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An asymmetric synthesis of 7-hydroxy-9-propylnonenolide (herbarumin III)

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Abstract—An asymmetric synthesis of herbarumin III has been developed using (*R*)-cyclohexylidene glyceraldehyde **1** as the chiral template. The key steps of the synthesis were the enantioselective preparation of the required homoallylic alcohol from **1**, an asymmetric dihydroxylation, and a ring-closing metathesis reaction for the macrolactonization.

1. Introduction

Lactone functionality is ubiquitous amongst natural products.[1a] Of these, γ- and δ-lactones are abundant as insect pheromones, constituents of butter fats, fruits, etc. Even large ring macrolides can be extensively found in various natural sources, showing a diverse array of bioactivity.[1b,c] However, lactones with a medium ring size (8–10 membered) are rare, while their syntheses are also challenging. One such compound, (7*R*,9*R*,5*E*)-7-hydroxy-9-propylnonenolide **I** has been isolated from the mycelium and culture broth of the fungus *Phoma herbarum* Westend (Sphaeropsidaceae).[2a] Previously, two other similar macrolides, one containing a hydroxyl group at C-8 and another with two hydroxyl groups at C-8 and C-2, were also isolated from the same fungus.[2b] The last two compounds and compound **I** have been trivially named as herbarumins I, II, and III, respectively. In an assay monitoring the radical elongation of *Amaranthus hypochondriacus* seedlings, all these compounds exhibited significant phytotoxic effects at very low concentrations.[2b] Compound **I** inhibited radical growth with 10 times higher potency than 2,4-dichlorophenoxyacetic acid,[2a] its antifungal activity was equal to that of herbarumin I and better than herbarumin II. The level of activity, together with the fact that closely related compounds such as pinolidoxin[3a] and lethaloxin,[3b] also show significant phytotoxicity renders this class of compounds as promising herbicidal agents. Furthermore, compound **I** also interacts with bovine-brain calmodulin and inhibits the activation of the calmodulin-dependent enzyme cAMP phosphodiesterase.[2a]

2. Results and discussion

In view of the above importance of **I**, we attempted its enantiomeric synthesis (Scheme 1). So far the asymmetric syntheses of the herbarumins I and II using various sugars, such as D-ribonolactone and L-arabinose,[4a–c] and asymmetric reactions[4d] have been reported. While the present work was under completion, three asymmetric syntheses of **I** have been reported from D-glucose.[4e–g] The present synthesis is based upon using (*R*)-cyclohexylidene glyceraldehyde **1**[5a–c] as a chiral template and a substrate-controlled asymmetric dihydroxylation (ADH)[6] with the Sharpless' reagent to incorporate the asymmetric centers, while the formation of the macrolide skeleton was accomplished by a ring-closing metathesis (RCM)[7] of a suitable diene. The cyclohexylidene group in **1** also provided one of the alkene groups required for the RCM reaction.

For the synthesis, *syn*-homoallylic alcohol **2** was prepared conveniently on a multi-gram scale following a known procedure.[8] The stereochemistry of **2** was confirmed from the ^{1}H NMR resonances of its –CH_2O and –CHO groups.[5a]

The presence of cyclohexylidene protection in the starting chiron increased its hydrophobicity, as well as that of the product carbinol, ensuring easy isolation by extraction with apolar organic solvents. Moreover, the

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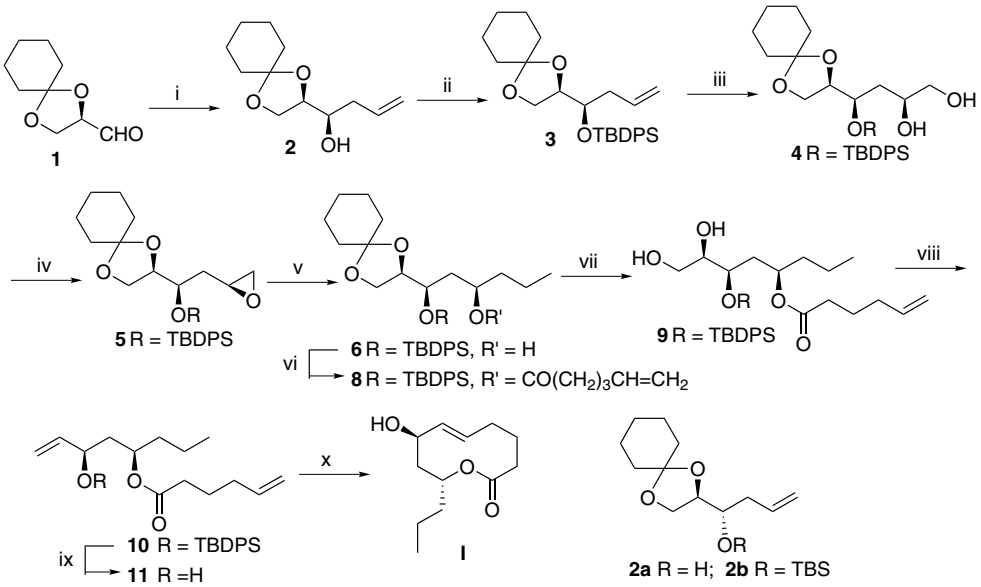


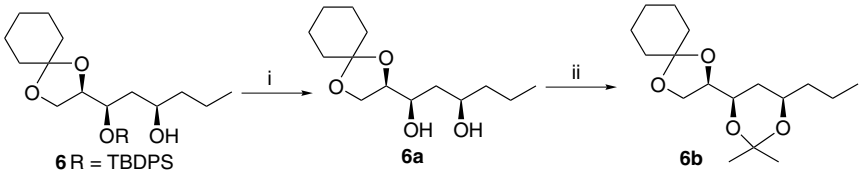
Scheme 1. Reagents and conditions: (i) Ref. 8, (ii) TBDPSCl/imidazole/CH_2Cl_2 (88%), (iii) AD mix-β/*t*-BuOH–H_2O (1:1) (78%), (iv) *p*-TsCl/pyridine (94%); K_2CO_3/MeOH (86%), (v) EtMgBr/Cu_2Br_2/THF/−78 °C (72%), (vi) CH_2=$CH(CH_2)_3COOH$ (**7**)/DCC/DMAP (cat.)/CH_2Cl_2 (69%), (vii) aqueous TFA (81%), (viii) MsCl/pyridine; Zn/NaI/DMF/Δ (63%), (ix) TBAF/THF/−78 °C (88%), (x) Grubb's second generation catalyst/CH_2Cl_2 (63%).

protecting group was quite stable, even under weakly acidic conditions allowing the required addition to be carried out in aqueous NH_4Cl solution.

Compound **2** was silylated with TBDPSCl to furnish **3**. Previously, we found[9] that irrespective of the ADH reagent[6] (AD mix-α[$K_2OsO_2(OH)_4$ and $(DHQ)_2$-PHAL] or AD mix-β[$K_2OsO_2(OH)_4$ and $(DHQD)_2$-PHAL]) used, the asymmetric dihydroxylation of the TBS-derivative **2b**, an epimer of **2** with a less bulky silyl substitution proceeds predominantly from the α-face, furnishing the 2,4-*syn*-product. However, while the *syn*:*anti* ratio was 77.5:22.5 with the AD mix-α reagent, the same was 95.5:4.5 with the β-reagent. It was of interest to investigate whether the reaction also follows a similar stereochemical course with the *syn*-compound **3** containing the β-silyloxy group. This observation was critical for the synthesis of **I**. Given that the AD mix-β reagent gave a better *syn*-selectivity with **2b**, compound **3** was subjected to the ADH reaction with the same reagent. It was gratifying to note that the reaction not only proceeded as per our expectation, but the bulky silyl protection (OTBDPS) actually ensured absolute 2,4-*syn*-selectivity and furnished **4** as the sole product. The 2,4-*syn*-stereochemistry of **4** could easily be assessed by comparison of its ^1H and ^{13}C NMR spectra with those of the product obtained earlier by the ADH reaction of **2b**.[9] This was further confirmed at a latter stage.

Regioselective monotosylation of the primary hydroxyl group of **4** with *p*-toluenesulfonyl chloride (*p*-TsCl)/pyridine, followed by base treatment, furnished epoxide **5**. The reaction of **5** with EtMgBr in the presence of catalytic CuBr proceeded smoothly thus furnishing alcohol **6** as the only product. There was no trace of the formation of the primary carbinol due to the ring opening at the secondary epoxide-site. The *syn*-stereochemistry at C-3 and C-5 centers of **6** was determined by its derivatization to the corresponding acetonide **6b** and analyzing the ^{13}C NMR resonances. Thus, desilylation of **6** afforded **6a**, which was converted to **6b** by acetalization with 2,2-dimethoxypropane (Scheme 2). In its ^{13}C NMR spectrum, the signals at δ 19.6 and 31.3 (two methyls) and at δ 98.4 (acetal carbon) of the six-membered acetonide moiety confirmed the 2,4-*syn* relationship[10a,b] of **6b**, and thus of **6**.

1,3-Dicyclohexylcarbodiimide (DCC) promoted the esterification of **6** with 5-hexenoic acid **7**, which proceeded very slowly. After stirring for 5 days at room



Scheme 2. Reagents and conditions: (i) TBAF/THF/−78 °C, (ii) 2,2-dimethoxypropane/*p*-TsOH.

temperature, ester **8** was obtained in ~45% yield. The overall yield could be improved upon to 69% by re-esterification of the recovered **6** with acid **7**. Its deacetalization in the presence of aqueous trifluoroacetic acid (TFA) furnished diol **9** uneventfully. Mesylation of **9** with excess mesyl chloride furnished the corresponding dimesylate, which on heating with NaI in the presence of Zn-dust in DMF, gave the olefin **10**.

Compound **10** possessed all the structural requirements, as well as the sense of chirality to be converted to the target macrolide, via a ring closing metathesis (RCM) reaction. The RCM reaction provides remarkable scope for the synthesis of medium-sized rings and macrocyclic products, and is being used extensively.[7] Although due to the inherent ring strain, construction of the medium sized 8–11-membered cycloalkenes via the RCM reaction is very challenging,[11a] some precedents exist.[11b–k] The presence of a suitable functionality and its distance from the olefins play key roles in the success of the reaction. It has been reported[7c] that the RCM reaction proceeds satisfactorily with substrates possessing a 5-hexenoate ester moiety as is present in **10**. All these considerations made us feel confident in the present endeavor.

However, the attempted RCM of **10** in the presence of Grubb's second generation catalyst led to undesired dimerization. Consequently, compound **10** was desilylated to **11** and subjected to the RCM reaction using the Grubb's second generation catalyst. We were pleased to find that the reaction proceeded smoothly under dilute conditions to afford the title compound **I** as the only major product, which was isolated in its pure form by chromatography over a $AgNO_3$-silica gel column. The compound was characterized from its chiroptical and spectral data. Compared to the reported[2a] $[\alpha]_D^{22} = +22.0$ (*c* 0.1, EtOH) of **I**, the specific rotation ($[\alpha]_D^{25}$) of our synthetic compound was +21.9 (*c* 0.88, EtOH).

It is worth mentioning that although the synthesis of alcohol **3** requires three steps, we have been preparing this very conveniently in multi-gram scales for its application in various syntheses. Overall, we have developed a highly asymmetric synthesis of **I** employing operationally simple reactions.

3. Experimental

3.1. General methods

General information regarding instruments, techniques, and source of chemicals used were the same as mentioned in our previous publications.[5a–c] The ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded in $CDCl_3$ with a Bruker AC 200. The optical rotations were recorded with a Jasco 364 DIP polarimeter.

3.1.1. (4*R*,5*R*)-4-*tert*-Butyldiphenylsilyloxy-5,6-cyclohexylidenedioxyhex-1-ene 3. To a well stirred solution of **2**[8] (2.8 g, 13.21 mmol) and imidazole (1.1 g, 16.1 mmol) in CH_2Cl_2 (40 mL) was added TBDPSCl (4.39 g, 16.0 mmol) in CH_2Cl_2 (20 mL) and the mixture was stirred overnight. This was then poured into water, the organic layer separated, and the aqueous layer extracted with $CHCl_3$. The combined organic extracts were washed with water and brine, and dried. Solvent removal and column chromatography of the residue (silica gel, 0–10% EtOAc/hexane) afforded **3** (5.23 g, 88%). Colorless liquid; $[\alpha]_D^{25} = -2.7$ (*c* 1.04, $CHCl_3$); IR: 3049, 991, 910 cm^{-1}; ^{1}H NMR: δ 1.09 (s, 9H), 1.27–1.61 (m, 10H), 2.18–2.24 (m, 2H), 3.68–3.72 (m, 1H), 3.82–3.94 (m, 2H), 4.08–4.15 (m, 1H), 4.88–4.97 (m, 2H), 5.65–5.73 (m, 1H), 7.38–7.42 (m, 6H), 7.71–7.75 (m, 4H); ^{13}C NMR: δ 19.5, 23.8, 25.3, 26.6, 26.8, 27.0, 34.5, 36.0, 37.9, 65.2, 73.8, 77.8, 109.8, 117.4, 127.7, 129.1, 129.6, 130.1, 133.9, 134.2, 134.9, 135.2, 136.1, 137.2; MS (EI, 70 eV): *m*/*z* (%) 450 (7.9, M^+), 394 (50), 295 (36), 278 (27), 253 (19), 218 (59), 200 (58), 183 (46), 140 (65), 136 (100), 117 (24), 83 (25), 59 (75). Anal. Calcd for $C_{28}H_{38}O_3Si$: C, 74.62; H, 8.50. Found: C, 74.77; H, 8.32.

3.1.2. (2*S*,4*R*,5*R*)-4-*tert*-Butyldiphenylsilyloxy-5,6-cyclohexylidenedioxyhexane-1,2-diol 4. A solution of **3** (2.25 g, 5.0 mmol) in a solvent mixture of *t*-BuOH/water (1:1, 25 mL) was added to a cooled (0 °C) and stirred suspension of AD mix-β (7.0 g) in the same solvent mixture (120 mL). The mixture was stirred at 0 °C for 18 h, treated with solid Na_2SO_3 (7.0 g), stirred for a further 1 h at room temperature, and extracted with $CHCl_3$. The organic extract was washed with water, brine and dried. Solvent removal and column chromatography of the residue (silica gel, 0–5% MeOH/$CHCl_3$) afforded **4** as the sole product (1.89 g, 78%). Colorless viscous oil; $[\alpha]_D^{25} = +11.9$ (*c* 0.94, $CHCl_3$); IR: 3418, 3071, 933 cm^{-1}; ^{1}H NMR δ 1.06 (s, 9H), 1.25–1.75 (m, 12H), 2.68 (br s, 2H), 3.18–3.42 (m, 2H), 3.63–3.80 (m, 1.5H), 3.89–3.97 (m, 1.5H), 4.07–4.23 (m, 2H), 7.37–7.40 (m, 6H), 7.67–7.70 (m, 4H); ^{13}C NMR: δ 13.8, 19.2, 23.7, 24.9, 26.7, 26.9, 34.6, 35.7, 37.7, 38.5, 66.6, 71.9, 73.4, 73.7, 75.5, 109.9, 126.0, 127.0, 127.7, 128.1, 129.9, 130.3, 133.2, 133.4, 134.5, 135.6, 135.8, 136.9; MS (EI, 70 eV): *m*/*z* (%) 484 (22, M^+), 427 (20), 350 (25), 298 (31), 269 (58), 252 (96), 234 (92), 221 (62), 200 (100), 181 (31), 139 (62), 117 (54), 113 (58), 81 (46), 57 (33). Anal. Calcd for $C_{28}H_{40}O_5Si$: C, 69.38; H, 8.32. Found: C, 69.52; H, 8.15.

3.1.3. (2*S*,4*R*,5*R*)-4-*tert*-Butyldiphenylsilyloxy-5,6-cyclohexylidenedioxy-1,2-epoxyhexane 5. To a cooled (0 °C) and stirred solution of **4** (1.7 g, 3.51 mmol) and pyridine (2.0 mL) in CH_2Cl_2 (20 mL) was added *p*-toluenesulfonyl chloride (*p*-TsCl) (0.669 g, 3.5 mmol) in portions. After stirring for 12 h, the mixture was poured into ice-water, the organic layer separated, and the aqueous portion was extracted with $CHCl_3$. The combined organic extracts were washed with aqueous 2 M HCl, water, and brine and dried. Removal of the solvent followed by column chromatography (silica gel, 0–20% EtOAc/hexane) of the residue afforded the monotosylate (2.10 g, 94%) as a colorless liquid; IR: 3450, 1588, 1364, 1176 cm^{-1}; ^{1}H NMR: δ 1.02 (s, 9H), 1.30–1.60 (m,

10H), 1.60–1.71 (m, 2H), 2.44 (s, 3H), 3.48–3.57 (m, 1H), 3.60–3.77 (m, 4H), 3.80–4.13 (m, 2H), 7.28–7.40 (m, 8H), 7.42–7.74 (m, 6H); ^{13}C NMR: δ 19.2, 21.5, 26.5, 26.7, 26.9, 37.4, 69.7, 70.9, 72.9, 74.8, 76.2, 109.1, 117.7, 127.7, 127.9, 129.2, 129.7, 129.9, 130.3, 132.4, 132.5, 133.2, 135.5, 135.8, 145.1.

To a stirred and cooled (0 °C) solution of the above tosylate (2.1 g, 3.29 mmol) in MeOH (15 mL) was added solid anhydrous K_2CO_3 (0.92 g, 6.5 mmol) and the mixture stirred at 0 °C for 3 h (cf. TLC). The mixture was filtered, concentrated in vacuo, the residue was extracted with EtOAc, the organic extract was washed with H_2O and brine, and dried. Removal of solvent and column chromatography (0–10% EtOAc/hexane) of the residue afforded the pure epoxide **5** (1.32 g, 86%) as a colorless liquid; $[\alpha]_D^{25} = -13.6$ (*c* 1.14, $CHCl_3$); IR: 1483, 1427, 1369, 1163 cm^{-1}; ^{1}H NMR: δ 1.05 (s, 9H), 1.25–1.73 (m, 12H), 2.25–2.29 (dd, $J = 2.6$ and 5.0 Hz, 1H), 2.63–2.67 (m, 1H), 2.93–3.15 (m, 1H), 3.60–3.75 (m, 1H), 3.87–3.94 (m, 2H), 4.05–4.20 (m, 1H), 7.37–7.44 (m, 6H), 7.66–7.73 (m, 4H); ^{13}C NMR: δ 19.4, 23.9, 25.2, 26.9, 27.1, 34.8, 36.1, 37.4, 48.9, 55.2, 66.5, 72.4, 75.1, 109.6, 127.7, 129.9, 133.5, 136.1; MS (EI, 70 eV): *m*/*z* (%) 466 (77, M^+), 423 (26), 409 (41), 384 (38), 351 (71), 334 (87), 322 (100), 310 (100), 294 (100), 266 (100), 254 (30), 225 (61), 200 (98), 183 (57), 136 (88), 117 (77), 84 (99), 69 (60), 56 (100). Anal. Calcd for $C_{28}H_{38}O_4Si$: C, 72.06; H, 8.21. Found: C, 72.24; H, 8.37.

3.1.4. (4*R*,6*R*,7*R*)-6-*tert*-Butyldiphenylsilyloxy-7,8-cyclohexylidenedioxyoctan-4-ol 6. A solution of EtMgBr [prepared from EtBr [0.86 g, 7.9 mmol] and Mg [0.19 g, 7.8 mmol]] in dry THF (20 mL) was added dropwise to a stirred and cooled (−30 °C) suspension of Cu_2Br_2 (0.5 g) in THF (20 mL). After stirring for 10 min, epoxide **5** (1.22 g, 2.62 mmol) in THF (15 mL) was added. Stirring was continued overnight, gradually warming the mixture to 0 °C. The mixture was poured into saturated NH_4Cl solution (20 mL) and extracted with ether. The extract was dried and concentrated in vacuum. The residue was purified by column chromatography (silica gel, 0–10% EtOAc/hexane) to give **6** (0.935 g, 72%) as a colorless liquid; $[\alpha]_D^{25} = +6.5$ (*c* 0.42, $CHCl_3$); IR: 3384, 1478, 1061 cm^{-1}; ^{1}H NMR: δ 0.84 (dist. t, 3H), 1.03 (s, 9H), 1.20–1.66 (m, 14H), 1.79–2.04 (m, 2H), 3.06–3.31 (m, 1H), 3.44–3.69 (m, 1H), 3.75–3.90 (m, 1H), 3.93–4.06 (m, 1H), 4.07–4.19 (m, 1H), 7.27–7.50 (m, 6H), 7.66–7.75 (m, 4H); ^{13}C NMR: δ 14.0, 18.7, 19.5, 23.7, 25.2, 26.9, 27.2, 34.5, 35.9, 39.8, 67.5, 73.1, 74.8, 75.2, 109.9, 125.8, 127.5, 128.1, 129.1, 131.7, 134.8, 135.9; MS (EI, 70 eV): *m*/*z* (%) 496 (27, M^+), 439 (26), 410 (29), 351 (47), 297 (56), 279 (62), 264 (99), 253 (100), 225 (98), 208 (69), 190 (99), 176 (98), 52 (89). Anal. Calcd for $C_{30}H_{44}O_4Si$: C, 72.53; H, 8.93. Found: C, 72.29; H, 8.78.

3.1.5. (4*R*,6*R*,7*R*)-6-*tert*-Butyldiphenylsilyloxy-7,8-cyclohexylidenedioxyoctan-4-yl 5′-hexenoate 8. A mixture of **6** (0.992 g, 2.0 mmol), acid **7** (0.365 g, 3.2 mmol), DCC (0.659 g, 3.2 mmol), and *N*,*N*-dimethylaminopyridine (DMAP) (0.122 g, 1.0 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 5 days. The mixture was filtered through a short pad of silica gel, which was washed with ether. After concentration, the residue was chromatographed (0–10% ether/hexane) to afford pure **8** (45%) and unreacted **6** (0.427 g, 43%). After a second acylation of the unreacted **6** with **7** as above, compound **8** (0.817, overall 69% from two reactions) was obtained as a colorless liquid; $[\alpha]_D^{25} = +7.4$ (*c* 2.3, $CHCl_3$); IR: 3060, 1730, 990, 910 cm^{-1}; ^{1}H NMR: δ 0.84 (t, $J = 6.6$ Hz, 3H), 1.02 (s, 9H), 1.27–1.80 (m, 12H), 1.83–2.04 (m, 6H), 2.21–2.35 (m, 2H), 2.51–2.77 (m, 2H), 3.59–3.87 (m, 4H), 4.45–4.59 (m, 1H), 4.85–5.10 (m, 2H), 5.65–5.81 (m, 1H), 7.25–7.36 (m, 6H), 7.57–7.75 (m, 4H); ^{13}C NMR: δ 14.1, 18.9, 19.5, 23.7, 25.3, 25.7, 26.9, 27.2, 32.8, 34.5, 35.9, 67.8, 74.9, 75.4, 78.1, 109.8, 116.1, 127.5, 128.1, 132.6, 134.8, 135.9, 174.1; MS (EI, 70 eV): *m*/*z* (%) 592 (25, M^+), 550 (13), 535 (26), 492 (16), 421 (28), 412 (26), 350 (37), 296 (66), 235 (51), 198 (96), 140 (92), 136 (100), 108 (74), 99 (98), 56 (51). Anal. Calcd for $C_{36}H_{52}O_5Si$: C, 72.93; H, 8.84. Found: C, 73.12; H, 8.88.

3.1.6. (2*R*,3*R*,5*R*)-3-*tert*-Butyldiphenylsilyloxy-5-(5′-hexenoyloxy)octane-1,2-diol 9. A mixture of **8** (0.500 g, 0.84 mmol) and 15% aqueous TFA was stirred at room temperature for 12 h. Most of the solvent was removed in vacuo, the residue taken in $CHCl_3$, the organic extract washed with water and brine, and dried. Solvent removal followed by column chromatography (silica gel, 0–5% MeOH/$CHCl_3$) of the residue gave **9** (0.350 g, 81%) as a colorless liquid; $[\alpha]_D^{25} = +2.7$ (*c* 1.16, $CHCl_3$); IR: 3440, 3060, 1727 cm^{-1}; ^{1}H NMR: δ 0.86 (dist. t, 3H), 1.04–1.25 (m containing a s at δ 1.05, 13H), 1.40–1.65 (m, 4H), 1.87–2.25 (m, 4H), 2.36 (br s, D_2O exchangeable, 2H), 3.61–3.66 (m, 4H), 4.48–4.65 (m, 1H), 4.95–5.02 (m, 2H), 5.62–5.77 (m, 1H), 7.38–7.42 (m, 6H), 7.54–7.62 (m, 4H); ^{13}C NMR: δ 14.2, 18.9, 23.7, 25.3, 25.5, 26.3, 27.2, 35.9, 67.3, 72.9, 73.1, 77.9, 116.1, 127.5, 128.1, 132.5, 134.7, 135.8, 171.8; MS (EI, 70 eV): *m*/*z* (%) 512 (22, M^+), 455 (17), 412 (15), 349 (26), 271 (32), 252 (61), 136 (92), 113 (30), 97 (100), 81 (68), 56 (55). Anal. Calcd for $C_{30}H_{44}O_5Si$: C, 70.27; H, 8.65. Found: C, 70.12; H, 8.59.

3.1.7. (3*R*,5*R*)-3-*tert*-Butyldiphenylsilyloxy-1-octen-5-yl 5′-hexenoate 10. To a cooled (0 °C) and stirred solution of **9** (0.350 g, 0.68 mmol) in pyridine (5.0 mL) was injected mesyl chloride (0.160 mL, 2.10 mmol) and the mixture stirred for 12 h at room temperature. The mixture was poured into ice-cold water, the organic layer separated, and the aqueous layer washed with water and brine, and dried. Removal of solvent gave the dimesylate, which was used for the next step. IR: 1740, 1375, 1175 cm^{-1}.

A mixture of the above mesylate, NaI (0.600 g, 4.0 mmol) and Zn-dust (0.670 g, 10.0 mmol) in DMF (15 mL) was heated at 90 °C for 8 h. The mixture was cooled to room temperature, ether then added, and the supernatant passed through a pad (2″ × 2″) of silica gel. Water was added to the eluent, the mixture was extracted with ether, and the ethereal layer was washed with water and brine, and dried. Removal of solvent

in vacuo followed by column chromatography of the residue (silica gel, 0–10% EtOAc/hexane) gave pure **10** (0.205 g, 63%) as a colorless liquid; $[\alpha]_D^{25} = -15.2$ (*c* 0.72, $CHCl_3$); IR: 1740, 1230, 990, 910 cm^{-1}; ^1H NMR: δ 0.86 (dist. t, 3H), 1.04–1.28 (m containing a s at δ 1.06, 13H), 1.47–1.62 (m, 4H), 1.95–2.38 (m, 4H), 4.18–4.26 (m, 1H), 4.41–4.56 (m, 1H), 4.89–5.04 (m, 4H), 5.71–5.82 (m, 2H), 7.36–7.44 (m, 6H), 7.54–7.64 (m, 4H); ^{13}C NMR: δ 13.8, 18.8, 23.7, 25.3, 25.5, 26.3, 27.1, 35.7, 74.8, 77.3, 116.1, 116.4, 127.5, 128.1, 132.5, 134.5, 135.8, 173.1; MS (EI, 70 eV): *m*/*z* (%) 478 (19, M^+), 421 (27), 381 (36), 378 (18), 365 (22), 236 (30), 218 (66), 113 (35), 102 (96), 97 (71), 81 (100), 56 (55). Anal. Calcd for $C_{30}H_{42}O_3Si$: C, 75.26; H, 8.84. Found: C, 75.52; H, 8.62.

3.1.8. (3*R*,5*R*)-5-(5′-Hexenoyloxy)-1-octen-3-ol 11. To a cooled (−78 °C) and stirred solution of **10** (0.4 g, 0.84 mmol) in THF (10 mL) was injected TBAF (1.0 mL, 1.0 M in THF mL). After stirring for 3 h, the mixture was concentrated in vacuo and the residue subjected to preparative TLC (silica gel, 10% EtOAc/hexane) to furnish **11**[4e] (0.177 g, 88%). Colorless liquid; $[\alpha]_D^{25} = +5.7$ (*c* 1.12, $CHCl_3$); IR: 3380, 1740, 1230, 990, 910 cm^{-1}; ^1H NMR: δ 0.84 (dist. t, 3H), 1.04–1.24 (m, 4H), 1.51–1.63 (m, 4H), 1.95–2.16 (m, 2H), 2.31 (t, $J = 7.2$ Hz, 2H), 2.70 (br s, 1H), 4.14–4.19 (m, 1H), 4.39–4.48 (m, 1H), 4.91–5.04 (m, 4H), 5.72–5.86 (m, 2H); ^{13}C NMR: δ 14.1, 17.6, 23.7, 25.5, 26.3, 33.7, 35.7, 67.9, 72.5, 116.1, 116.4, 132.5, 171.4; MS (EI, 70 eV): *m*/*z* (%) 240 (21, M^+), 222 (36), 197 (16), 179 (78), 171 (32), 153 (100), 113 (38), 97 (72), 61 (51), 55 (71).

3.1.9. (7*R*,9*R*,5*E*)-7-Hydroxy-9-propylnonenolide (herbarumin III) I. A solution of **11** (0.175 g, 0.73 mmol) and Grubb's II catalyst (0.07 mmol) in CH_2Cl_2 (250 mL) were refluxed for 18 h. After quenching the reaction with ethyl vinyl ether (1.0 mL), the mixture was concentrated in vacuo, and the residue chromatographed (silica gel, 0–10% ether/hexane) to give **I** (0.142 g, 63%). Colorless liquid; $[\alpha]_D^{25} = +21.9$ (*c* 0.88, EtOH), (lit.[2a] $[\alpha]_D^{22} = +22.0$ (*c* 0.1, EtOH)); IR: 3380, 1710, 980 cm^{-1}; ^1H NMR δ 0.88 (dist. t, 3H), 1.32–1.42 (m, 2H), 1.49–1.76 (m, 2H), 1.77–1.85 (m, 2H), 1.98–2.02 (m, 3H), 2.02 (m, 1H), 2.24–2.29 (m, 1H), 2.37–2.42 (m partially D_2O exchangeable, 2H), 4.42–4.47 (m, 1H), 5.10–5.21 (m, 1H), 5.34–5.44 (m, 1H), 5.59–5.64 (m, 1H); ^{13}C NMR: δ 14.1, 17.7, 24.2, 33.3, 33.9, 34.6, 39.7, 67.7, 70.1, 124.6, 134.1, 175.8; MS (EI, 70 eV): *m*/*z* (%) 212 (12, M^+), 194 (30), 169 (18), 151 (67), 143 (36), 125 (98), 113 (41), 97 (100), 55 (75), 41 (34).

References

1. (a) Belitz, H. D.; Grosch, W. In *Food Chemistry*; Springer: Berlin, 1986; Chapter 5; (b) Pawar, A. S.; Chattopadhyay, S.; Chattopadhyay, A.; Mamdapur, V. R. *J. Org. Chem.* **1993**, *58*, 7535; (c) Sharma, A.; Sankaranarayanan, S.; Chattopadhyay, S. *J. Org. Chem.* **1996**, *61*, 1814.
2. (a) Rivero-Cruz, J. F.; Macías, M.; Cerda-García-Rojas, C. M.; Mata, R. *J. Nat. Prod.* **2003**, *66*, 511–514; (b) Rivero-Cruz, J. F.; García-Aguirre, G.; Cerda-García-Rojas, C. M.; Mata, R. *Tetrahedron* **2000**, *56*, 5337–5344.
3. (a) de Napoli, L.; Messere, A.; Palomba, D.; Piccialli, V.; Evidente, A.; Piccialli, G. *J. Org. Chem.* **2000**, *65*, 3432; (b) Arnone, A.; Assante, G.; Montorsi, M.; Nasini, G.; Ragg, E. *Gazz. Chim. Ital.* **1993**, *123*, 71.
4. (a) Furstner, A.; Radkowski, K. *Chem. Commun.* **2001**, 671–672; (b) Furstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061–7069; (c) Díez, E.; Dixon, D. J.; Ley, S. V.; Polara, A.; Rodríguez, F. *Helv. Chim. Acta* **2003**, *86*, 3717–3729; (d) Sabino, A. A.; Pilli, R. A. *Tetrahedron Lett.* **2002**, *43*, 2819–2822; (e) Gurjar, M. K.; Karmakar, S.; Mohapatra, D. K. *Tetrahedron Lett.* **2004**, *45*, 4525–4526; (f) Nanda, S. *Tetrahedron Lett.* **2005**, *46*, 3661–3663; (g) Gurjar, M. K.; Nagaprasad, R.; Ramana, C. V.; Mohapatra, D. K. *ARKIVOC* **2005**, *part 3*, 237–257.
5. (a) Chattopadhyay, A. *J. Org. Chem.* **1996**, *61*, 6104–6107; (b) Sharma, A.; Chattopadhyay, S. *Tetrahedron: Asymmetry* **1999**, *10*, 883–890; (c) Sharma, A.; Chattopadhyay, S. *Enantiomer* **2000**, *5*, 175–179.
6. Kolb, H. C.; van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
7. For general reviews on olefin metathesis in organic synthesis, see the following leading references: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446–452; (b) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: New York, 1997; (c) Furstner, A.; Langemann, K. *Synthesis* **1997**, 792–803; (d) Furstner, A. *Top. Catal.* **1997**, *4*, 285–299; (e) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450; (f) Grubbs, R. H. *Handbook of Metathesis*, 1st ed.; Wiley-VCH: Weinheim, 2003.
8. Dhotare, B.; Salaskar, A.; Chattopadhyay, A. *Synthesis* **2003**, 2571–2575.
9. Chattopadhyay, A.; Salaskar, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 785–789.
10. (a) Richnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945–948; (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099–7100.
11. (a) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073–2077; (b) Furstner, A.; Muller, T. *Synlett* **1997**, 1010–1012; (c) Chang, S.; Grubbs, R. H. *Tetrahedron Lett.* **1997**, *38*, 4757–4760; (d) Delgado, M.; Martin, J. D. *J. Org. Chem.* **1999**, *64*, 4798–4816; (e) Bamford, S. J.; Goubitz, K.; van Lingen, H. L.; Luker, T.; Schenk, H.; Hiemstra, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 345–351; (f) Nakashima, K.; Ito, R.; Sono, M.; Tori, M. *Heterocycles* **2000**, *53*, 301–314; (g) Oishi, T.; Nagumo, Y.; Hirama, M. *Chem. Commun.* **1998**, 1041–1042; (h) Fürstner, A.; Piquet, M.; Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **1998**, 1315–1316; (i) Gerlach, K.; Quitschalle, M.; Kalesse, M. *Tetrahedron Lett.* **1999**, *40*, 3553–3556; (j) Barrett, A. G. M.; Baugh, S. P. D.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Giles, M. R.; Marshall, E. L.; Procopiou, P. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1998**, *63*, 7893–7907; (k) Furstner, A.; Thiel, O. R.; Blanda, G. *Org. Lett.* **2000**, *2*, 3731–3734.