Studies towards the total synthesis of novel marine diterpene havellockate. Construction of the tetracyclic core

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Abstract—The synthesis of the tetracyclic core present in the novel marine diterpenoid havellockate **1** has been accomplished from the readily available *endo*-dicyclopentadienone-10-ethylene ketal **3** as a prelude to the projected total synthesis of the natural product.

Diterpenes in general and particularly those of marine origin are rich in skeletal diversity and structural complexity and many of them possess impressive and wide ranging biological activities.[1] These attributes make diterpenenoids from marine sources attractive and challenging targets of synthesis.[1] In 1998, a new diterpenoid named havellockate **1**, bearing a novel skeleton, was isolated from the soft coral species *Sinularia granosa* collected from the Havellock island of the Andaman and Nicobar group of Islands in the Indian ocean.[2] The structure of havellockate **1** was determined on the basis of spectral data and confirmed by single-crystal X-ray analysis.[2] The skeleton of **1** is biogenetically quite intriguing and is probably derived from a cembranoid precursor through extensive restructuring and concomitant oxy-functionalization. The tetracyclic core present in the complex structure of **1** with eight stereogenic centers and many functionalities consists of a *cis*-fused hydrindane moiety to which two γ-lactone units are appended, one of them being spiro-fused. These structural features of **1** aroused our interest in its total

synthesis. As the first objective, we targeted the tetracyclic core structure **2**, identified through retrosynthetic considerations indicated in Scheme 1. It was surmised that with the acquisition of the tetracyclic ketolactone **2**, the overall strategy could be tactically modified and adopted for the synthesis of **1**. Herein, we report a synthesis of tetracyclic ketolactone **2** with complete regio- and stereocontrol.

For the synthesis of **2**, readily available[3] *endo*-dicyclopentadienone **3** was chosen as the starting material as the *cis*-hydrindane moiety is embedded into this framework (see bold portion in **3**) and can be unravelled by removing the ketal bearing C-10 carbon bridge.[4] Stereoselective epoxidation of the enone moiety in **3** to *exo*-epoxide **4** and hydride reduction furnished the *trans* 1,3-diol **5** (Scheme 2).[5] The *endo* hydroxyl group in **5** was protected through intramolecular halo-etherification to furnish tetracyclic bromoether **6**.[5] The *exo*-hydroxyl group in **6** was now inverted through oxidation to ketone **7** and stereoselective reduction
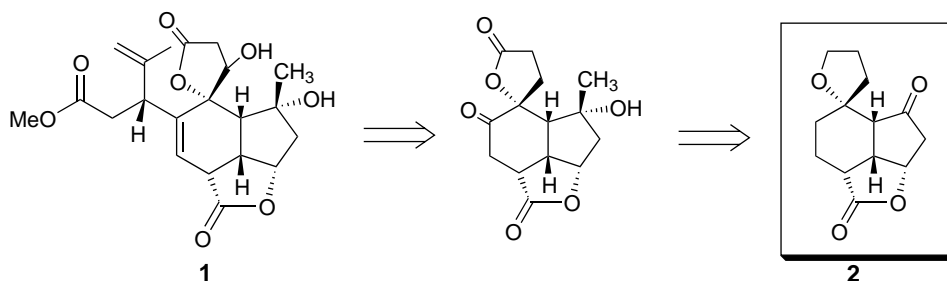
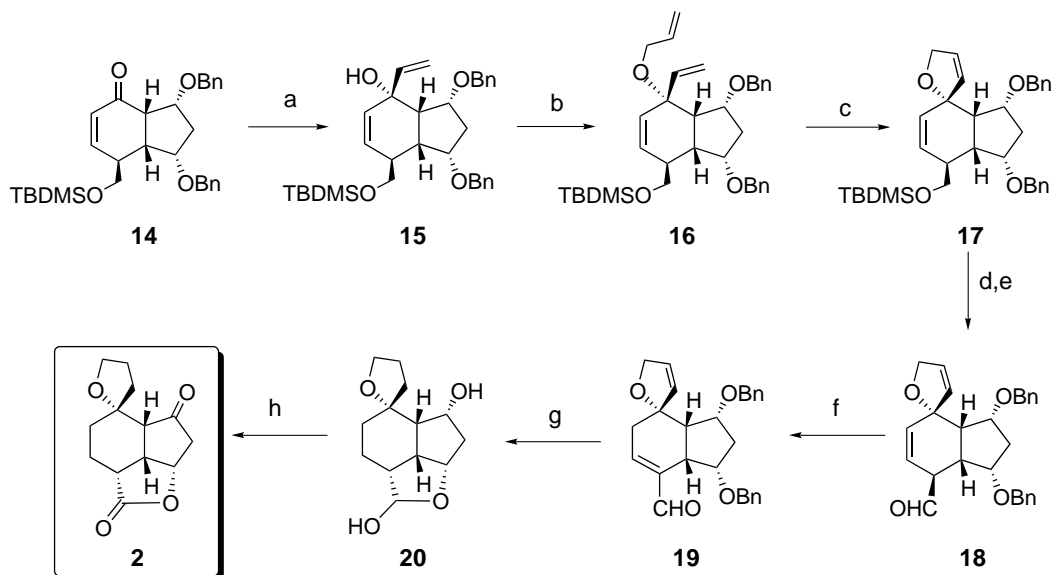**Scheme 1.**

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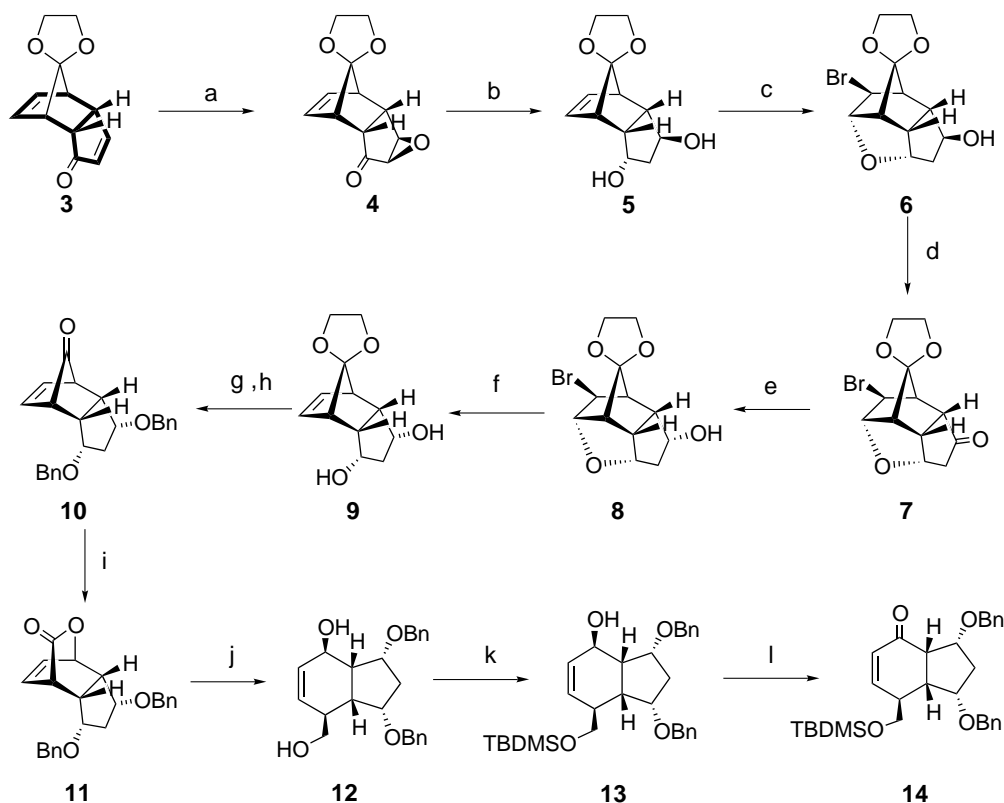
Scheme 2. *Reagents and conditions*: (a) 30% H$_2$O$_2$, 6N NaOH, MeOH, 0°C, 30 min, 80%; (b) LAH, THF, 0°C to reflux, 4.5 h, 88%; (c) NBS, DCM, rt, 3 h, 90%; (d) PCC, DCM, 4 Å molecular sieves, 0°C to rt, 1 h, 85%; (e) NaBH$_4$, MeOH, 0°C, 15 min, 80%; (f) Zn/NH$_4$Cl, THF/H$_2$O (9:1), 50°C, 2 h, 65%; (g) BnBr, NaH, ^{n}Bu$_4$NI (cat.), 0°C to rt, 10 h, 72%; (h) Amberlyst-15, CH$_3$COCH$_3$, 65°C, 15 h, 80%; (i) 90% aq. HOAc, 30% H$_2$O$_2$, CH$_3$COONa, 0°C to rt, 6 h, 45%; (j) LAH, THF, 0°C, 2 h, 90%; (k) TBDMSCl, imidazole, DMAP (cat.), DCM, rt, 3 h, 70%; (l) PCC, DCM, 4 Å molecular sieves, 0°C to rt, 45 min, 89%.

from the *exo*-face to deliver the *endo*-alcohol **8** (Scheme 2).[5] On exposure to zinc metal, the olefinic and the hydroxyl groups could be released back from the bromoether **8** to furnish the symmetrical *endo,endo*-1,3-diol **9**.[5] Besides having the requisite stereochemistry of the hydroxyl groups, the symmetrical nature of **9** circumvented any regiochemical problems that could surface during the opening of the C-10 bridge (vide infra). The two *endo*-hydroxyl groups in **9** were protected as the benzyl ethers, then ketal deprotection led to the norbornenone derivative **10** (Scheme 2). Carefully controlled Baeyer–Villiger oxidation on **10** delivered a single lactone **11**, which was reductively cleaved to unravel the *cis*-hydrindane **12** with secured stereochemistry at six stereogenic centers. The primary hydroxyl group in **12** was selectively protected as the TBDMS-ether **13** and the secondary alcohol oxidized with PCC to deliver enone **14**, a key substrate on which two lactone moieties present in the target compound **2** were to be installed (Scheme 2).

For the stereoselective spiro-lactone annulation at the carbonyl site in **14**, a RCM based protocol was preferred.[6] Addition of vinylmagnesium bromide to **14** occurred exclusively from the convex face to give vinyl alcohol **15** (Scheme 3). Allylation of the tertiary hydroxy group in **15** was smooth and the allyl-ether **16** was readily realized. Exposure of **16** to Grubbs' catalyst gave spiro-annulated dihydrofuran **17** in excellent yield

(Scheme 3). The spiro-fused dihydrofuran moiety in **17** could be further oxidized to the corresponding γ-lactone.[7] The TBDMS protective group in **17** was now dispensed with and the resulting primary hydroxyl group was oxidized in a controlled manner to give the *exo*-aldehyde **18**. The next task was to invert the aldehyde stereochemistry in **18** and for this purpose the cyclohexene double bond in it was isomerized in the presence of DBU to deliver the α,β-unsaturated aldehyde **19**. Catalytic hydrogenation of **19**, besides liberating the benzyl protected hydroxyl groups, also reduced the α,β-unsaturated aldehyde functionality from the preferred *exo*-face to deliver the *endo*-aldehyde group, which was concomitantly captured by the appropriately positioned *endo*-hydroxyl group resulting in the lactol **20**. PCC oxidation of **20** led to the target compound **2**, in the process generating not only the second γ-lactone ring but also the cyclopentanone moiety required to set-up the tertiary alcohol unit present in the natural product **1**.

In short, we have accomplished a synthesis of the tetracyclic core **2** present in the marine diterpenoid havellockate **1**, with good regio- and stereochemical control, from a readily available dicyclopentadienone derivative **3**. The overall synthetic strategy delineated here for havellockate **1** is also amenable to adaptation for the synthesis of many novel but related diterpenoid

Scheme 3. *Reagents and conditions*: (a) vinylmagnesium bromide, THF, 0°C to rt, 10 h, 70%; (b) allyl bromide, NaH, ^{n}Bu$_4$NI (cat.), THF, 0°C, 1 day, 78%; (c) Grubbs' catalyst (20 mol%), DCM, rt, 2 h 90%; (d) ^{n}Bu$_4$NF, THF, 0°C to rt, 10 h, 65%; (e) PCC, DCM, 4 Å molecular sieves, 10 min, 0°C, 70%; (f) DBU, DCM, 0°C to rt, 1.5 h, 60%; (g) H$_2$, 10% Pd–C, EtOAc, rt, 2 h, 50%; (h) PCC, DCM, 4 Å molecular sieves, 0°C to rt, 15 h, 70%.

skeleta of marine origin like mandapamate and isomandapamate.[8]

References

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5. All new compounds reported here were racemic and characterized on the basis of spectroscopic data (IR, v in cm^{-1}, ^{1}H and ^{13}C NMR, J in Hz) and elemental analyses. Selected spectral data. **14**: IR: 1674; (300 MHz, CDCl$_3$): δ_H 7.37–7.18 (10H, m), 7.10 (1H, dd, *J* 10, 2), 6.16 (1H, dd, *J* 10, 2.5), 4.59–4.35 (4H, m), 4.22–4.20 (1H, m), 4.09 (1H, dd, *J* 9.5, 3.5), 4.02–3.95 (1H, m), 3.61 (1H, dd, *J* 9.5, 7.2), 2.96 (1H, m), 2.66–2.58 (2H, m), 2.48–2.38 (1H, m), 1.96 (1H, ddd, *J* 14, 8.5, 3), 0.87 (9H, s), 0.00 (6H, s); (75 MHz, CDCl$_3$): δ_C 198.01 (C=O), 154.62 (CH), 138.40 (C), 138.24 (C), 129.92 (CH), 128.38 (CH), 128.17 (CH), 127.61 (CH), 127.36 (CH), 127.22 (CH), 127.04 (CH), 100.56 (C), 80.93 (CH), 79.06 (CH), 72.02 (CH$_2$), 71.42 (CH$_2$), 65.28 (CH$_2$), 51.36 (CH), 40.74 (CH), 37.82 (CH), 37.41 (CH$_2$), 25.87 (CH$_3$), 18.24 (C), −5.36 (CH$_3$). **17**: IR: 1607; (300 MHz, CDCl$_3$): δ_H 7.35–7.20 (10H, m), 5.78–5.64 (4H, m), 4.76–4.45 (6H, m), 4.00 (1H, m), 3.96–3.87 (2H, m), 3.58 (1H, dd, *J* 9.6, 6.6), 2.70–2.66 (1H, m), 2.41–2.34 (2H, m), 1.91–1.82 (2H, m), 0.88 (9H, s), 0.00 (6H, s); (75 MHz, CDCl$_3$): δ_C 140.10 (C), 138.84 (C), 135.01 (CH), 130.83 (CH), 130.37 (CH), 128.27 (CH), 127.90 (CH), 127.32 (CH), 127.24 (CH), 126.91 (CH), 126.58 (CH), 124.11 (CH), 88.40 (C), 81.59 (CH), 78.43 (CH), 74.56 (CH$_2$), 71.67 (CH$_2$), 71.43 (CH$_2$), 66.30 (CH$_2$), 50.09 (CH), 38.80 (CH), 37.68 (CH$_2$), 36.62 (CH), 25.97 (CH$_3$), 18.32 (C), −5.26 (CH$_3$), −5.39 (CH$_3$). **19**: IR: 1683, 1647; (300 MHz, CDCl$_3$): δ_H 9.46 (1H, s), 7.28–7.20 (10H, m), 6.77 (1H, m), 5.83–5.78 (2H, m), 4.72 (2H, br s), 4.50 (2H, q, *J* 12.5), 4.47–4.28 (2H, m), 4.18–4.17 (1H, m), 3.41 (1H, t, *J* 8.4), 3.31 (1H, td, *J* 18, 3), 2.29–2.17 (3H, m), 1.61–1.52 (2H, m); (75 MHz, CDCl$_3$): δ_C 193.69, 147.91, 140.74, 139.21, 138.85, 134.10, 128.03, 127.98, 127.93, 127.30, 127.14, 126.91, 124.92, 90.06, 81.11, 80.01, 74.68, 72.44, 70.83, 49.14, 40.93, 37.14, 36.73. **2**: IR: 1766, 1739; (300 MHz,

CDCl$_3$): δ_H 5.08 (1H, t, J 6.6), 3.67 (2H, m), 3.41–3.32 (1H, m), 2.92 (1H, t, J 9.9), 2.74–2.52 (3H, m), 2.40 (1H, d, J 10.8), 2.35–2.24 (1H, m), 2.05–1.61 (5H, m), 1.25 (1H, td, J 9.9, 14.1); (75 MHz, CDCl$_3$): δ_C 216.08 (CO), 179.37 (CO), 82.12 (C), 77.12 (CH), 68.35 (CH$_2$), 51.47 (CH), 44.45 (CH$_2$), 38.72 (CH$_2$), 35.86 (CH), 34.15 (CH$_2$), 31.15 (CH$_2$), 25.28 (CH$_2$), 17.45 (CH$_2$).

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7. PCC oxidation of **17** readily gave the spiro fused α,β-unsaturated γ-lactone (i). The double bond in (i) was suitable for the introduction of the hydroxyl group in this ring as present in the natural product **1**.

17 → **(i)**

PCC, py(cat.), DCM

40%
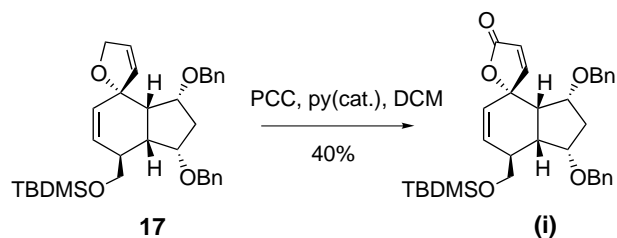
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