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Formal and total syntheses of herbarumin I and II, respectively from (*R*)-2,3-cyclohexylideneglyceraldehyde

Dibakar Goswami, Angshuman Chattopadhyay *

Bio-Organic Division, Bhabha Atomic Research Centre, Mumbai 400 085, India

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ABSTRACT

Vinyl Grignard addition to **2**, obtained via a nitroaldol reaction of (*R*)-2,3-cyclohexylideneglyceraldehyde **1**, afforded **3** with absolute stereoselectivity. This was transformed into **7,** a known intermediate for the formal synthesis of herbarumin I **A**. Condensation of **7** with **10**, another intermediate obtained from **1** afforded **11**. The RCM reaction of **11** in the presence of Grubbs second generation catalyst **Ru II** and global debenzylation of the product in the presence of $TiCl_4$ furnished **B**. The efficacy of the entire route was due to its operational simplicity, the easy accessibility of **1**, all of the reactions being inexpensive and the high stereoselectivity of the asymmetric C–C bond forming reactions involved, as well as *E*-selectivity of the RCM reaction.

1. Introduction

Herbarumin-I **A** and herbarumin-II **B** are two nonenolides that were discovered by Mata et al.[1] through bioassay guided fractionation of a culture broth fungus *Phoma herbarum*. These macrolides showed high levels of phytotoxic effects on seedling growth and were found to be structurally closely related to several other recently discovered[2] naturally occurring 10-membered macrolides, such as herbarumin III **C**,[1b] microcarpalide **D**,[3] lethaloxin **E**,[4] decarestrictine D **F**[5] as shown in Figure 1. Both herbarumin-I **A** and herbarumin-II **B** exhibited significant phytotoxic effects in assay monitoring germination and the growth of *Amaranthus hypochondriacus* seedlings, with IC_{50} values as low as 5.43×10^{-5} for compound **A**.[6] The discovery of this class of macrolides gave rise to promising new lead structures in the search for novel herbicidal agents.

In addition to their remarkable biological activities as mentioned above, both **A** and **B** bear a novel structural feature due to the presence of three consecutive oxygenated stereocenters at the C7, C8, and C9 positions in the lactone ring with an *anti* relationship between any two adjacent oxygens in this scaffold. Needless to say, due to these structural characteristics, both **A** and **B** are challenging synthetic targets. As a result, there are several reports in the literature for the synthesis of **A**, which exploit different chiral templates, such as D-ribose,[7a,b] L-arabinose,[7c] D-(−)-isoascorbic acid[7d] and L-ascorbic acid,[7e] by employing an asymmetric aldol,[7f] or asymmetric epoxidation[7g] protocols. In comparison, only a very few reports[7b,h–j] are available for the synthesis of **B**. Among these, Furstner et al.[7b] reported the synthesis of both **A** and **B** and their structural characterization.

In our ongoing research related to the synthesis of bioactive compounds, we have been exploiting (*R*)-2,3-cyclohexylideneglyceraldehyde **1**[8a] as a useful template for the asymmetric construction of different structural units that are present in a wide range of target biomolecules.[8] Herein we report our successful exploitation of **1** to develop a simple and stereoselective route leading to the formal synthesis of **A** and an easy access to **B**.

2. Results and discussion

Retrosynthetic analysis (Scheme 1) of both **A** and **B** suggested that both could be obtained via an appropriate chain extension of common intermediate **7**, which in turn could be derived from a known aldehyde **2**[8n] obtained from **1**. Accordingly, our synthesis began with O-silylated hydroxyaldehyde **2**, which was obtained by the nitroaldol reaction of **1** in an aqueous medium.[8n] Compound **2** was subjected to vinyl Grignard addition, which produced isomer **3** stereoselectively. Desilylation of **3**, followed by benzylation of both hydroxyls of diol **4** produced **5** in good yield. Deketalisation of **5** under acidic conditions produced the known diol **6**,[7d] in almost quantitative yield. With regards to the preparation of **6**, it is worth mentioning that our protocol is simpler and more straightforward involving the generation of both hydroxyls at C-3 and C-4 with absolute stereoselectively via the corresponding nucleophilic additions [nitroaldol[8n] reaction of **1** and vinyl Grignard addition of **2** (Scheme 2, step ii), respectively] compared to the reported method[7d] where C-3 hydroxyl was produced by starting from D-isoascorbic acid following either a longer route or through

* Corresponding author.
E-mail addresses: achat@barc.gov.in, achat@apsara.barc.ernet.in (A. Chattopadhyay).

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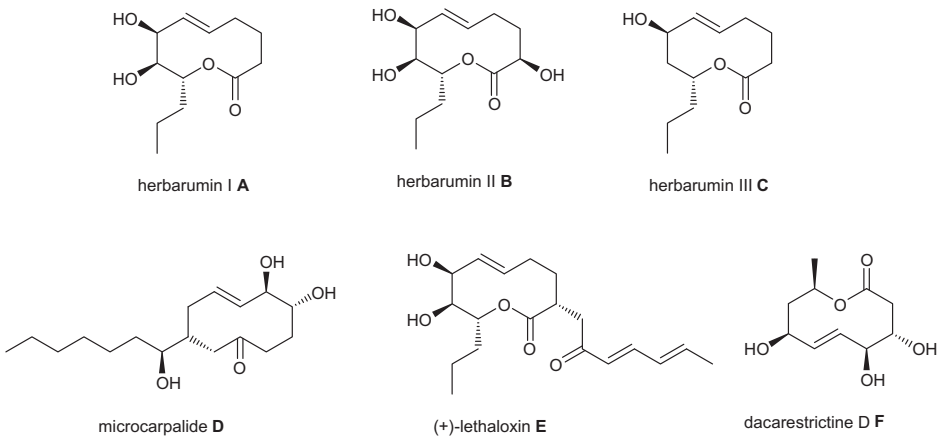
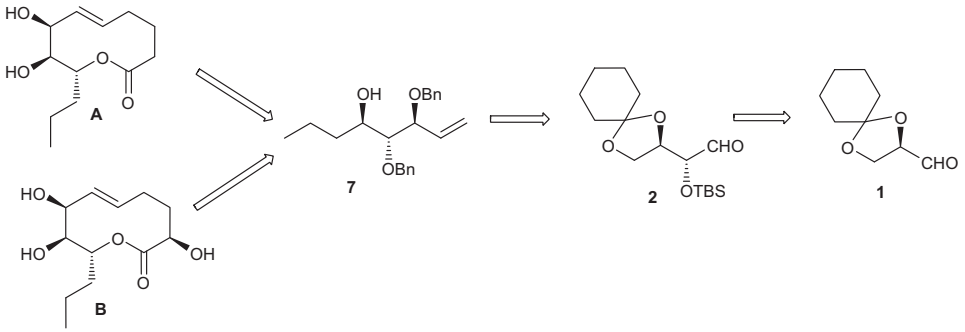


Fig. 1.



Scheme 1.

hydride reduction of a ketone, which did not take place with absolute stereoselectivity. Furthermore, due to our reaction being a series of operationally simple and inexpensive reactions starting from easily accessible **1**, the present route appears to be more viable with respect to the reported one.[7d] Next, with a modification of the reported protocol,[7d] **6** was transformed into the known intermediate **7** thus constituting a formal synthesis of **A**.

We next turned our attention to the synthesis of **B** for which we chose to start with *syn* alcohol **8a**, which had been derived from **1**.[8h] This was benzylated to produce **8b**, which upon deketalisation under acidic conditions produced diol **9**. Sodium periodate cleavage of 1,2-dihydroxyl in **9**, followed by PDC oxidation of the resulting aldehyde afforded **10** in reasonably good yield in two steps. Compound **10** has recently been prepared,[7j] however our protocol seems simpler and scaleable since it is originated from **1**. In the next step, **10** was condensed with **7** in the presence of DCC in dichloromethane to afford diolefin **11** in good yield. In the next crucial step, compound **11** was subjected to a ring closing metathesis reaction (RCM) in boiling CH_2Cl_2 using Grubbs second generation catalyst **Ru II**.[9] The RCM product, thus obtained was used without further purification and subjected to exhaustive debenzylation upon treatment with $TiCl_4$ to furnish **B** in good yield. Its optical and spectroscopic data were in good agreement with the reported values.[7b,h] This suggested that the metathesis reaction of diolefin **11** with **Ru II** (Scheme 2, step xii) produced only the (*E*)-lactone, which was similar to what had been observed earlier[7h] in the same reaction with the corresponding tri-O-silylated substrate. It is worth mentioning that the RCM reaction of another terminal bisolefin compound with Grubbs first generation catalyst **Ru I** predominantly afforded the *E*-olefin.[10]

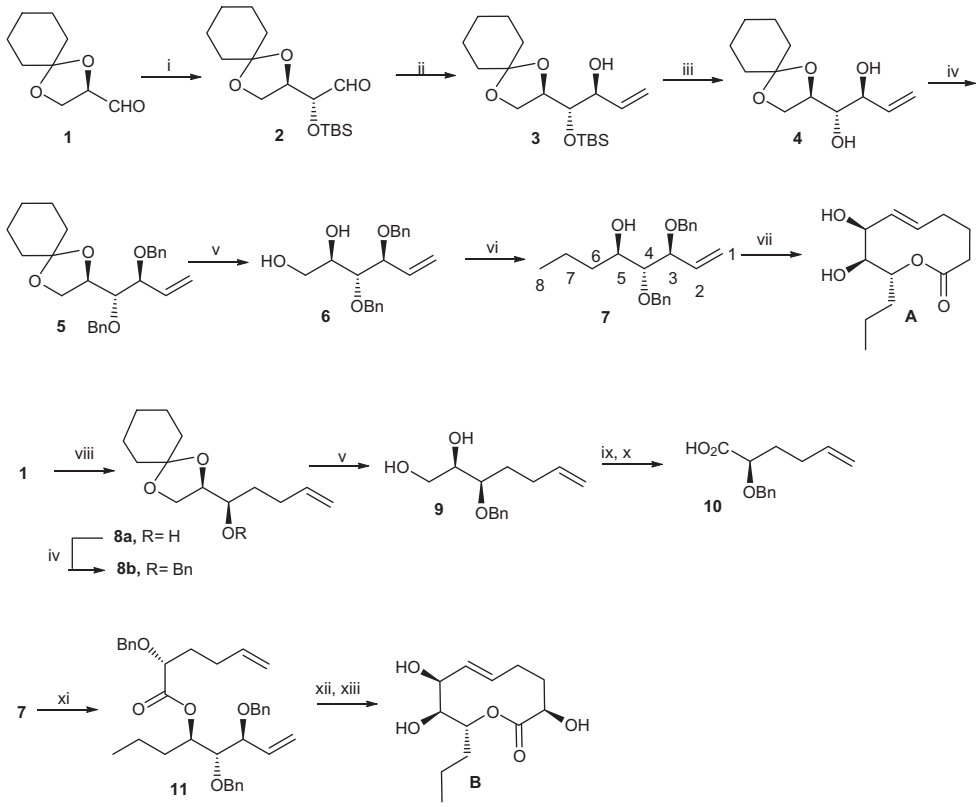
3. Conclusion

Compound **1** has been utilized as a novel template in the development of a divergent route to the formal synthesis of herbarumin I **A** and herbarumin II **B**, respectively. In our approach, **1** has been transformed stereoselectively into **7**, a known intermediate to give product **11**, which was finally utilized for the synthesis of **B** via an RCM approach. It is worth noting that two of the three oxygenated stereocenters of the common intermediate **7** were generated through crucial asymmetric C–C bond forming reactions, the nitroaldol reaction of **1**[8n] and vinyl-Grignard addition to **2** (step ii, Scheme 2) which took place with absolute stereoselectivity, while the third stereocenter was inherited from **1**. Regarding the synthesis of **B**, the only stereocenter of intermediate **10** originated from **8a**, which itself was prepared from **1** with absolute stereoselectivity.[8h] Lastly, the selective formation of the desired *E*-olefin in the RCM reaction[9] of **11** (step xii, Scheme 2) further established the novelty of this approach for the preparation of **B**. The easy availability of **7** is of high importance in the synthesis due to the fact that in addition to this work, it could also be utilized as a useful chiral template for the synthesis of lethaloxin following a reported approach[7j] and gives access to several other biologically relevant macrolides that have some structural resemblance with **A** and **B**.

4. Experimental

4.1. General

Chemicals used as starting materials were commercially available and used without further purification. All solvents used



Scheme 2.

for extraction and chromatography were distilled twice at atmospheric pressure prior to use. The ^1H and ^{13}C NMR spectra were recorded with a Bruker Ac-200 (200 MHz) instrument. The organic extracts were desiccated over dry Na_2SO_4.

4.2. (2*R*,3*S*,4*S*)-1,2-Cyclohexylidene-3-*O*-*tert*-butyldimethylsilyl hex-5-ene-1,2,3,4-tetrol 3

Vinylmagnesium bromide (1 M solution in THF, 19.20 ml, 19.20 mmol) was added dropwise to a cooled (−78 °C) solution of aldehyde **2** (4.0 g, 12.74 mmol) in dry THF under an argon atmosphere. The solution was stirred for 6 h (TLC) and then gradually brought to room temperature. Water and EtOAc were added to the mixture, the organic layer separated and the aqueous layer extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with aqueous HCl, water and brine, and dried. Solvent removal in vacuo and chromatographic purification (silica gel, 0–10% EtOAc/Hexane) of the crude residue afforded pure alcohol **3**. Yield: 3.14 g (72%); colorless oil; $[\alpha]_D^{24} = +11.3$ (*c* 1.2, $CHCl_3$); ^1H NMR: δ 0.10 (s, 6H), 0.88 (s, 9H), 1.19–1.59 (m, 10H), 2.03 (broad s, 1H), 3.78–3.88 (m, 2H), 3.92–4.04 (m, 2H), 4.23–4.25 (m, 1H), 5.17–5.37 (m, 2H), 5.80–5.92 (m, 1H); ^{13}C NMR: δ −4.4, −4.2, 18.2, 23.9, 24.1, 25.3, 25.9, 35.1, 36.3, 65.9, 75.3, 75.5, 75.7, 109.1, 116.8, 136.2. Anal. Calcd for $C_{18}H_{34}O_4Si$: C, 63.11; H, 10.00%. Found, C, 63.32; H, 10.14%.

4.3. (2*R*,3*S*,4*S*)-1,2-Cyclohexylidenehex-5-ene-1,2,3,4-tetrol 4

To a cooled (0 °C) and stirred solution of **3** (3.0 g, 8.77 mmol) in THF (30 mL) was added Bu_4NF (14.90 ml, 14.90 mmol, 1 M in THF), and the mixture stirred for approximately 2 h (TLC). Next, the mixture was poured into water, and extracted with EtOAc (15 mL). The organic extract was washed with H_2O (5 mL) and brine, and dried. Removal of solvent *in vacuo* followed by column chromatography (silica gel, 0–5% MeOH/$CHCl_3$) of the residue furnished pure diol **4**. Yield: 1.56 g (78%); colorless oil; $[\alpha]_D^{22} = +23.4$ (*c* 1.4, $CHCl_3$); ^1H NMR: 1.39–1.65 (m, 10H), 2.37 (broad s, 1H), 2.75 (broad s, 1H), 3.70 (t, *J* = 4.2 Hz, 1H), 3.93–4.08 (m, 3H), 4.32 (t, *J* = 5.7 Hz, 1H), 5.28–5.44 (m, 2H), 5.88–5.99 (m, 1H); ^{13}C NMR: δ 23.9, 24.1, 25.1, 34.9, 36.3, 66.1, 73.7, 74.5, 76.1, 109.7, 118.1, 136.0. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83%. Found, C, 63.29; H, 8.61%.

4.4. (2*R*,3*S*,4*S*)-1,2-Cyclohexylidene-3,4-*O*-dibenzylhex-5-ene-1,2,3,4-tetrol 5

To a suspension of sodium hydride (0.74 g, 50% suspension in oil, 15.35 mmol) in dry THF (50 ml), a solution of **4** (1.40 g, 6.14 mmol) in dry THF (50 ml) was added dropwise over a period of 10 min under an argon atmosphere. The mixture was heated at 60 °C for 1 h. Then the mixture was cooled to room temperature followed by the addition of benzyl bromide (2.62 g, 15.35 mmol) in THF (50 ml). The mixture was stirred for a further 1 h and then heated at 60 °C for 2 h. Upon completion of the reaction (TLC), it was cooled with ice-water, quenched by the addition of water, and extracted with EtOAc. The organic layer was washed successively with water, 5% aqueous HCl, water, brine, and then dried over Na_2SO_4. Solvent removal under reduced pressure and column chromatography of the residue (silica gel, 0–5% EtOAc in hexane) afforded pure **5**. Yield: 2.25 g (90%); colorless oil; $[\alpha]_D^{24} = +38.8$ (*c*

1.06, $CHCl_3$); ^1H NMR: 1.35–1.59 (m, 10H), 3.74 (dd, J = 3.0 Hz and 6.3 Hz, 1H), 3.87–3.98 (m, 2H), 4.03–4.13 (m, 2H), 4.40 (d, J = 12.3 Hz, 1H), 4.67 (dd, J = 9.3 Hz and 11.4 Hz, 2H), 4.83 (d, J = 11.4 Hz, 1H), 5.30–5.38 (m, 2H), 5.86–5.98 (m, 1H), 7.26–7.34 (m, 10H); ^{13}C NMR: δ 23.9, 24.1, 25.3, 35.0, 36.4, 66.3, 70.6, 74.2, 74.9, 81.6, 81.7, 109.5, 119.5, 127.5, 127.6, 127.7, 128.1, 128.4, 134.9, 138.7. Anal. Calcd for $C_{26}H_{32}O_4$: C, 76.44; H, 7.90%. Found, C, 76.12; H, 7.80%.

4.5. (2*R*,3*S*,4*S*)-3,4-*O*-Dibenzylhex-5-ene-1,2,3,4-tetrol 6

To a stirred and cooled (0 °C) solution of **5** (2.0 g, 4.90 mmol) in CH_2Cl_2 (30 mL) was added portionwise 80% aqueous trifluoroacetic acid (15 mL). The mixture was stirred for 2.5 h at 0 °C until completion of the reaction (TLC). Solid $NaHCO_3$ (5.0 g) was then added in order to decompose the excess TFA, followed by the addition of water. The mixture was extracted with $CHCl_3$ (3 × 30 ml). The combined organic extracts were washed with water and brine, and dried over Na_2SO_4. Removal of the solvent in vacuum followed by column chromatography (silica gel, 5% MeOH in $CHCl_3$) of the residue afforded pure **6**. Yield: 1.16 g (72%); colorless oil; $[\alpha]_D^{24} = +47.4$ (*c* 1.6, $CHCl_3$); lit.[7d] $[\alpha]_D^{20} = +47.8$ (*c* 0.7, $CHCl_3$); ^1H NMR: 2.32 (broad s, 1H), 3.19 (broad s, 1H), 3.62 (t, J = 6.0 Hz, 1H), 3.68–3.82 (m, 3H), 4.05–4.09 (m, 1H), 4.38 (d, J = 11.7 Hz, 1H), 4.57–4.72 (m, 3H), 5.37–5.44 (m, 2H), 5.85–5.97 (m, 1H), 7.26–7.39 (m, 10H); ^{13}C NMR: δ 63.5, 70.6, 72.4, 74.2, 81.2, 82.1, 120.1, 127.9, 128.2, 128.5, 128.6, 135.4, 137.8, 137.9.

4.6. (4*R*,5*R*,6*S*)-5,6-*O*-Dibenzyl-oct-7-en-4-ol 7

To a cooled (0 °C) solution of **6** (1.0 g, 3.05 mmol) in pyridine (10 mL) containing DMAP (50 mg), *p*-toluenesulfonylchloride (0.581 g, 3.05 mmol) was slowly added over a period of 2 h. The mixture was then stirred at 0 °C for 2 h. After completion of the reaction (TLC), it was quenched by the addition of water and extracted with $CHCl_3$. The organic layer was washed successively with 5% aqueous HCl, water, brine, and then dried over Na_2SO_4. The solvent was removed under reduced pressure to obtain the crude residue, which was quickly purified by passing through a short silica gel column eluting with 5–15% EtOAc in hexane to obtain the product in quantitative yield. This was immediately dissolved in MeOH (15 mL) and mixed with solid K_2CO_3 (0.635 g, 4.60 mmol). The mixture was stirred at room temperature for three hours until the reaction was complete (TLC). The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$. The organic layer was washed successively with water, 5% aqueous HCl, water, brine, and then dried over Na_2SO_4. Solvent removal under reduced pressure afforded the corresponding terminal epoxide[7d] (0.65 g) in its crude form. This was used as such for the next reaction without further purification.

A Grignard suspension of bromoethane in THF (50 mL) was prepared from ethyl bromide (0.467 ml, 6.30 mmol) and Mg (0.202 g, 8.40 mmol) in the usual manner. The suspension was cooled (−50 °C) and Cu(I) bromide (0.452 g, 3.15 mmol) was added. The mixture was stirred at −50 °C for 15 min. To this cooled organometallic suspension, a solution of epoxide (0.650 g, 2.10 mmol) in THF (40 mL), prepared as above, was added. The mixture was stirred at the same temperature for 1 h and then gradually brought to room temperature. The mixture was then stirred overnight at room temperature. The reaction was quenched by the addition of aqueous saturated NH_4Cl (10 mL) and extracted with EtOAc. The organic layer was washed with 5% aqueous HCl, water, brine and then dried over Na_2SO_4. Solvent removal under reduced pressure and column chromatography of the residue (silica gel, 0–10% EtOAc in hexane) afforded pure **7**. Yield: 0.54 g (52% in 3 steps); colorless oil; $[\alpha]_D^{25} = +9.3$ (*c* 2.4, MeOH); lit.[7d] $[\alpha]_D^{20} = +9.1$ (*c* 3.0, MeOH); ^1H NMR: 0.89 (t, J = 6.9 Hz, 3H), 1.25–1.64 (m, 4H), 2.41 (d, J = 4.8 Hz, 1H), 3.44 (t, J = 6.0 Hz, 1H), 3.70–3.82 (m, 1H), 4.00–4.05 (m, 1H), 4.37 (d, J = 12.0 Hz, 1H), 4.54–4.74 (m, 3H), 5.34–5.40 (m, 2H), 5.88–6.01 (m, 1H), 7.26–7.37 (m, 10H); ^{13}C NMR: δ 14.2, 18.9, 34.9, 70.4, 72.5, 74.3, 82.0, 83.9, 119.5, 127.7, 127.8, 127.9, 128.1, 128.4, 128.5, 136.1, 138.1, 138.4.

4.7. (2*R*,3*R*)-1,2-Cyclohexylidene-3-*O*-benzylhept-6-ene-1,2,3-triol 8b

To a suspension of sodium hydride (0.576 g, 50% suspension in oil, 12.0 mmol) in dry THF (50 ml), a solution of **8a**[8h] (2.26 g, 10.0 mmol) in dry THF (40 ml) was added dropwise over a period of 10 min under an argon atmosphere. The mixture was heated at 60 °C for 1 h. Then the mixture was cooled to room temperature followed by the addition of benzyl bromide (2.05 g, 12.0 mmol) in THF (50 ml). The mixture was stirred for a further 1 h and then heated at 60 °C for 2 h. Upon completion of the reaction (TLC), it was cooled with ice-water, quenched by the addition of water and extracted with EtOAc. The organic layer was washed successively with water, 5% aqueous HCl, water, brine, and then dried over Na_2SO_4. Solvent removal under reduced pressure and column chromatography of the residue (silica gel, 0–5% EtOAc in hexane) afforded pure **8b**. Yield: 2.68 g (85%); colorless oil; $[\alpha]_D^{24} = +13.4$ (*c* 1.0, $CHCl_3$); ^1H NMR: 1.39–1.68 (m, 12H), 2.08–2.16 (m, 1H), 2.23–2.30 (m, 1H), 3.44–3.48 (m, 1H), 3.67 (t, J = 7.5 Hz, 1H), 3.99 (dd, J = 6.5 and 8.0 Hz, 1H), 4.21 (q, J = 7.0 Hz, 1H), 4.62 (d, J = 11.5 Hz, 1H), 4.83 (d, J = 11.5 Hz, 1H), 4.95–5.01 (m, 2H), 5.74–5.82 (m, 1H), 7.26–7.38 (m, 5H); ^{13}C NMR: δ 23.9, 24.0, 25.2, 29.7, 30.1, 34.9, 36.3, 65.7, 73.0, 78.3, 79.4, 109.9, 114.9, 127.5, 128.0, 128.3, 138.3. Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92%. Found, C, 76.12; H, 8.80%.

4.8. (2*R*,3*R*)-3-*O*-Benzylhept-6-ene-1,2,3-triol 9

To a stirred and cooled (0 °C) solution of **8b** (2.5 g, 7.91 mmol) in CH_2Cl_2 (30 mL) was added portionwise 80% aqueous trifluoroacetic acid (15 mL). The mixture was stirred for 2.5 h at 0 °C until completion of the reaction (TLC). Solid $NaHCO_3$ (5 g) was then added in order to decompose the excess TFA, followed by the addition of water. The mixture was extracted with $CHCl_3$ (3 × 30 ml). The combined organic extracts were washed with water and brine, and dried over Na_2SO_4. Removal of the solvent in vacuum followed by column chromatography (silica gel, 5% $CHCl_3$/MeOH) of the residue afforded pure **9**. Yield: 1.27 g (68%); colorless oil; $[\alpha]_D^{24} = +18.2$ (*c* 1.2, $CHCl_3$); ^1H NMR: 1.67–1.82 (m, 2H), 2.15–2.20 (m, 2H), 2.42 (broad s, 1H), 2.74 (broad s, 1H), 3.51 (q, J = 5.5 Hz, 1 H), 3.59–3.63 (m, 1H), 3.67–3.69 (m, 2H), 4.50 (d, J = 11.0 Hz, 1H), 4.66 (d, J = 11.0 Hz, 1H), 4.98–5.06 (m, 2H), 5.80–5.87 (m, 1H), 7.27–7.38 (m, 5H); ^{13}C NMR: δ 29.3, 29.4, 64.0, 72.3, 72.8, 79.1, 115.0, 127.9, 128.5, 138.0. Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53%. Found, C, 71.33; H, 8.71%.

4.9. (*R*)-2-*O*-Benzylhex-5-enoic acid 10

To a stirred solution of **9** (1.20 g, 5.1 mmol) in 60% aqueous CH_3CN (20 mL) was added portionwise $NaIO_4$ (1.86 g, 8.67 mmol). After stirring for 2 h, the mixture was filtered, and the filtrate extracted with $CHCl_3$. The organic layer was washed with water and brine, and concentrated *in vacuo* to give the aldehyde, which was utilized for next reaction without further purification.

This aldehyde (1.0 gm, 4.9 mmol) was added to a stirred solution of pyridinium dichromate (9.21 g, 24.5 mmol) in DMF (5 ml), and stirring was continued at rt. The reaction was monitored by TLC. When no starting material could be detected, water (10 ml) and ether (20 ml) were added to the reaction. The organic layer

was separated and the aqueous phase was extracted with ether. The combined ether phases were dried over $MgSO_4$ and concentrated, to yield an oil, which was subjected to column chromatography (silica gel, 0–15% MeOH/$CHCl_3$) to afford pure **10**. Yield: 0.79 g (71% over two steps); colorless oil; $[\alpha]_D^{24} = +20.8$ (*c* 1.2, $CHCl_3$); lit[7j] $[\alpha]_D^{24} = +22.3$ (*c* 0.45, $CHCl_3$); ^1H NMR: δ 1.88–1.95 (m, 2H), 2.18–2.24 (m, 2H), 4.02 (t, *J* = 6.0 Hz, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 4.73 (d, *J* = 11.4 Hz, 1H), 4.98–5.04 (m, 2H), 5.71–5.84 (m, 1H), 7.28–7.42 (m, 5H); ^{13}C NMR: δ 29.4, 32.0, 72.9, 77.7, 116.0, 128.4, 128.8, 137.3, 177.4.

4.10. (2*R*)-(4*R*,5*R*,6*S*)-5,6-Dibenzyloct-7-en-4-yl-2-benzylhex-5-enoate 11

To a stirred solution of compound **7** (0.20 g, 0.59 mmol) in dry CH_2Cl_2 (5 ml), DCC (0.243 g, 1.18 mmol), **10** (0. 150 g, 0.68 mmol) and DMAP (catalytic amount) were added at 0 °C and stirred at room temperature for 3 h. After completion of the reaction (TLC), the reaction mixture was filtered through Celite and extracted with $CHCl_3$, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 0–5% EtOAc/hexane) to afford **11**. Yield: 0.262 g (82%); colorless oil; $[\alpha]_D^{22} = +68.4$ (*c* 1.1, $CHCl_3$); ^1H NMR: 0.92 (t, *J* = 6.9 Hz, 3H), 1.18–1.39 (m, 2H), 1.41–1.75 (m, 4H), 2.20–2.26 (m, 2H), 3.62 (t, *J* = 4.5 Hz, 1H), 3.82 (dd, *J* = 6.0 Hz and 7.5 Hz, 1H), 4.12 (t, *J* = 6.9 Hz, 1H), 4.34 (d, *J* = 12.0 Hz, 1H), 4.45–4.73 (m, 5H), 4.94–5.07 (m, 2H), 5.14–5.20 (m, 1H), 5.28–5.41 (m, 2H), 5.65–5.89 (m, 2H), 7.26–7.33 (m, 15H); ^{13}C NMR: δ 15.0, 19.1, 24.2, 32.9, 68.1, 70.0, 73.7, 74.1, 80.3, 82.1, 83.3, 115.6, 119.8, 127.7, 128.1, 128.2, 128.4, 128.4, 133.4, 133.6, 135.4, 137.3, 138.3, 138.6, 170.8. Anal. Calcd. for $C_{35}H_{42}O_5$: C, 77.46; H, 7.80%. Found, C, 77.54; H, 7.66%.

4.11. Herbarumin II (B)

Second generation Grubbs' catalyst (0.068 g, 0.08 mmol) was added to a solution of diene ester **11** (0.228 g, 0.42 mmol) in degassed anhydrous CH_2Cl_2 (150 ml) and the mixture was heated at 50 °C under an argon flow for 12 h. After completion of the reaction (TLC), most of the solvent was evaporated and then air was bubbled to decompose catalyst. The remaining solvent was evaporated under reduced pressure, to afford a dark brown oily residue, which was quickly passed through a short silica gel column eluting with 30% EtOAc in hexane to obtain the RCM product (0.186 g) in its crude form. This was used for the next step without further purification.

A cooled (0 °C) solution of this crude RCM product (0.170 g, 0.33 mmol) in dry CH_2Cl_2 (5 ml), containing $TiCl_4$ (0.073 ml, 0.66 mmol) was stirred for 15 min. After completion of the reaction (cf. TLC), more CH_2Cl_2 (20 ml) was added to it. The mixture was washed with saturated aqueous sodium bicarbonate (10 mL) and water (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 0–30% EtOAc/hexane) to afford **B**. Yield: 0.055 g (54% over 2 steps); colorless solid; $[\alpha]_D^{24} = +16.8$ (*c* 1.0, MeOH); lit[7b] $[\alpha]_D^{20} = +17.3$ (*c* 0.63, MeOH); The spectroscopic data were in agreement with the literature. [7b,h]

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