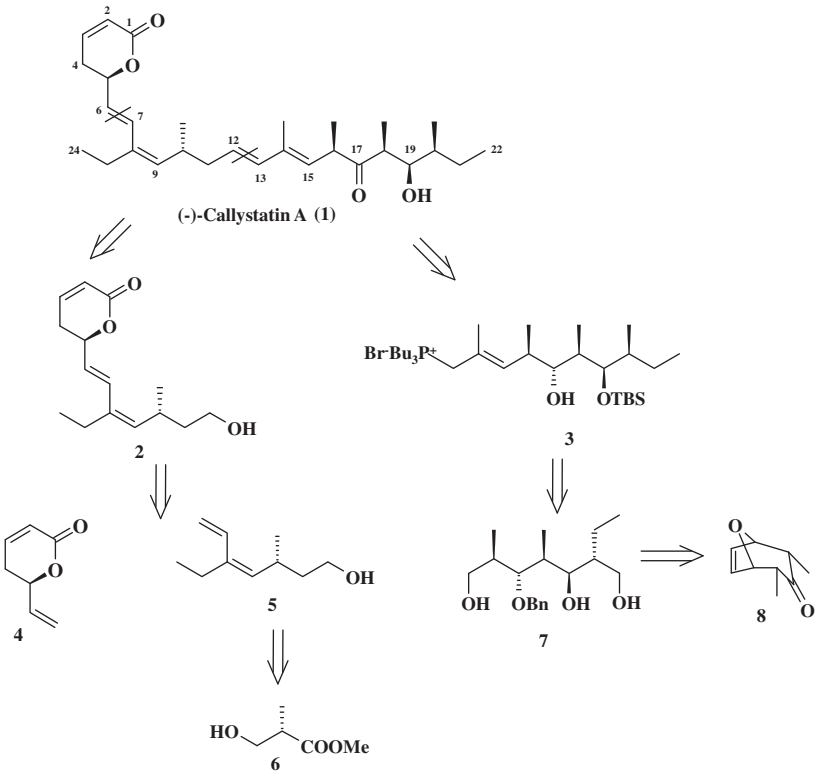
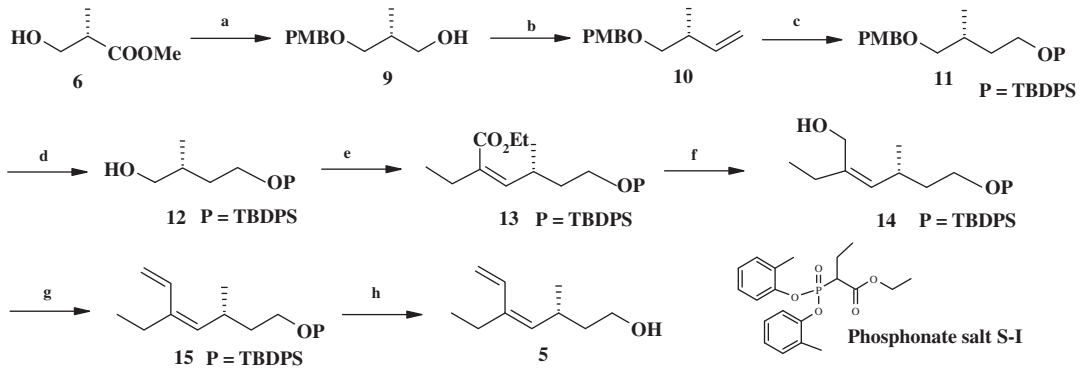
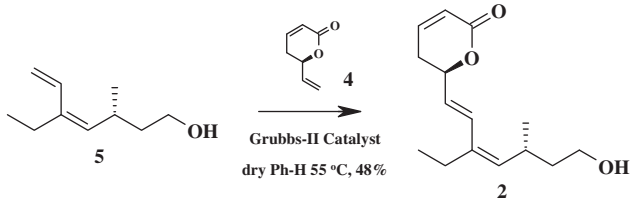


Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions. (a) (i) NaH, PMBBr, dry THF, 0 °C-rt, 3 h, 90%; (ii) $LiBH_4$, EtOH, THF, −10 °C, 2 h. 90%; (b) (i) IBX, DMSO, dry CH_2Cl_2, 0 °C-rt, 2 h, 85%; (ii) $CH_3PPh_3^+Br^-$, *n*-BuLi, dry THF, −78 °C −0 °C, 5 h, 60%; (c) (i) $BH_3{\cdot}Me_2S$, NaOH, H_2O_2, dry THF, 0 °C, 4 h, 65%; (ii) imidazole, TBDPSCl, CH_2Cl_2, 0 °C-rt, 2 h, 92%; (d) DDQ, CH_2Cl_2:H_2O (9:1), 0 °C-rt, 2.5 h, 85%; (e) (i) IBX, DMSO, dry CH_2Cl_2, 0 °C-rt, 2 h, 82%; (ii) NaH, S-I, dry THF, 0 °C- −78 °C 1.5 h, 88%; (f) DIBAL-H, −78 °C, CH_2Cl_2, 2 h, 90%; (g) (i) IBX, DMSO, dry CH_2Cl_2, 0 °C-rt, 2 h, 80%; (ii) $CH_3PPh_3^+Br^-$, *n*-BuLi, dry THF, −78 °C −0 °C, 5 h, 65%; (h) TBAF, THF, 0 °C-rt, 1 h, 85%.

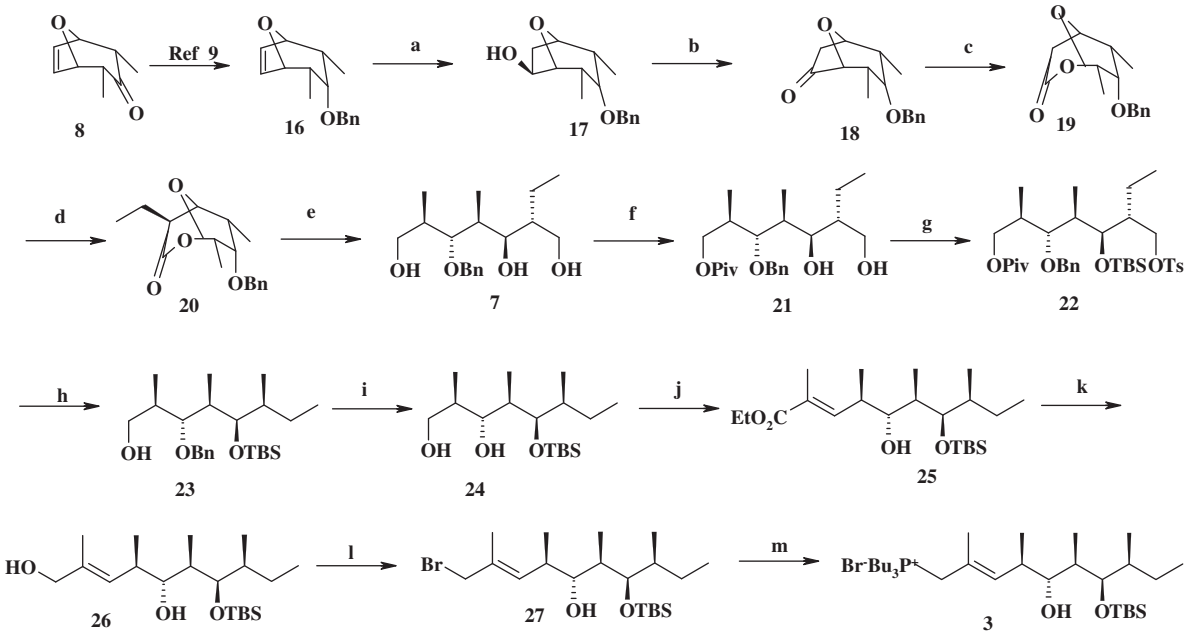


Scheme 3.

THF using *n*-BuLi (1.6 M) to afford diene **15** in 65% yield. The TBDPS group of compound **15** was deprotected to afford the alcohol **5** in 85% yield using TBAF in THF, which completed the synthesis of C_7–C_{12} fragment in an overall 6% yield (Scheme 2).

Coupling of C_7–C_{12} fragment with a vinyl lactone (C_1–C_6 fragment): the fragment **5** and the known vinyl lactone **4**[9] in hand our next attention was turned to couple them together (Scheme 3). Thus the cross-metathesis reaction of **4** and **5** using Grubb's second generation catalyst[10] in dry benzene at 55 °C afforded the key fragment **2** in 48% yield along with the dimer of **4**.

Synthetic strategy for C_{13}–C_{22} fragment (**3**): the synthesis of the C_{13}–C_{22} fragment was started from a bicyclic olefin **16** (Scheme 4), prepared from ketone **8** as reported earlier.[11] Asymmetric hydroboration of olefin **16** using (−)-diisopinocamphenylborane[12] proceeded smoothly to give the alcohol **17** with high enantiomeric purity in 96% yield. The alcohol **17** was converted to the lactone **19** by a two step sequence, PCC oxidation of alcohol **17** followed by Baeyer–Villiger oxidation of the resulting ketone **18**. Alkylation at the α-position of the lactone **19** was achieved by treating it with ethyl iodide in the presence of LDA in dry THF at −78 °C to give a

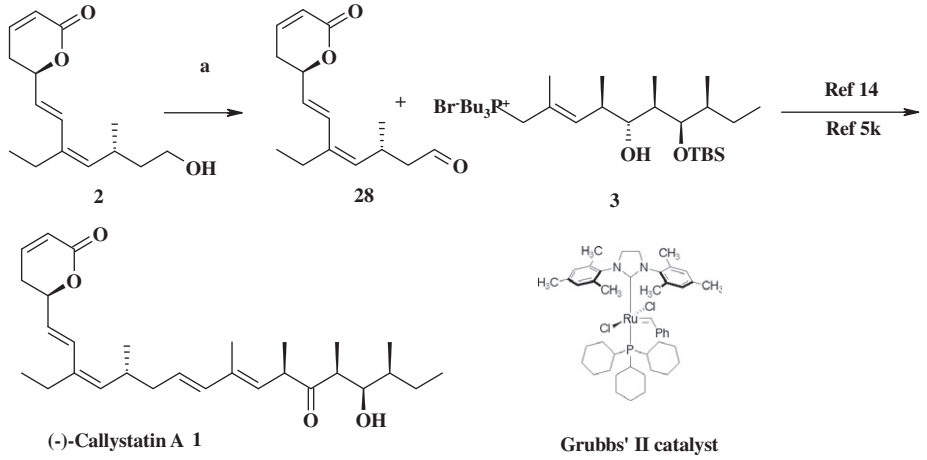


Scheme 4. Reagents and conditions. (a) (−)-Ipc$_2$BH, NaOH, H_2O_2, 7d, 96%; (b) PCC dry CH_2Cl_2, 0 °C-rt, 3 h, 85%; (c) *m*-CPBA, $NaHCO_3$, 0 °C-rt, 2 h, 90%; (d) LDA, Ethyl iodide, dry THF, −78 °C 5 h, 85%; (e) LAH, dry THF, 0 °C-rt, 4 h, 80%; (f) (i) 2,2-DMP, PPTS, 0 °C-rt, dry CH_2Cl_2, 12 h, 80%; (ii) pivolyl chloride, Et_3N, dry CH_2Cl_2, 0 °C-rt, 12 h, 85%; (iii) *p*-TsOH, MeOH, 0 °C-rt, 10 h, 75%; (g) (i) *p*-TsCl, *n*-Bu_2SnO, Et_3N, dry CH_2Cl_2, 0 °C-rt, 10 h, 70%; (ii) TBSTf, 2,6-lutidine, dry CH_2Cl_2, 0 °C-rt, 1 h, 85%; (h) LAH, dry THF, 0 °C-rt, 4 h, 85%; (i) Li, liq. NH_3, dry THF, 30 min, 80%; (j) (i) dry DMSO, $(COCl)_2$, Et_3N, dry CH_2Cl_2, −78 °C; (ii) PPh_3=CCH_3CO_2Et, dry benzene, rt, 12 h, 80% (over two steps); (k) DIBAL-H, dry CH_2Cl_2, −78 °C, 2 h, 80%; (l) CBr_4, PPh_3, 2,6-lutidine, CH_3CN, 30 min, 93%; (m) PBu_3, CH_3CN, 30 min.

compound **20** in 85% yield. Now, the attention was directed towards the opening of lactone ring. Lactone **20** on treatment with LAH in dry THF gave a polar compound in 80% yield, which was found to be the expected triol **7** with the required five chiral centres (Scheme 4). 1,3-Diol group in **7** was protected as its acetonide and the primary hydroxyl group was protected as its pivolate ester using pivolyl chloride and Et_3N in dry CH_2Cl_2 at 0 °C followed by deprotection of acetonide group using catalytic amount of *p*-TsOH in methanol to yield diol **21** in 75% yield. Diol **21** on selective primary tosylation with *p*-TsCl, Et_3N and catalytic amount of *n*-dibutyltin oxide at room temperature furnished mono tosylate and the protection of secondary hydroxyl group as TBS ether using TBSOTf, 2,6-lutidine in dry CH_2Cl_2 which afforded **22** in 85% yield. Compound **22** was refluxed with 2 equiv of LAH in dry THF which resulted in tosyl group removal as well as pivolyl deprotection to yield compound **23** in 80% yield. The compound **23** was subjected to debenzylation using 10 equiv of Li metal in liq NH_3 giving diol **24** in 80% yield. The primary hydroxyl group of diol **24** was selectively oxidized under Swern[13] oxidation conditions followed by Wittig reaction with carbethoxyethylidene triphenylphosphorane in refluxing dry CH_2Cl_2 to give α,β-unsaturated ester **25** in 80% yield for the two step sequence. The ester **25** on DIBAL-H reduction gave allylic alcohol **26** in 80% yield, which was then converted to allyl bromide **27** using PPh_3, 2,6-lutidine and CBr_4 in dry CH_3CN in 80% yield. The allylic bromide **27** was converted to its phosphonium salt **3** using PBu_3, thus completing the synthesis of C_{13}-C_{22} fragment in an overall 6.1% yield.

The alcohol **2** was converted to the corresponding aldehyde **28** in 65% yield using IBX in DMSO/CH_2Cl_2 (Scheme 5). Since the coupling[14] of **28** with the phosphonium salt **3** and the conversion of coupling product to the synthesis of (−)-callystatin A is already reported,[5k] this constitutes a formal synthesis of (−)-callystatin A.

In conclusion, we have accomplished the C_1–C_{12} and C_{13}–C_{22} Fragments of (−)-callystatin A in a highly convergent way, by using



Scheme 5. Reagents and conditions. (a) IBX, dry CH_2Cl_2, DMSO, 2 h, 65%.

desymmetrization strategy, HWE and cross-metathesis reactions as key steps.

Acknowledgments

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Selected spectral data: 1-methoxy-4-([(2R)-2-methyl-3-butenyl]oxymethyl) benzene (**10**): $[\alpha]_D^{25}$: (−)22.2 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.19 (d, 2H, *J* = 8.3 Hz), 6.81 (d, 2H, *J* = 8.3 Hz), 5.81–5.69 (m, 1H), 5.01–4.96 (m, 2H), 4.41 (s, 2H), 3.79 (s, 3H), 3.34–3.19 (m, 2H), 2.51–2.41 (m, 1H), 1.02 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159, 141.2, 130.5, 129.1, 113.9, 113.6, 74.6, 72.5, 55.1, 37.7, 16.5; IR (neat): 2959, 2854, 1612, 1515, 1247, 1092, 1036, 914 cm^{-1}; EIMS: 229 (M^++23).
(2R)-4-[1-(tert-Butyl)-1,1-diphenylsilyl]oxy-2-methylbutan-1-ol (**12**): $[\alpha]_D^{25}$: (+)6.8 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.66 (m, 4H), 7.41–7.35 (m, 6H), 3.78–3.64 (m, 2H), 3.51–3.41 (m, 2H), 2.29 (br s, 1H), 1.88–1.77 (m, 1H), 1.67–1.56 (m, 1H), 1.53–1.41 (m, 1H), 1.05 (s, 9H), 0.91 (d, 3H, *J* = 6.7 Hz); IR (neat): 3349, 3062, 2938, 2868, 1468, 1428, 1106, 1003, 815, 702 cm^{-1}; EIMS: 343 (M^++1).
Ethyl (Z,4R)-6-[1-(tert-butyl)-1,1-diphenylsilyl]oxy-2-ethyl-4-methyl-2-hexenoate (**13**): $[\alpha]_D^{25}$: (+)25.6 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.66–7.61 (m, 4H), 7.41–7.33 (m, 6H), 5.51 (d, 1H, *J* = 10.1 Hz), 4.14 (q, 2H, *J* = 7.1, 14.3 Hz), 3.61 (dt, 2H, *J* = 1.3, 5.8 Hz), 3.18–3.07 (m, 1H), 2.21 (q, 2H, *J* = 7.5, 15.2 Hz), 1.62–1.51 (m, 2H), 1.24 (t, 3H, *J* = 7.1 Hz), 1.02 (s, 9H), 0.99 (d, 3H, *J* = 3.3 Hz), 0.96 (t, 3H, *J* = 2.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 168.2, 144.9, 135.5, 133.9, 132.7, 129.4, 127.5, 62.2, 59.9, 40, 30.2, 27.2, 26.7, 20.8, 20.4, 19.2, 14.2, 13.6; IR (neat): 2961, 2932, 1713, 1644, 1107, 703 cm^{-1}; EIMS: 439 (M^++1).
tert-Butyl[(3R,4Z)-5-ethyl-3-methyl-4,6-heptadienyl]oxydiphenylsilane (**15**): $[\alpha]_D^{25}$: (−)4.4 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.64–7.59 (m, 4H), 7.38–7.29 (m, 6H), 6.69 (dd, 1H, *J* = 11.3, 17.4 Hz), 5.19 (d, 1H, *J* = 17.4 Hz), 5.02 (dd, 2H, *J* = 9.2, 21.5 Hz), 3.59 (t, 2H, *J* = 7.1 Hz), 2.92–2.84 (m, 1H), 2.16 (q, 2H, *J* = 7.1, 14.3 Hz), 1.63–1.56 (m, 1H), 1.46–1.36 (m, 1H), 1.03 (s, 9H), 1.02 (t, 3H, *J* = 7.1 Hz), 0.95 (d, 3H, *J* = 6.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137, 135.5, 134, 133.2, 129.4, 127.5, 112.6, 61.8, 40.7, 27.8, 26.9, 25.8, 21.3, 19.1, 13.4; IR (neat): 2959, 2930, 2861, 1640, 1592, 1463, 1107, 988, 702 cm^{-1}; EIMS: 393 (M^++1).
(3R,4Z)-5-Ethyl-3-methyl-4,6-heptadien-1-ol (**5**): $[\alpha]_D^{25}$: (−)30.0 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 6.66 (dd, 1H, *J* = 10.7, 17.5 Hz), 5.22 (d, 1H, *J* = 17.5 Hz), 5.09 (dd, 2H, *J* = 10.7, 20.5 Hz), 3.62–3.52 (m, 2H), 2.83–2.76 (m, 1H), 2.20 (q, 2H, *J* = 7.8, 15.6 Hz), 1.66–1.59 (m, 1H), 1.48–1.4 (m, 1H), 1.06 (t, 3H, *J* = 7.8 Hz), 0.99 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 139.8, 134.9, 132.7, 113.8, 61.2, 40.3, 28.3, 25.8, 21.5, 13.4;IR (neat): 3484, 2962, 2873, 1639, 1457, 1057, 993, 902 cm^{-1}; EIMS: 177 (M^++23).
2R,3R,4S,5R,6R)-5-(Benzyloxy)-2-ethyl-4,6-dimethylheptane-1,3,7-triol (**7**): $[\alpha]_D^{25}$: (−) 4.5 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.30 (m, 5H), 4.65 (s, 2H), 3.96–3.49 (m, 6H), 2.07–1.84 (m, 2H), 1.65–1.51 (m, 1H), 1.29–1.17 (m, 1H), 1.12 (d, 3H, *J* = 7.5 Hz), 1.10–0.98 (m, 1H), 0.96 (d, 3H, *J* = 7.5 Hz), 0.92 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 137.5, 128.6, 128.1, 127.8, 127.1, 88.5, 76.3, 74.9, 65.3, 65.0, 43.8, 37.8, 35.5, 20.7, 14.7, 11.7, 11.3; IR (neat): 3419, 3295, 2963, 1042 cm^{-1}; FAB mass: *m*/*z* 311 (M^++1).
(2R,3R,4R,5R,6R)-3-(Benzyloxy)-5-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-2,4-dimethyl-6-([(4-methylphenyl)sulfonyl]oxymethyl)octyl pivalate (**22**): $[\alpha]_D^{25}$: (+) 5.4 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.72 (d, 2H, *J* = 8.1 Hz), 7.33–7.29 (m, 7H), 4.57 (s, 2H), 4.27–4.07 (m, 2H), 3.98–3.89 (m, 3H), 3.33–3.27 (m, 1H), 2.44 (s, 3H), 2.16–1.68 (m, 3H), 1.34–1.41 (m, 2H), 1.20 (s, 9H), 1.10 (s, 3H), 0.88 (d, 3H, *J* = 6.8 Hz), 0.86 (s, 9H), 0.80 (t, 3H, *J* = 7.6 Hz), 0.06 (s, 3H), 0.01 (s, 3H); IR (neat): 2970, 1723, 1300, 1170 cm^{-1}; FAB mass: *m*/*z* 663 (M^++1).
(E, 4R, 5R, 6R, 7R, 8S)-7-[1-(tert-Butyl)-1,1-dimethylsilyl] oxy-2,4,6,8-tetramethyl-2-decene-1, 5-diol (**26**): $[\alpha]_D^{25}$: (+) 16.3 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ = 5.55 (d, 1H, *J* = 9.5), 4.01 (s, 2H), 3.70 (t, 1H, *J* = 2.9 Hz), 3.61 (dd, 1H, *J* = 10.2, 2.2 Hz), 2.4–2.6 (m, 1H), 1.78–1.70 (m, 1H), 1.68 (d, 3H, *J* = 1.1 Hz), 1.6 (m, 1H), 1.40–1.20 (m, 2H), 1.05 (d, 3H, *J* = 6.9 Hz), 0.99 (d, 3H, *J* = 6.9 Hz), 0.91 (s, 9H), 0.90 (t, 3H, *J* = 7.3 Hz), 0.73 (d, 3H, *J* = 6.9 Hz), 0.10 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 134.4, 126.5, 79.9, 76.1, 68.8, 40.8, 35.5, 34.5, 28.4, 25.4, 17.6, 14.9, 13.4, 11.6, −4.6, −5.1; IR (neat): 3423, 2930, 2360, 1219, 1013 cm^{-1}; FAB mass: *m*/*z* 359 (M^++1).
(6R)-6-[(1E,3Z,5R)-3-Ethyl-7-hydroxy-5-methyl-1,3-heptadienyl]-5,6-dihydro-2H-2-pyranone (**2**): $[\alpha]_D^{25}$: (−) 38.5 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ = 6.92–6.82 (m, 1H), 6.68 (d, 1H, *J* = 15.8 Hz), 6.03 (d, 1H, *J* = 9.8 Hz), 5.75 (dd, 1H, *J* = 6.6, 15.8 Hz), 5.19 (d, 1H, *J* = 9.8 Hz), 5.04–4.99 (m, 1H), 3.65–3.45 (m, 2H), 2.88–2.75 (m, 1H), 2.52–2.42 (m, 2H), 2.19 (q, 2H, *J* = 7.3 Hz), 1.68–1.56 (m, 1H), 1.49–1.37 (m, 1H), 1.07 (t, 3H, *J* = 7.3 Hz), 1.00 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 164.5, 145.5, 140.8, 138.0, 137.2, 122.8, 121.8, 79.0, 61.2, 40.1, 30.1, 28.2, 21.2, 20.1, 13.8; IR (neat): 3430, 2967, 1715, 1647, 1457, 1382, 1248, 1052 cm^{-1}; FAB mass: *m*/*z* 273 (M^++23).