RSC Advances

PAPER

View Article Online
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Cite this: *RSC Adv.*, 2014, **4**, 63342

# A relay ring-opening/double ring-closing metathesis strategy for the bicyclic macrolide-butenolide core structures†

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Received 22nd September 2014
Accepted 11th November 2014

DOI: 10.1039/c4ra10937f

www.rsc.org/advances

A concise strategy has been developed for the synthesis of the bicyclic macrolide-butenolide core structures of various natural products with the macrolide ring size ranging from 12- to 16-membered. The bicyclic structure was easily assembled using the relay ring-opening/double ring-closing metathesis strategy. An efficient synthesis of (±)-desmethyl manshurolide has been achieved as an application of this strategy.



## Introduction

The bicyclic macrolide-butenolide core structure **1** is present in many natural products (Fig. 1). The macrolide size may vary and there could be the presence of one or more double bonds. Selected examples are shown in Fig. 1 with the macrolide size varying from 12- to 14-membered (**2a–e**) being the most common. Gersemolide **2a** (12-membered macrolide) is a pseudopterane, isolated from the soft coral *Gersemia rubiformis*.[1] Manshurolide **2b**, also a 12-membered macrolide is a sesquiterpene lactone isolated from the stems of *Aristolochia manshuriensis*.[2] It has three *trans*-double bonds in the macrolide ring (the butenolide double bond is apparently *trans*- in the macrolide ring but geometrically *cis*- in the butenonide).

Okilactomycins C **2c** and D **2d** have a 13-membered bicyclic macrolide-butenolide structure with an annulated cyclohexene and additional spiro functionality. These were isolated from *Streptomyces scabrisporus*.[3] The cembranoid diterpenes, sarcophytonolides A-L were isolated from the soft coral of the genus *Sarcophyton*.[4] These possess the 14-membered bicyclic macrolide-butenolide structure. The simpler member is sarcophytonolide L **2e**. The bicyclic macrolide-butenolide structure is also present in many other natural products with various substituents and functionalities. Often there is the furan ring[5] (or the oxidized diketo form) as another common feature in most of them (Fig. 1). These could be the furano-pseudopterane type **3a**, furano-gersolene type **3b** or the furano-cembrane type **3c** (Fig. 1).[5] The butenolide moiety gains it significance in medicinal chemistry as Michael acceptor to various biological nucleophiles.

With our continued interest in the synthesis of γ-lactones, butenolides and strained macrolides[6] and considering the importance of these bicyclic structures we embarked on developing a strategy to rapidly construct both the rings (butenolide and macrolide) in an efficient manner based on a relay ring-opening/multiple ring-closing metathesis.[7]

## Results and discussion

As shown in the retrosynthetic analysis (Scheme 1) the core structure **1** could be assembled through a double ring-closing metathesis of the tetraene **4**. However this design would impose issues of regioselectivity in the ring-closure considering the competition of three available terminal mono-substituted double bonds. While the butenolide ring closure could occur with ease, the macrolide ring closure would be challenging. The latter would predominantly depend on ring size and would occur separately of the first ring-closure. We sought an alternative path to prevent competition by reducing the number of double bonds and hence the triene **5** seemed obvious choice. In this case during metathesis there would be carbene cascade which appeared promising for the challenging macrolide ring closure unlike the case of compound **4** where the two ring closures would occur separately. The substrate **5** can be considered as synthetic equivalent to compound **4**. Compound **5** can easily be assembled through vinyl Grignard reaction on aldehyde **6** (of varying chain length) followed by esterification with cyclobutene carboxylic acid **7**. An advantage of this strategy is the ready adaptability for chiral version where in the intermediate allyl alcohol **9** can be resolved through Sharpless kinetic resolution.[8]

The forward synthesis towards the bicyclic core structure **1** with macrolide ring size varying from 12- to 16-membered is shown in Scheme 2. The vinyl Grignard addition to various aldehydes from the alcohols **8a–e** gave the corresponding allyl alcohols **9a–e** in 84–89% yields. The esterification of **9a**

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† Electronic supplementary information (ESI) available: Copies of $^{1}H$ and $^{13}C$ NMR spectra for all the compounds. See DOI: 10.1039/c4ra10937f

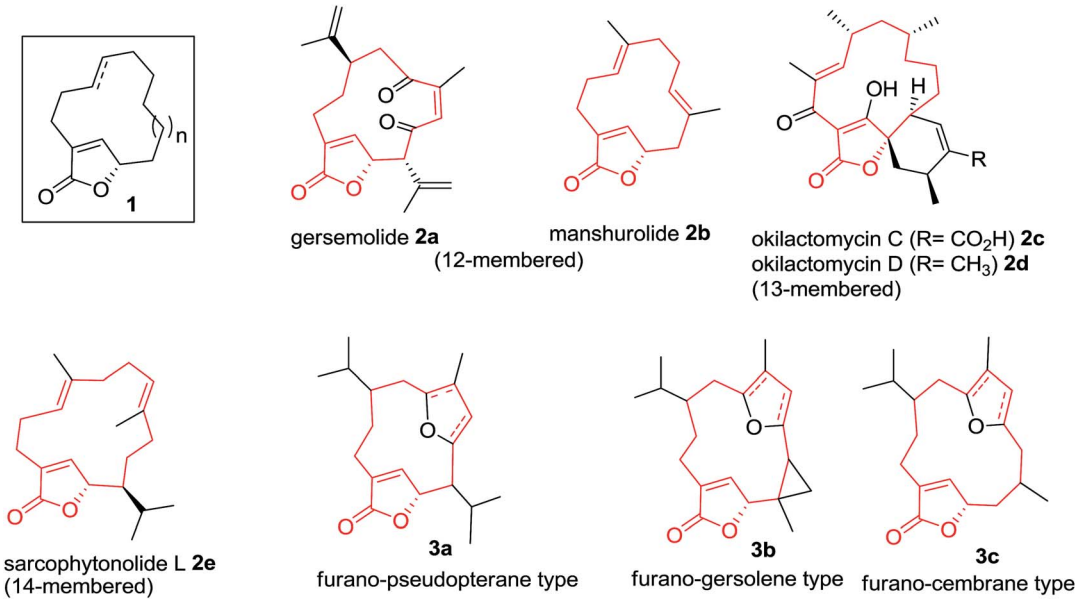
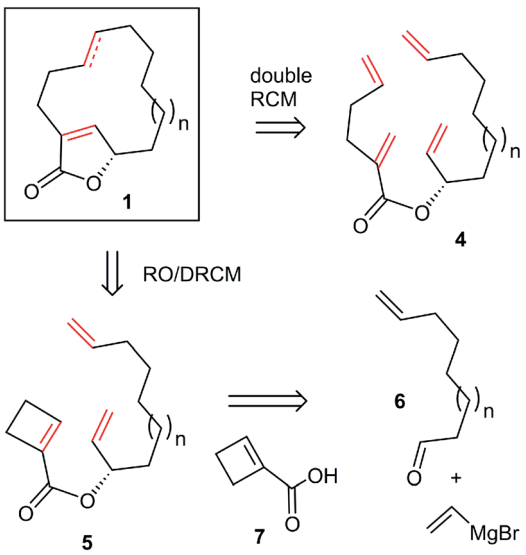



Fig. 1 Bicyclic macrolide-butenolide natural products and related furano-structures.



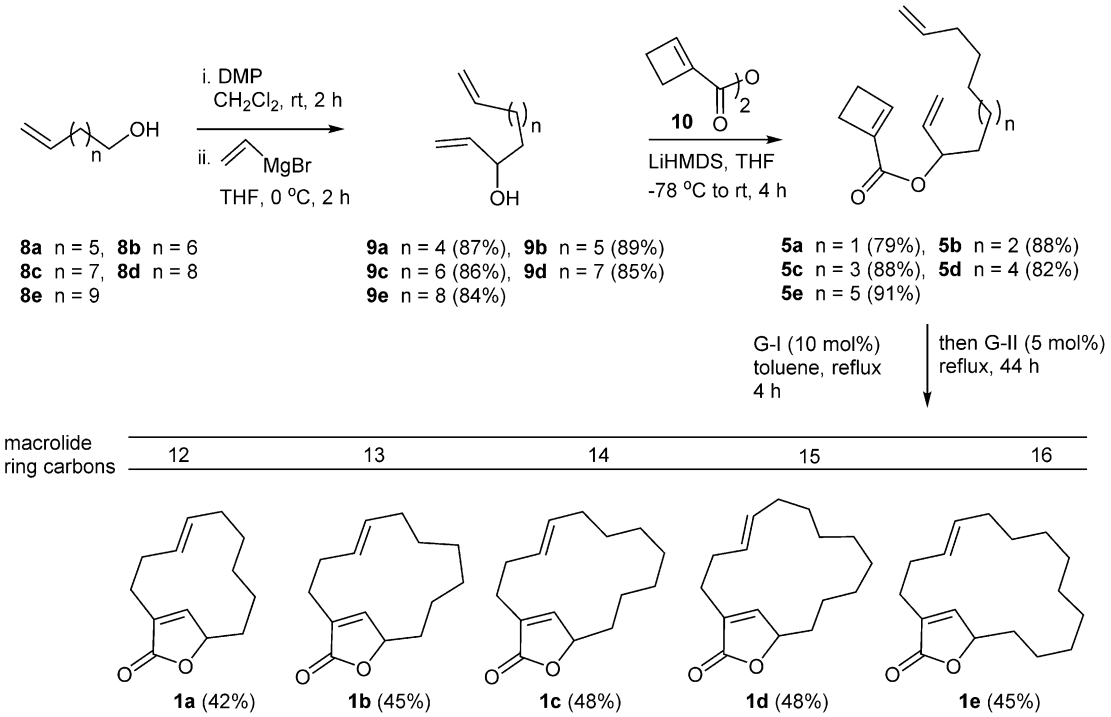

Scheme 1 Retrosynthesis of bicyclic core structure 1.

with the cyclobutene carboxylic acid 7 using DCC gave the corresponding ester **5a** in 38% yield. The reaction using Yamaguchi conditions[9] delivered **5a** in 51% yield. This was further improved with the use of the anhydride of 7, *i.e.* **10**, and LiHMDS that delivered the ester **5a** in good 79% yield. Similarly, other esters **5b–e** were prepared in 82–91% yields. The relay ring-opening/double ring-closing metathesis (RO/DRCM) reaction on **5a–e** was carried out using Grubbs catalysts (G-I and G-II) and Grubbs-Hoveyda catalysts (GH-I and GH-II) in toluene, benzene and hexane solvent. The best results were obtained through a sequential addition of first G-I catalyst (10 mol%) followed by addition of G-II catalyst (5 mol%) in toluene solvent providing the macrolide-butenolide bicyclic compounds **1a–e** in 42–48% yields with *E*-selectivity for the macrolide double bond.[10] We believe, G-I catalyst is known for ring-opening metathesis of strained small rings (in this case the cyclobutene ring). Thus the above catalysts combination worked well in this case. However, we did not isolate any of the intermediate compounds in this relay metathesis reaction which may require quenching with ethylene.

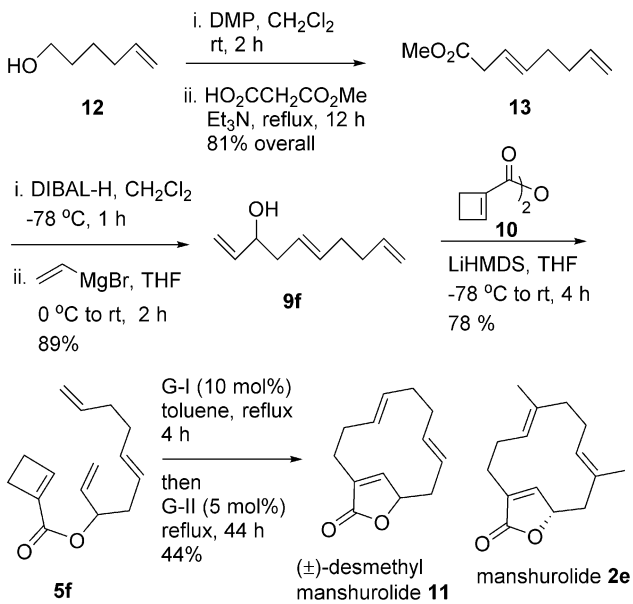
The strategy was extended towards the protecting group free synthesis of (±)-desmethyl manshurolide **11** as shown in Scheme 3. Commercially available 5-hexene-1-ol **12** was oxidized to aldehyde and the subsequent modified decarboxylative deconjugative Knoevenagel condensation[11] with half ester of malonic acid gave the ester **13** in 81% overall yield. DiBAL-H reduction of the ester group to aldehyde and subsequent vinyl Grignard reaction furnished the triene **9f** (89% from **13**). The esterification of **9f** with the anhydride **10** using LiHMDS gave **5f** in 78% yield. The subsequent relay RO/DRCM using G-I (10 mol%) and G-II (5 mol%) catalysts in toluene solvent delivered (±)-desmethyl manshurolide **11** in 44% yield.

## Conclusions

In conclusion an efficient strategy for bicyclic macrolide-butenolide core structures of various natural products has been developed. The macrolide rings ranging from 12- to 16-membered have been synthesized. The efficiency of the relay ring-opening/double ring-closing metathesis strategy was further demonstrated by the protecting group free synthesis of (±)-desmethyl manshurolide. The strategy has potential towards the synthesis of bicyclic macrolide-butenolide natural products.




Scheme 2 Synthesis of the macrolide-butenolides **1a–e** using the relay RO/DRCM strategy.




Scheme 3 Synthesis of (±)-desmethyl manshurolide **11**.

# Experimental section

### General information

Flasks were oven- or flame-dried and cooled in a desiccator. Dry reactions were carried out under an atmosphere of Ar or $N_2$. Solvents and reagents were purified by standard methods. Thin-layer chromatography was performed on EM250 Kieselgel 60 F254 silica gel plates. The spots were visualized by staining with $KMnO_4$ or by UV lamp. $^1H$ NMR and $^{13}C$ NMR were recorded with Bruker AVANCE III 400 or 500 and 100 or 125 MHz, respectively, and chemical shifts are based on TMS peak at $\delta = 0.00$ pm for proton NMR and $CDCl_3$ peak at $\delta = 77.00$ ppm ($t$) in carbon NMR. IR samples were prepared by evaporation from $CHCl_3$ on CsBr plates. High-resolution mass spectra were obtained using positive electrospray ionization by TOF method.

### General procedure for synthesis of allyl alcohols 9a–e

To a solution of alcohol **8** (2.0 mmol) in $CH_2Cl_2$ (20 mL) was added Dess–Martin periodinate (DMP, 1.87 g, 4.40 mmol, 2.2 equiv.). The resulting mixture was stirred at room temperature for 2 h. It was then quenched with a solution of 10% aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$ (1 : 1, 15 mL) and the solution extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were washed with brine, dried ($Na_2SO_4$) and concentrated. The residue was loaded on a short pad of silica gel and washed with petroleum ether/EtOAc (2 : 1) to give the aldehyde which was used directly for next step. Vinyl magnesium bromide (3.0 mL, 3.0 mmol, 1.5 equiv., 1 M solution in THF) was added to the aldehyde dissolved in THF (30 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and warmed to room temperature. Saturated aq. $NH_4Cl$ (15 mL) was added and the mixture extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried ($Na_2SO_4$) and concentrated. The residue was purified by silica gel flash column chromatography using petroleum ether/EtOAc (4 : 1) as eluent to give the alcohols **9a–e** in 84–89% yield.

**Deca-1,9-dien-3-ol (9a).** Isolated yield of **9a** (0.268 g, 87%); colorless oil; IR ($CHCl_3$): $\nu_{max}$ 3417, 2925, 2851, 1637, 1459,

1371, 1305, 1245, 1023, 910, 666 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, ppm) $\delta$ 5.91–5.75 (m, 2H), 5.27–5.10 (m, 2H), 5.04–4.90 (m, 2H), 4.11 (brq, $J = 6.3$ Hz, 1H), 3.30 (brs, 1H), 2.09–2.00 (m, 2H), 1.61–1.50 (m, 2H), 1.50–1.30 (m, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$, ppm) $\delta$ 141.3, 139.0, 114.5, 114.2, 73.2, 37.0, 33.7, 29.0, 28.8, 25.1; HRMS *m*/*z* calcd for $[C_{10}H_{18}ONa]^+$ 177.1250, found 177.1256.

**Undeca-1,10-dien-3-ol (9b).** Isolated yield of **9b** (0.3 g, 89%); colorless oil; IR ($CHCl_3$): $\nu_{max}$ 3367, 3076, 2927, 2854, 1637, 1464, 1440, 991, 911, 663 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$, ppm) $\delta$ 5.90–5.75 (m, 2H), 5.25–5.18 (m, 2H), 5.04–4.91 (m, 2H), 4.09 (brq, $J = 6.2$ Hz, 1H), 3.35 (brs, 1H), 2.09–2.01 (m, 2H), 1.61–1.48 (m, 2H), 1.45–1.25 (m, 8H); $^{13}C$ NMR (125 MHz, $CDCl_3$, ppm) $\delta$ 141.3, 139.1, 114.6, 114.2, 73.3, 37.0, 33.7, 29.4, 29.0, 28.8, 25.3; HRMS *m*/*z* calcd for $[C_{11}H_{20}ONa]^+$ 191.1395, found 191.1392.

**Dodeca-1,11-dien-3-ol (9c).** Isolated yield of **9c** (0.313 g, 86%); colorless oil; IR ($CHCl_3$): $\nu_{max}$ 3369, 3071, 2926, 2854, 1640, 1464, 1437, 1259, 1166, 991, 911, 718 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, ppm) $\delta$ 5.90–5.75 (m, 2H), 5.25–5.18 (m, 2H), 5.04–4.91 (m, 2H), 4.09 (brq, $J = 6.2$ Hz, 1H), 3.35 (brs, 1H), 2.09–2.01 (m, 2H), 1.61–1.48 (m, 2H), 1.45–1.25 (m, 10H); $^{13}C$ NMR (100 MHz, $CDCl_3$, ppm) $\delta$ 141.3, 139.2, 114.5, 114.1, 73.3, 37.0, 33.8, 29.5, 29.4, 29.0, 28.9, 25.3; HRMS *m*/*z* calcd for $[C_{12}H_{22}ONa]^+$ 205.1545, found 205.1539.

**Trideca-1,12-dien-3-ol (9d).** Isolated yield of **9d** (0.334 g, 85%); colorless oil; IR ($CHCl_3$): $\nu_{max}$ 3364, 3071, 2927, 2855, 1640, 1462, 1434, 992, 911, 718 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, ppm) $\delta$ 5.90–5.75 (m, 2H), 5.25–5.18 (m, 2H), 5.04–4.91 (m, 2H), 4.09 (brq, $J = 6.2$ Hz, 1H), 2.09–2.01 (m, 2H), 1.61–1.48 (m, 2H), 1.45–1.25 (m, 12H); $^{13}C$ NMR (100 MHz, $CDCl_3$, ppm) $\delta$ 141.3, 139.2, 114.5, 114.1, 73.3, 37.0, 33.8, 29.5, 29.5, 29.4, 29.1, 28.9, 25.3; HRMS *m*/*z* calcd for $[C_{13}H_{24}ONa]^+$ 219.1702, found 219.1697.

**Tetradeca-1,13-dien-3-ol (9e).** Isolated yield of **9e** (0.353 g, 84%); colorless oil; IR ($CHCl_3$): $\nu_{max}$ 3351, 3076, 2926, 2851, 1637, 1459, 1314, 990, 910 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, ppm) $\delta$ 5.90–5.75 (m, 2H), 5.25–5.18 (m, 2H), 5.04–4.91 (m, 2H), 4.09 (q, $J = 6.2$ Hz, 1H), 2.09–2.00 (m, 2H), 1.61–1.48 (m, 2H), 1.45–1.25 (m, 14H); $^{13}C$ NMR (100 MHz, $CDCl_3$, ppm) $\delta$ 141.3, 139.2, 114.5, 114.1, 73.3, 37.0, 33.8, 29.53, 29.5, 29.5, 29.45, 29.1, 28.9, 25.3; HRMS *m*/*z* calcd for $[C_{14}H_{26}OK]^+$ 249.1621, found 249.1619.

### General procedure for synthesis of esters 5a–e

To a solution of allyl alcohol **9a–e** (1.0 mmol) in dry THF (15 mL) at −78 °C was gradually added LiHMDS (0.75 mL, 1.5 mmol, 1.5 equiv., 2 M solution in THF) over a period of 5 min. After stirring for 15 min, a solution of anhydride **10** (0.267 g, 1.50 mmol, 1.5 equiv.) in dry THF (5 mL) was added and the reaction mixture stirred for 4 h at −78 °C. It was slowly warmed to room temperature and a solution of sat. aq. $NH_4Cl$ (5 mL) was added. The mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed with brine, dried ($Na_2SO_4$) and concentrated. The residue was purified by silica gel flash column chromatography using petroleum ether/EtOAc (4 : 1) as eluent to give the esters **5a–e** in 79–91% yield.

**Deca-1,9-dien-3-yl cyclobut-1-enecarboxylate (5a).** Isolated yield of **5a** (0.185 g, 79%); colorless oil; IR ($CHCl_3$): $\nu_{max}$ 2927, 2854, 1730, 1646, 1462, 1367, 1250, 1173, 1114, 1050, 988, 966, 920, 695, 667 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, ppm) $\delta$ 6.77 (s, 1H), 5.84–5.74 (m, 2H), 5.30–5.14 (m, 3H), 5.00–4.91 (m, 2H), 2.73–2.72 (m, 2H), 2.47–2.45 (m, 2H), 2.09–2.01 (m, 2H), 1.61–1.48 (m, 2H), 1.45–1.22 (m, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$, ppm) $\delta$ 161.7, 146.4, 139.0, 138.9, 136.6, 116.5, 114.3, 74.4, 34.1, 33.6, 29.7, 29.1, 28.8, 27.0, 24.8; HRMS *m*/*z* calcd for $[C_{15}H_{22}O_2Na]^+$ 257.1512, found 257.1518.

**Undeca-1,10-dien-3-yl cyclobut-1-enecarboxylate (5b).** Isolated yield of **5b** (0.219 g, 88%); colorless oil; IR ($CHCl_3$): $\nu_{max}$ 2918, 2850, 1727, 1463, 1369, 1303, 1264, 1181, 1035, 984, 916, 666 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$, ppm) $\delta$ 6.77 (s, 1H), 5.84–5.74 (m, 2H), 5.30–5.14 (m, 3H), 5.00–4.91 (m, 2H), 2.73–2.72 (m, 2H), 2.48–2.46 (m, 2H), 2.09–2.00 (m, 2H), 1.68–1.50 (m, 2H), 1.45–1.22 (m, 8H); $^{13}C$ NMR (125 MHz, $CDCl_3$, ppm) $\delta$ 161.6, 146.3, 139.1, 138.9, 136.6, 116.5, 114.2, 74.4, 34.1, 33.7, 29.2, 29.1, 28.9, 28.8, 27.0, 24.0; HRMS *m*/*z* calcd for $[C_{16}H_{24}O_2Na]^+$ 271.1669, found 271.1673.

**Dodeca-1,11-dien-3-yl cyclobut-1-enecarboxylate (5c).** Isolated yield of **5c** (0.231 g, 88%); colorless oil; IR ($CHCl_3$): $\nu_{max}$ 2929, 2857, 1732, 1641, 1465, 1414, 1371, 1253, 1175, 1090, 991, 918, $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, ppm) $\delta$ 6.77 (t, $J = 1.2$ Hz, 1H), 5.85–5.73 (m, 2H), 5.31–5.14 (m, 3H), 5.01–4.90 (m, 2H), 2.73–2.72 (m, 2H), 2.47–2.45 (m, 2H), 2.08–2.00 (m, 2H), 1.61–1.48 (m, 2H), 1.46–1.22 (m, 10H); $^{13}C$ NMR (100 MHz, $CDCl_3$, ppm) $\delta$ 161.7, 146.3, 139.2, 138.9, 136.6, 116.5, 114.1, 74.4, 34.1, 33.8, 29.7, 29.3, 29.1, 29.0, 28.9, 27.0, 25.0; HRMS *m*/*z* calcd for $[C_{17}H_{26}O_2Na]^+$ 285.1825, found 285.1818.

**Trideca-1,12-dien-3-ylcyclobut-1-enecarboxylate (5d).** Isolated yield of **5d** (0.215 g, 82%); colorless oil; IR ($CHCl_3$): $\nu_{max}$ 2928, 2851, 1731, 1644, 1459, 1374, 1308, 1251, 1171, 1127, 1045, 669, 631 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, ppm) $\delta$ 6.77 (s, 1H), 5.84–5.74 (m, 2H), 5.30–5.14 (m, 3H), 5.02–4.91 (m, 2H), 2.73–2.72 (m, 2H), 2.47–2.45 (m, 2H), 2.09–2.00 (m, 2H), 1.61–1.48 (m, 2H), 1.45–1.22 (m, 12H); $^{13}C$ NMR (100 MHz, $CDCl_3$, ppm) $\delta$ 161.7, 146.3, 139.2, 138.9, 136.6, 116.5, 114.1, 74.4, 34.2, 33.8, 29.4, 29.36, 29.3, 29.1, 29.07, 28.9, 27.0, 25.0; HRMS *m*/*z* calcd for $[C_{18}H_{28}O_2Na]^+$ 299.1987, found 299.1979.

**Tetradeca-1,13-dien-3-yl cyclobut-1-enecarboxylate (5e).** Isolated yield of **5e** (0.264 g, 91%); colorless oil; IR ($CHCl_3$): $\nu_{max}$ 2927, 2856, 1731, 1656, 1462, 1407, 1371, 1308, 1256, 1182, 1130, 1045, 968, 823 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, ppm) $\delta$ 6.77 (t, $J = 1.2$ Hz, 1H), 5.85–5.75 (m, 2H), 5.30–5.15 (m, 3H), 5.01–4.91 (m, 2H), 2.73–2.71 (m, 2H), 2.47–2.45 (m, 2H), 2.09–2.00 (m, 2H), 1.61–1.48 (m, 2H), 1.45–1.22 (m, 14H); $^{13}C$ NMR (100 MHz, $CDCl_3$, ppm) $\delta$ 161.7, 146.3, 139.2, 138.9, 136.6, 116.5, 114.1, 74.4, 34.2, 33.8, 29.4, 29.3, 29.1, 28.9, 27.0, 25.2, 25.18, 25.0; HRMS *m*/*z* calcd for $[C_{19}H_{30}O_2Na]^+$ 313.2116, found 313.2121.

### General procedure for synthesis of macrolide-butenolides 1a–e

To a solution of **5a–e** (0.20 mmol) in dry and degassed toluene (150 mL) was added Grubbs-I catalyst (16.5 mg, 0.02 mmol,

10 mol%). The mixture was refluxed for 4 h under nitrogen atmosphere and then cooled and Grubbs-II catalyst (8.5 mg, 0.01 mmol, 5 mol%) was added. The mixture was further refluxed for 44 h under nitrogen atmosphere and then cooled and concentrated. The residue was purified by silica gel flash column chromatography using petroleum ether/EtOAc (4 : 1) as eluent to give the macrolide-butenolides**1a–e**.

**(*E*)-12-Oxabicyclo[9.2.1]tetradeca-1(14),4-dien-13-one (1a).** Isolated yield of **1a** (17.3 mg, 42%); colorless oil; IR ($CHCl_3$): $\nu_{max}$ 3016, 2923, 2857, 1754, 1657, 1591, 1454, 1336, 1119, 971, 858, 669, 628 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$, ppm) $\delta$ 6.90–6.87 (m, 1H), 5.26–5.13 (m, 2H), 5.12–5.08 (m, 1H), 2.67–2.56 (m, 1H), 2.48–2.38 (m, 1H), 2.36–2.29 (m, 2H), 2.20–2.11 (m, 2H), 1.70–1.50 (m, 2H), 1.40–1.20 (m, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$, ppm) $\delta$ 173.8, 149.4, 133.9, 131.8, 130.0, 81.1, 31.6, 30.1, 29.9, 27.4, 25.7, 25.6, 21.7; HRMS *m*/*z* calcd for $[C_{13}H_{18}O_2Na]^+$ 229.1199, found 229.1190.

**(*E*)-13-Oxabicyclo[10.2.1]pentadeca-1(15),4-dien-14-one (1b).** Isolated yield of **1b** (19.8 mg, 45%); colorless oil; IR ($CHCl_3$): $\nu_{max}$ 2922, 2846, 1755, 1646, 1459, 1369, 1333, 1242, 1094, 1042, 965, 858, 694 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, ppm) $\delta$ 7.00 (d, $J$ = 1.3 Hz 1H), 5.43–5.33 (m, 1H), 5.30–5.22 (m, 1H), 5.06–5.01 (m, 1H), 2.58–2.45 (m, 2H), 2.36–2.25 (m, 2H), 2.10–2.0 (m, 2H), 1.82–1.71 (m, 2H), 1.45–1.10 (m, 8H); $^{13}C$ NMR (125 MHz, $CDCl_3$; ppm) $\delta$ 174.3, 149.4, 133.9, 132.9, 128.8, 80.8, 33.2, 31.0, 29.6, 29.0, 28.7, 25.8, 24.5, 21.5; HRMS *m*/*z* calcd for $[C_{14}H_{20}O_2Na]^+$ 243.1333, found 243.1327.

**(*E*)-14-Oxabicyclo[11.2.1]hexadeca-1(16),4-dien-15-one (1c).** Isolated yield of **1c** (22.5 mg, 48%); colorless oil; IR ($CHCl_3$): $\nu_{max}$ 2923, 2851, 1755, 1646, 1456, 1437, 1369, 1242, 1094, 1042, 965, 691 $cm^{-1}$;$^1H$ NMR (400 MHz, $CDCl_3$, ppm) $\delta$ 7.00 (d, $J$ = 1.4 Hz, 1H), 5.43–5.28 (m, 1H), 5.28–5.22 (m, 1H), 5.04–4.99 (m, 1H), 2.58–2.45 (m, 1H), 2.36–2.25 (m, 3H), 2.10–1.98 (m, 2H), 1.83–1.71 (m, 2H), 1.45–1.10 (m, 10H); $^{13}C$ NMR (100 MHz, $CDCl_3$, ppm) $\delta$ 174.2, 149.3, 133.4, 132.7, 129.5, 80.8, 31.7, 29.7, 29.65, 26.7, 25.0, 24.4, 23.9, 18.4; HRMS *m*/*z* calcd for $[C_{15}H_{22}O_2Na]^+$ 257.1512, found 257.1518.

**(*E*)-15-Oxabicyclo[12.2.1]heptadeca-1(17),4-dien-16-one (1d).** Isolated yield of **1d** (23.5 mg, 48%); colorless oil; IR ($CHCl_3$): $\nu_{max}$ 2929, 2857, 1748, 1621, 1459, 1108, 872, 666, 603 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, ppm) $\delta$ 7.00 (d, $J$ = 1.3 Hz, 1H), 5.45–5.36 (m, 1H), 5.35–5.25 (m, 1H), 5.02–4.95 (m, 1H), 2.53–2.45 (m, 2H), 2.42–2.30 (m, 2H), 2.10–2.00 (m, 2H), 1.89–1.79 (m, 2H), 1.45–1.25 (m, 12H); $^{13}C$ NMR (125 MHz, $CDCl_3$, ppm) $\delta$ 174.2, 148.4, 133.5, 132.1, 129.2, 81.2, 31.7, 31.3, 29.0, 28.2, 27.9, 27.1, 27.0, 25.8, 24.3, 21.1; HRMS *m*/*z* calcd for $[C_{16}H_{24}O_2Na]^+$ 271.1669, found 271.1662.

**(*E*)-16-Oxabicyclo[13.2.1]octadeca-1(18),4-dien-17-one (1e).** Isolated yield of **1e** (23.6 mg, 45%); colorless oil; IR ($CHCl_3$): $\nu_{max}$ 2923, 2851, 1755, 1592, 1436, 1259, 1094, 1043, 960, 872, 771, 592 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, ppm) $\delta$ 7.06 (d, $J$ = 1.5 Hz, 1H), 5.48–5.41 (m, 1H), 5.32–5.25 (m, 1H), 4.92–4.85 (m, 1H), 2.52–2.41 (m, 2H), 2.40–2.25 (m, 2H), 2.06–1.95 (m, 2H), 1.88–1.78 (m, 2H), 1.48–1.15 (m, 14H); $^{13}C$ NMR (100 MHz, $CDCl_3$, ppm) $\delta$ 173.9, 149.0, 133.4, 132.2, 128.4, 81.2, 32.3, 31.4, 29.4, 27.9, 26.9, 26.6, 26.3, 25.4, 25.38, 24.8, 21.8; HRMS *m*/*z* calcd for $[C_{17}H_{26}O_2Na]^+$ 285.1802, found 285.1810.

**(*E*)-Methyl octa-3,7-dienoate (13).** To a solution of alcohol **12** (0.6 g, 6.0 mmol) in $CH_2Cl_2$ (30 mL) was added Dess–Martin periodinate (5.1 g, 12.0 mmol, 2.0 equiv.). The resulting mixture was stirred at room temperature for 2 h. It was then quenched with a solution of 10% aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$ (1 : 1, 15 mL) and the solution extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were washed with brine, dried ($Na_2SO_4$) and concentrated. The residue was loaded on a short pad of silica gel and washed with petroleum ether/EtOAc (2 : 1) to give the aldehyde which was used for the next step. To the aldehyde (0.582 g) was added mono methylmalonate (1.06 g, 9.0 mmol, 1.5 equiv.) followed by $Et_3N$ (1.2 mL, 12.0 mmol, 2.0 equiv.). The reaction mixture was refluxed for 12 h. It was then cooled and concentrated. The residue was purified by silica gel flash column chromatography using petroleum ether/EtOAc (9 : 1) as eluent to give ester **13** (0.748 g, 81%) as colorless oil (analysis showed it to contain <9% α,β-unsaturated isomer. This was accounted for yield calculation). IR ($CHCl_3$): $\nu_{max}$ 3070, 2926, 2849, 1741, 1641, 1437, 1256, 1199, 1164, 996, 971, 914, 667 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, ppm) $\delta$ 5.81–5.71 (m, 1H), 5.52–5.50 (m, 2H), 4.99–4.90 (m, 2H), 3.63 (s, 3H), 2.99 (d, $J$ = 5.0 Hz, 2H), 2.10–2.02 (m, 4H); $^{13}C$ NMR (100 MHz, $CDCl_3$, ppm) $\delta$ 172.4, 137.9, 133.8, 121.9, 114.6, 51.6, 37.7, 33.2, 31.7; HRMS *m*/*z* calcd for $[C_9H_{14}O_2Na]^+$ 177.0863, found 177.0859.

**(*E*)-Deca-1,5,9-trien-3-ol (9f).** To a solution of the ester **13** (0.51 g, 3.3 mmol) in $CH_2Cl_2$ (20 mL) was added DIBAL-H (3.6 mL, 3.6 mmol, 1.1 equiv., 1 M solution in toluene) drop wise at −78 °C. The reaction mixture was stirred for 1 h. It was then quenched by adding a saturated aq. solution of potassium–sodium-tartrate (10 mL) and stirred for 2 h. It was then extracted with $CH_2Cl_2$ (3 × 20 mL) and the combined organic extracts were washed with water, brine, dried ($Na_2SO_4$), and concentrated. The residue was used for next reaction without further purification.

To a solution of above aldehyde in THF (15 mL) was added vinyl magnesium bromide (5.0 mL, 5.0 mmol, 1.51 equiv., 1 M solution in THF) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and then warmed to room temperature. Saturated aq. $NH_4Cl$ (10 mL) was added and the mixture extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried ($Na_2SO_4$) and concentrated. The residue was purified by silica gel flash column chromatography using petroleum ether/EtOAc (4 : 1) as eluent to give the allyl alcohol **9f** (0.448 g, 89%) as colorless oil. IR ($CHCl_3$): $\nu_{max}$ 3444, 3077, 2926, 2855, 1641, 1618, 1577, 1481, 1467, 1378, 1252, 1176, 1127, 1070, 971, 914, 810, 694 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, ppm) $\delta$ 5.90–5.83 (m, 1H), 5.82–5.75 (m, 1H), 5.57–5.53 (m, 1H), 5.44–5.37 (m, 1H), 5.24 (dt, $J$ = 17.2, 1.5 Hz, 1H), 5.13 (dt, $J$ = 10.5, 1.4 Hz, 1H), 5.03–4.94 (m, 2H), 4.1 (brd, $J$ = 1.6 Hz, 1H), 2.31–2.19 (m, 1H), 2.18–2.16 (m, 1H), 2.14–2.12 (m, 4H), 1.7 (brs, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$, ppm) $\delta$ 140.4, 138.3, 134.1, 125.6, 114.8, 114.6, 71.8, 40.5, 33.6, 32.0; HRMS *m*/*z* calcd for $[C_{10}H_{16}ONa]^+$ 175.1093, found 175.1085.

**(*E*)-Deca-1,5,9-trien-3-yl cyclobut-1-enecarboxylate (5f).** To a solution of allyl alcohol **9f** (0.1 g, 0.657 mmol) in dry THF (10 mL) at −78 °C was gradually added LiHMDS (0.5 mL, 1.0 mmol,

1.52 equiv., 2 M soln. in THF) over a period of 5 min. After stirring for 15 min, a solution of anhydride **10** (0.176 g, 0.985 mmol, 1.5 equiv.) in dry THF (5 mL) was added and the reaction mixture stirred for 4 h at −78 °C. It was warmed to room temperature and a solution of saturated aq. $NH_4Cl$ (5 mL) was added. The mixture was extracted with EtOAc (3 × 30 mL) and the combined organic layers were washed with brine, dried ($Na_2SO_4$) and concentrated. The residue was purified by silica gel flash column chromatography using petroleum ether/EtOAc (4 : 1) as eluent to give the ester **5f** (0.12 g, 78%) as colorless oil. IR ($CHCl_3$): $\nu_{max}$ 3075, 2929, 2857, 1731, 1641, 1464, 1252, 1180, 1046, 991, 917, 668 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$, ppm) $\delta$ 6.8 (s, 1H), 5.86–5.76 (m, 2H), 5.55–5.45 (m, 1H), 5.41–5.33 (m, 1H), 5.32–5.22 (m, 2H), 5.21–5.16 (m, 1H), 5.08–4.82 (m, 2H), 2.78–2.70 (m, 2H), 2.49–2.44 (m, 2H), 2.40–2.30 (m, 2H), 2.12–2.00 (m, 4H); $^{13}C$ NMR (125 MHz, $CDCl_3$, ppm) $\delta$ 161.5, 146.4, 138.9, 138.2, 136.1, 133.3, 124.8, 116.6, 114.6, 73.8, 37.6, 33.6, 32.0, 29.7, 27.0; HRMS *m*/*z* calcd for $[C_{15}H_{20}O_2Na]^+$ 255.1356, found 255.1361.

**(4*E*,8*E*)-12-Oxabicyclo[9.2.1]tetradeca-1(14),4,8-trien-13-one (11).** To a solution of **5f** (0.050 g, 0.213 mmol) in dry and degassed toluene (150 mL) was added Grubbs-I catalyst (17.5 mg, 0.0213 mmol, 10 mol%). The mixture was refluxed for 4 h under nitrogen atmosphere and then cooled and Grubbs-II catalyst (9.1 mg, 0.0107 mmol, 5 mol%) was added. The mixture was further refluxed for 44 h under nitrogen atmosphere and then cooled and concentrated. The residue was purified by silica gel flash column chromatography using petroleum ether/EtOAc (4 : 1) as eluent to give the desmethyl manshurolide **11** (19.1 mg, 44%) as colorless oil. IR ($CHCl_3$): $\nu_{max}$ 2923, 2851, 1753, 1651, 1593, 1434, 1360, 1259, 1122, 1091, 1039, 1017, 957, 932, 869, 666 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, ppm) $\delta$ 6.75 (s, 1H), 5.18–5.11 (m, 1H), 5.06–5.02 (m, 2H), 5.00–4.98 (m, 2H), 2.80–2.75 (m, 1H), 2.56–2.52 (m, 1H), 2.36–2.18 (m, 6H), 1.88–1.79 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$, ppm) $\delta$ 173.8, 150.5, 135.3, 133.7, 132.9, 129.8, 123.3, 80.1, 34.1, 31.8, 31.5, 29.7, 25.5; HRMS *m*/*z* calcd for $[C_{13}H_{16}O_2Na]^+$ 227.1043, found 227.1044.

## Acknowledgements

We thank the Board of Research in Nuclear Sciences (BRNS), Government of India (Basic Sciences, Grant no. 2013/37C/59/BRNS/2443) for financial support. M.B.H. thanks the Council of Scientific and Industrial Research (CSIR), New Delhi for senior research fellowship.

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