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Synthetic studies on C14 cembranoids: synthesis of C4–12 fragment of sarcophytonolides E–G and L and C5–11 fragment of sarcophytonolide L

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This paper is dedicated to Professor Raymundo Cea Olivares on the occasion of his 61st birthday

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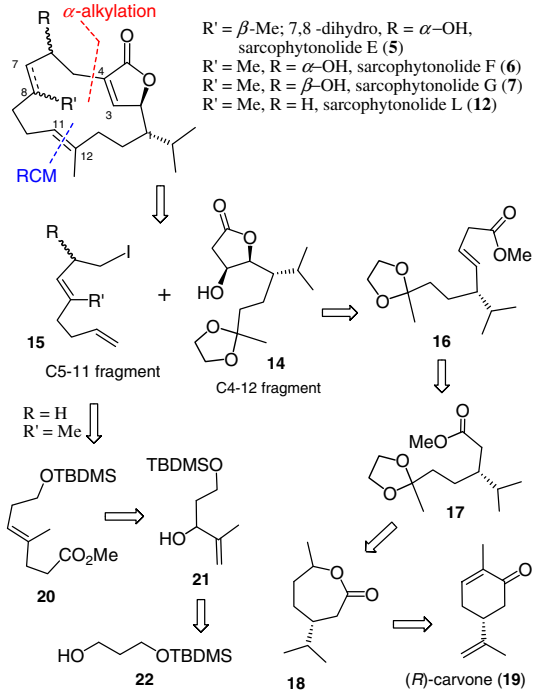
ABSTRACT

An efficient stereoselective synthesis of C4–12 fragment of the cembranoids, sarcophytonolides E–G and L and C5–11 fragment of sarcophytonolide L is described. The C4–12 building block is efficiently assembled starting from chiral pool material (*R*)-carvone employing the Baeyer–Villiger oxidation, modified Knoevenagel condensation and asymmetric dihydroxylation as the key steps. The synthesis of C5–11 fragment is based on orthoester Johnson–Claisen rearrangement as the key step.

Cembranoid diterpenes are used as chemical defence compounds by octocorals against predators such as other corals, fishes and against settlement of microorganisms such as fungi or bacteria.[1] Most of these 14-membered cembrane diterpenes show various bioactivities such as ichthyotoxic, cytotoxic, anti-inflammatory, antiarthritic, Ca-antagonistic, and antimicrobial properties.[2] Guo and co-workers[3] have isolated a series of cembranoid diterpenes, sarcophytonolides A–L (**1**–**12**, Fig. 1) from the soft corals of the genus *Sarcophyton*. The discovery of farnesyl transferase inhibition by a cembranoid diterpene **13**[4] has further enhanced the interest in this group of secondary metabolites. There are no reports on the synthesis of this class of sarcophytonolides. We wish to report in this communication our initial synthetic studies on sarcophytonolides E–G and L. Sarcophytonolides E–G (**5**–**7**) and L (**12**) could be targeted from the C4–12 fragment **14** by α-alkylation of the γ-lactone enolate with C5–11 fragment **15** (R = protected OH for **5**–**7**, R = H for **12** and R′ = β-Me and 3,4-dihydro for **5**) and subsequent β-hydroxy elimination, ketal deprotection, Wittig olefination, ring-closing metathesis (RCM) and OH deprotection reactions (Scheme 1). The fragment **14** can be assembled from ester **17** by reduction to aldehyde, modified Knoevenagel condensation[5] to get β,γ-unsaturated ester **16** and subsequent asymmetric dihydroxylation. The ester **17** could be traced back to the chiral



Scheme 1. Retrosynthetic analysis of sarcophytonolides E–G and L.

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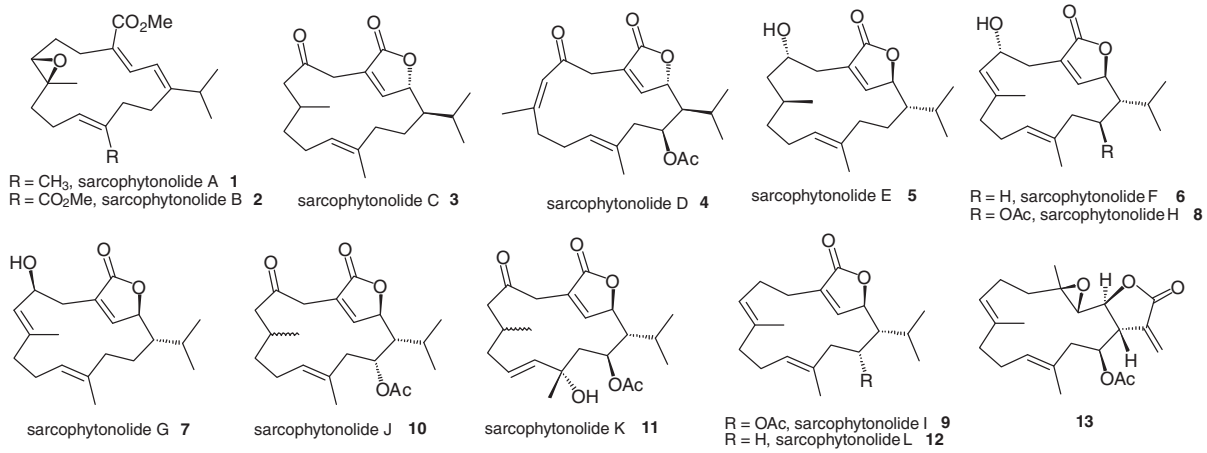
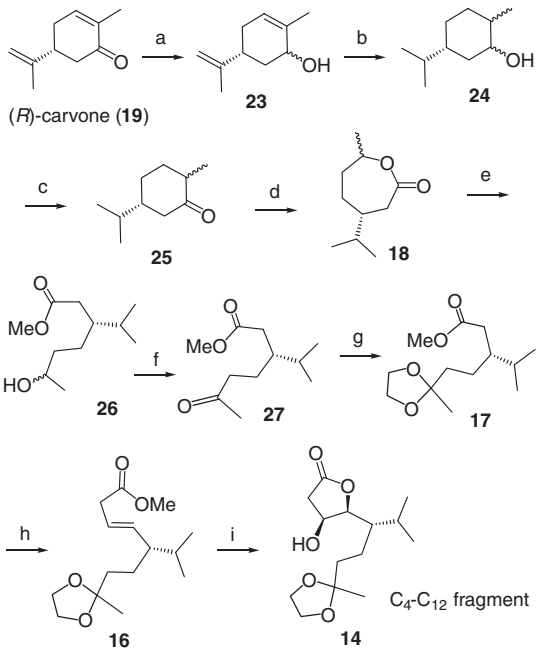


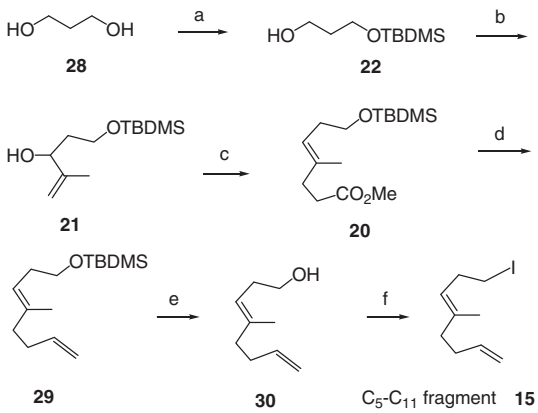
Figure 1. Sarcophytonolides A–L and cembranoid **13**.

pool material (*R*)-carvone (**19**) through reduction of the diene, Baeyer–Villiger oxidation, hydroxyl group oxidation and ketal formation. Thus the C-5 isopropene group in **19** would become the isopropyl group in the target molecules with the required stereochemistry. The iodide **15** (R = H, R′ = Me for the synthesis of **12**) could be obtained from ester **20** by usual terminal functional groups manipulation. The Johnson–Claisen rearrangement of allylalcohol **21** would produce the ester **20**. Allylalcohol **21** can be prepared from **22** by oxidation and isopropenyl-Grignard addition.



Scheme 2. Synthesis of C4–12 fragment **14**. Reagents and conditions: (a) $NaBH_4$ (1.2 equiv), MeOH, 0 °C to rt, 5 h, quant.; (b) H_2, Pd/C, MeOH, rt, 24 h, 80%; (c) PCC (1.5 equiv), mol sieves 4 Å, CH_2Cl_2, 0 °C to rt, 4 h, 83%; (d) *m*-CPBA (1.2 equiv), CAN (10.0 mol %), CH_2Cl_2, 0 °C to rt, 6 h, 75%; (e) K_2CO_3 (1.5 equiv), MeOH, rt, 3 h, 95%; (f) PCC (2.0 equiv), mol sieves 4 Å, CH_2Cl_2, 0 °C to rt, 4 h, 90%; (g) $(CH_2OH)_2$ (10.0 equiv), *p*-TsOH (catalytic), C_6H_6, reflux, 14 h, 91%; (h) (i) DIBAL-H (1.1 equiv), CH_2Cl_2, −78 °C to −40 °C, 4 h; (ii) $HO_2CCH_2CO_2Me$ (2.0 equiv), Et_3N, reflux, 12 h, 52% (two-steps); (i) $K_3Fe(CN)_6$ (3.0 equiv), K_2CO_3 (3.0 equiv), $MeSO_4NH_2$ (1.0 equiv), $(DHQ)_2PHAL$ (1.0 mol %), $K_2OsO_4{\cdot}2H_2O$ (0.4 mol %), *t*-BuOH:H_2O (1:1), 0 °C, 24 h, rt, 12 h, 74%.

The synthesis of fragment C4–12 (**14**) was initiated from the chiral pool material (*R*)-carvone (**19**, Scheme 2). Reduction of the diene unit in **19** through hydrogenation directly to deliver **25** gave poor yields. In this reaction aromatization is known to be a side reaction.[6] Hence we attempted stepwise synthesis of **25**. Reduction of the keto-group in **19** with $NaBH_4$ delivered the alcohol **23** in quantitative yield. The hydrogenation of the diene now provided **24** (80%). Further PCC oxidation of **24** afforded the ketone **25** (83%).[7] The Baeyer–Villiger oxidation[8] of **25** with *m*-CPBA gave the ω-lactone **18** (75%). This was converted into the ω-hydroxy methylester **26** (95%). The oxidation of hydroxyl group in **26** to the ketone **27** (90%) and ketal formation provided the ester **17** in 91% yield. The reduction of ester to the aldehyde and subsequent modified Knoevenagel condensation[5] with the half ester of malonic acid gave the β,γ-unsaturated ester **16** in 52% yield over two-steps. The asymmetric dihydroxylation[9] of **16** with $(DHQ)_2PHAL$ as stereoinducing ligand gave a 10:1 diastereomer mixture[10] of the γ-lactone. The diastereomer **14**[11] was easily separated by flash column chromatography in 74% yield. This completed the synthesis of C4–12 fragment having the required stereochemistry at C-1 and C-2 centers with the isopropene group in **19** now efficiently placed as the isopropyl group of the target molecules **5–7** and



Scheme 3. Synthesis of C5–11 fragment **15**. Reagents and conditions: (a) NaH (1.05 equiv), TBDMSCl (1.0 equiv), THF, 0 °C to rt, 3 h, 95%; (b) (i) PCC (2.0 equiv), NaOAc (2.0 equiv), CH_2Cl_2, 0 °C to rt, 4 h; (ii) isopropenylMgCl (1.2 equiv), THF, 0 °C to rt, 1 h, 81% (two-steps); (c) $(MeO)_3CMe$ (10.0 equiv), toluene, $EtCO_2H$ (catalytic), reflux, 12 h, 92%; (d) (i) DIBAL-H (1.0 equiv), CH_2Cl_2, −78 °C, 1.5 h; (ii) $Ph_3P^+MeI^-$ (1.5 equiv), *n*BuLi (1.5 equiv), THF, 0 °C to rt, 2 h, 75% (two-steps); (e) nBu_4NF (2.0 equiv), THF, rt, 2 h, 90%; (f) I_2 (1.1 equiv), Ph_3P (1.2 equiv), imidazole (1.1 equiv), CH_2Cl_2, 0 °C to rt, 4 h, 91%.

12. The β-hydroxyl group in the lactone **14** is correctly placed and is to be eliminated after α-alkylation to generate the γ-butenolide unit.

The synthesis of C5–11 fragment **15** (R = H, R′ = Me for **12**) began with the monoprotection of 1,3-propane diol **28** to give alcohol **22** (95%, Scheme 3). Oxidation of **22** to the aldehyde and subsequent isopropenyl-Grignard addition afforded the allylalcohol **21** in 81% yield. The orthoester Johnson–Claisen rearrangement of **21** gave the ester **20** in 92% yield. Reduction of the ester group to the aldehyde and subsequent Wittig olefination provided the diene **29** in 75% yield. Removal of the TBDMS group gave the alcohol **30** (90%) and conversion of hydroxyl to the iodide afforded the C5–11 fragment **15**[12] in 91% yield.

In summary we have designed and successfully accomplished the synthesis of the C4–12 fragment of sarcophytonolides E–G and L and the C5–11 fragment of sarcophytonolide L. This first synthetic effort towards the target molecules involved the orthoester Johnson–Claisen rearrangement as the key step in the synthesis of the C5–11 fragment while the C4–12 fragment was efficiently assembled from the chiral pool material (*R*)-carvone which fixes the isopropyl group of the target molecules and the Baeyer–Villiger oxidation, modified Knoevenagel condensation and asymmetric dihydroxylation as the key steps. The completion of total synthesis of sarcophytonolide L and related molecules is underway in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.093.

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10. Diastereomer ratio was determined by ^{1}H NMR spectroscopy of the mixture.
11. *Data for compound* **14**: $[\alpha]_D^{25}$ −43.7 (*c* 2.2, $CHCl_3$). IR ($CHCl_3$): ν = 3437, 3019, 2961, 2878, 1774, 1520, 1468, 1407, 1370, 1329, 1217, 1167, 1063, 1038, 1024, 981, 950, 900, 848 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.94 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 1.11–1.19 (m, 1H), 1.32 (s, 3H), 1.40–1.49 (m, 1H), 1.74–1.79 (m, 1H), 1.86–1.96 (m, 2H), 2.06–2.12 (m, 2H, OH), 2.54 (d, *J* = 17.4 Hz, 1H), 2.74 (dd, *J* = 17.4, 5.2 Hz, 1H), 3.83–4.07 (m, 4H), 4.11 (dd, *J* = 11.3, 2.7 Hz, 1H), 4.44–4.46 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$/$CHCl_3$): δ = 18.2, 19.4, 19.5, 23.4, 28.0, 37.7, 39.0, 41.7, 64.3, 64.5, 68.5, 86.1, 110.4, 176.0. HRMS (ESI-TOF) (*m*/*z*) [M$^+$+Na] calcd for $C_{14}H_{24}O_5Na$: 295.1521, found 295.1526.
12. For some of the intermediates towards the synthesis of **15** see: (a) Schinzer, D.; Limberg, A.; Böhm, O. M. *Chem. Eur. J.* **1996**, *2*, 1477–1482; (b) Feducia, J. A.; Gagne, M. R. *J. Am. Chem. Soc.* **2008**, *130*, 592–599; c *Data for compound* **15**: IR (CHCl3): ν = 3077, 2977, 2931 2857, 1694, 1640, 1447, 1378, 1246, 1217, 1167, 1112, 994, 974, 914, cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.61 (s, 3H), 2.05–2.20 (m, 4H), 2.58 (q, *J* = 7.2 Hz, 2H), 3.11 (t, *J* = 7.3 Hz, 2H), 5.01 (dd, *J* = 17.0, 1.5 Hz, 1H), 5.02 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.11 (t, *J* = 7.0 Hz, 1H), 5.75–5.85 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$/$CHCl_3$): δ = 6.0, 16.3, 32.1, 32.3, 38.9, 114.5, 123.2, 137.6, 138.4. HRMS (ESI-TOF) (*m*/*z*) [M$^+$+Na] calcd for $C_9H_{15}INa$: 273.0110, found 273.0108.