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Expedient asymmetric synthesis of a functionalized 5-7-6 fused tricyclic skeleton present in caribenol A through ring opening-ring closing metathesis of a norbornene derivative

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ABSTRACT

A concise approach towards the synthesis of the highly biologically active terpenoid caribenol A is described involving sequential aldol condensation-ring opening-ring closing metathesis of a norbornene derivative.

Caribenol A **1** is a norditerpene isolated[1] from the West Indian gorgonian octocoral *Pseudopterogorgia elisabethae*. It possesses an unusual C_{19} rearranged carbon skeleton previously not encountered in the terpenoid family. It exhibits strong inhibitory activity against *Mycobacterium tuberculosis* ($H_{37}Rv$). Infection by this organism causes tuberculosis, a disease that results in over three million deaths worldwide each year.[2] It also exhibits weak *in vitro* antiplasmodial activity against chloroquine-resistant *Plasmodium falciparum* W2. Intrigued by the interesting biological activities and intricate structure, we felt worthwhile to launch a program aimed at developing a flexible route for the synthesis of caribenol A and its analogues.

Herein we report a convergent asymmetric route to caribenol A using a domino metathesis involving ring opening-ring closing metathesis (RO-RCM) of a norbornene derivative as the key step.

Domino metathesis involving RO-RCM[3] of strained cycloalkenes has emerged as a powerful tool in the synthesis of a variety of polycyclic ring systems. Recently we have demonstrated[4] its utility in the rapid construction of bridged- as well as condensed-ring systems which are otherwise difficult to make. We envisioned that a tandem RO-RCM of the norbornene derivative **4** would generate directly the tricycle **3**, the tricyclic core structure of caribenol A **1** (Scheme 1). The intermediate **3** is functionalized enough for the incorporation of the butenolide unit through the carboxylic acid **2**. The norbornene derivative **4** would be available from an aldol condensation between the aldehyde **5** and *S*-(+)-carvone **6**.

Initially we chose the aldehyde **7** for carrying out the aldol reaction with *R*-(-)-carvone. Aldol condensation of carvone with aldehydes usually proceeds stereoselectively[5] to produce adducts in which the electrophiles preferentially add from the side opposite to the isopropylidene unit producing trans-5,6-disubstituted compounds. However, reaction of the lithium enolate of *ent*-**6** with the aldehyde **7** failed to produce the desired aldol condensation product **9**. The only product (1:2 diastereomeric mixture) that could be isolated after column chromatography in 40% yield was assigned the structure **8** based on the spectral data.[6] The enolate of carvone failed to add to the aldehyde **7**[7] possibly due to the steric bulk of the latter. At this juncture we thought of exploring an alternative route for accessing the norbornene derivative **4** or its analogue using the concept delineated in Scheme 2.

In order to avoid the formation of the Michael addition product **8**, we chose reaction of dihydrocarvone **10**[8] with the less sterically demanding aldehyde acrolein. The reaction of lithium enolate of **10** with acrolein afforded exclusively the aldol product **11** in 70% yield. The stereochemical assignment to **11** follows from the reaction of lithium enolate of dihydrocarvone with aldehyde to form adduct in which C_2- and C_3- substituents bear a trans relationship.[9] Further, ^{1}H NMR spectrum of the aldol product **11** showed that H_2 appeared at δ 3.36 as a doublet with J = 11.2 Hz and H_3 appeared at δ 2.08 as a dd with J = 11.3, 2.3 Hz. This large coupling constant between H_2 and H_3 indicated their trans diaxial relationship. Oxidation of this compound with Dess–Martin periodinane (DMP)

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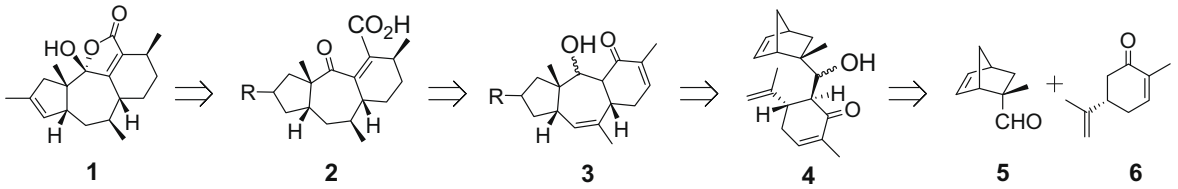
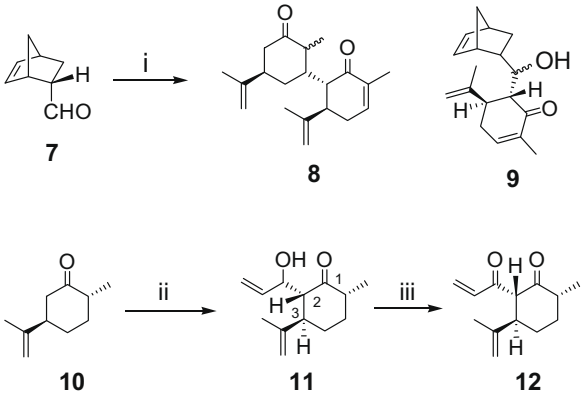


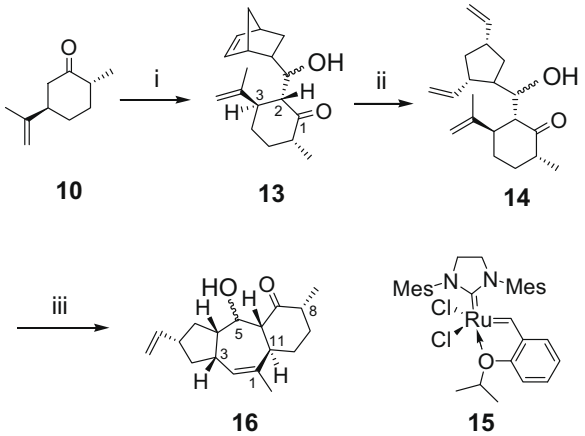
Scheme 1. General retro synthetic analysis.



Scheme 2. Reagents and conditions: (i) LDA, THF–HMPA, −100 °C, *R*-carvone, 15 min, 40%; (ii) LDA, THF, −78 °C, acrolein, 10 min, 70%; (iii) DMP, CH_2Cl_2, 1 h, 92%.

afforded the enedione **12** along with its enol (3:1) in 92% yield. However, Diels–Alder reaction of the enedione **12** with cyclopentadiene gave a complex mixture of products from which no Diels–Alder adduct could be isolated.

After successful realization of aldol reaction between dihydrocarvone and acrolein, we focused on reaction of dihydrocarvone with the aldehyde **7**. In contrast to the failure of the enolate of carvone **6** to add to the aldehyde **7**, addition of the enolate of dihydrocarvone **10** proceeded smoothly to produce the adduct **13** (as a 1:2 epimeric mixture at the center bearing the hydroxyl group) in 70% yield (Scheme 3). The trans stereochemical relationship between H_2 and H_3 in **13** is based on analogy to the formation of the adduct **11** from reaction of the enolate of **10** to acrolein. Treatment of the norbornene derivative **13** in dichloromethane with Grubbs' 1st generation catalyst $Cl_2(PCy_3)_2Ru{=}CHPh$ under ethylene atmosphere at rt for 6 h provided quantitatively the ring



Scheme 3. Reagents and conditions: (i) LDA, THF–HMPA, −100 °C, **7**, 15 min, 70%; (ii) 5 mol % Grubbs' I, $CH_2{:}CH_2$, CH_2Cl_2, 6 h, quant.; (iii) 30 mol % of cat. **15**, toluene, 110 °C, 2 h, 45%.

opened product **14** only. Reaction of **14** with the same catalyst for longer reaction time at elevated temperature failed to undergo ring closure. Attempted ring closure of **14** with Grubbs' 2nd generation catalyst led exclusively to a dimeric product. Finally ring closure of **14** was achieved using Hoveyda-Grubbs' catalyst **15** to produce the tricycle **16** as a C-5 epimeric mixture in 45% yield. The compound **16** closely resembles the tricyclic unit present in caribenol A. Following this protocol the dihydro derivative of *S*-(+)-carvone will provide an analogue of the tricycle **16** with desired stereochemistry at the ring fusion of caribenol A. Currently we are working on its total synthesis following the protocol described here starting with the aldehyde **5** and the results will be described elsewhere.

In conclusion we have developed an expedient convergent route towards the synthesis of caribenol A. The key steps involve an aldol condensation of dihydrocarvone with norbornene 2-carbaxaldehyde followed by RO-RCM of the resulting adduct.

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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.2009.07.012.

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6. All new compounds were characterized through IR, ^1H, ^{13}C NMR and HRMS spectroscopy. Physical data for selected compounds: Compound **8**: IR (neat): 1661, 1709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.14 (3H, d, J = 6.2 Hz), 1.25–1.41 (2H, m), 1.61 (3H, s), 1.71(3H, s), 1.87 (3H, s), 2.16–2.23 (2H, m), 2.29–2.40 (2H, m), 2.53–2.57 (3H, m), 2.78–2.89 (2H, m), 4.62 (1H, br s), 4.71 (1H, br s), 4.83 (1H, br s), 4.98 (1H, br s), 6.81 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) (for the major diastereomer): δ 12.2 (CH_3), 16.0 (CH_3), 20.4 (CH_3), 22.5 (CH_3), 28.5 (CH_2), 34.0 (CH_2), 43.5 (CH), 45.0 (CH), 45.1 (CH), 46.5 (CH), 46.8 (CH_2), 48.1 (CH), 109.9

(CH_2), 112.5 (CH_2), 136.8 (C), 144.7 (C), 144.9 (CH), 147.4 (C), 201.4 (CO), 212.0 (CO); HRMS (ESI) calcd for $C_{20}H_{28}O_2Na$ $(M+Na)^+$, 323.1987; found 323.1988. Compound **11**: IR (neat): 1698, 3526 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.97 (3H, d, J = 6.2 Hz), 1.31–1.45 (1H, m), 1.72 (3H, s), 1.79–1.82 (2H, m), 2.08 (1H, dd, J = 2.3, 11.3 Hz), 2.41–2.50 (2H, m), 2.70–2.80 (1H, m), 3.36 (1H, J = 11.2 Hz), 4.0 (1H, m), 4.89 (2H, d, J = 6.4 Hz), 5.07 (1H, d, J = 10.5 Hz), 5.17 (1H, d, J = 17.2 Hz), 6.03 (1H, ddd, J = 6.1, 10.5, 17.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (CH_3), 18.6 (CH_3), 31.2 (CH_2), 35.7 (CH_2), 46.3 (CH), 50.8 (CH), 57.4 (CH), 71.2 (OCH), 113.4 (CH_2), 114.3 (CH_2), 140.8 (CH), 145.3 (C), 215.8 (CO); HRMS (ESI) calcd for $C_{13}H_{20}O_2Na$ $(M+Na)^+$, 231.1361; found 231.1364. Compound **12** (as 3:1 mixture of keto-enol tautomers): IR (neat): 1651, 1714, 3458 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (for the diketone **12** from the mixture): δ 1.01 (3H, d, J = 7.7 Hz), 1.48 (1H, dt, J = 3.3, 13.0 Hz), 1.70 (3H, s), 1.73–1.75 (1H, m), 1.95 (1H, q, J = 3.3 Hz), 2.07–2.12 (1H, m), 2.40–2.50 (1H, m), 2.88 (1H, dt, J = 3.6, 12.3 Hz), 3.81 (1H, d, J = 12.3 Hz), 4.66 (1H, br s), 4.72 (1H, br s), 5.71 (1H, d, J = 10.6 Hz), 6.14 (1H, d, J = 17.6 Hz), 6.40 (1H, dd, J = 10.5, 18.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (for the diketone **12** from the mixture): δ 14.3 (CH_3), 20.4 (CH_3), 31.0 (CH_2), 34.7 (CH_2), 45.6 (CH), 49.3 (CH), 64.1 (CH), 111.6 (CH_2), 127.8 (CH_2), 136.0 (CH), 145.8 (C), 197.4 (CO), 209.5 (CO). Enol form of **12** in the mixture: ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 (3H, d, J = 7.3 Hz), 1.63–1.67 (1H, m), 1.77 (3H, s), 1.80–1.83 (1H, m), 2.0 (1H, q, J = 3.3 Hz), 2.13–2.17 (1H, m), 2.44 (1H, m), 3.21 (1H, m), 4.57 (1H, br s), 4.89 (1H, br s), 5.64 (1H, dd, J = 2.2, 10.1 Hz), 6.31 (1H, dd, J = 2.2, 17.6 Hz), 6.44 (1H, m), 17.0 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.7 (CH_3), 21.8 (CH_3), 23.0 (CH_2), 24.9 (CH_2), 36.2 (CH), 41.0 (CH), 114.0 (CH_2), 127.0 (CH_2), 130.6 (CH), 148.1 (C), 195.2 (CO); HRMS (ESI) calcd for $C_{13}H_{18}O_2Na$ $(M+Na)^+$, 229.1205; found 229.1209. Compound **13** (for both diastereomers): IR (neat): 1693, 3535 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.26–0.31 (1H, m), 0.98 (3H, d, J = 6.3 Hz), 1.14–1.23 (2H, m), 1.34–1.44 (2H, m), 1.60 (3H, s), 1.73–1.82 (3H, m), 2.02–2.11 (1H, m), 2.29 (1H, d, J = 12.1 Hz) 2.36–2.56 (2H, m), 2.65–2.76 (2H, m), 3.08 (1H, br s), 3.27 (1H, d, J = 12.0), 4.78–4.85 (2H, m), 5.98–6.08 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 14.2 (CH_3), 18.6 (CH_3), 19.1 (CH_3), 30.0 (CH_2), 30.5 (CH_2), 31.5 (CH_2), 31.6 (CH_2), 36.2 (CH_2), 36.4 (CH_2), 42.4 (CH), 42.5 (CH), 43.6 (CH), 44.2 (CH), 44.4 (CH), 44.7 (CH), 46.7(CH), 46.8 (CH), 49.0 (CH_2), 50.0 (CH_2), 51.4 (CH), 51.6 (CH), 54.7 (CH), 55.6 (CH), 74.2 (OCH), 74.9 (OCH), 113.0 (CH_2), 113.3 (CH_2), 130.8 (CH), 133.4 (CH), 136.8 (CH), 138.7 (CH), 145.3 (C), 145.4 (C), 217.2 (CO), 217.5 (CO); HRMS (ESI) calcd for $C_{18}H_{26}O_2Na$ $(M+Na)^+$, 297.1830; found 297.1830. Compound **14** (for both diastereomers): IR (neat): 1703, 3473 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$):δ 0.97 (3H, d, J = 6.3 Hz), 1.27–1.39 (2H, m), 1.50–1.61 (1H, m), 1.66 (3H, s), 1.75–1.78 (2H, m), 2.03–2.18 (3H, m), 2.33–2.58 (4H, m) 2.62–2.73 (1H, m), 2.89–3.02 (2H, m), 3.26–3.41 (1H, m), 4.82–5.02 (6H, m), 5.70–5.85 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 18.7 (CH_3), 19.4 (CH_3), 31.3 (CH_2), 31.5 (CH_2), 35.7 (CH_2), 36.0 (CH_2), 36.5 (CH_2), 36.6 (CH_2), 37.4 (CH_2), 39.9 (CH), 41.8 (CH_2) 42.6 (CH), 44.4 (CH), 45.4 (CH), 46.6 (CH), 46.7 (CH), 48.3 (CH), 48.6(CH), 51.2 (CH), 51.9 (CH), 54.7 (CH), 55.1 (CH), 70.7 (OCH), 71.7 (OCH), 112.4 (CH_2), 112.6 (CH_2), 113.2 (CH_2), 113.4 (CH_2), 114.5 (CH_2), 139.8 (CH), 140.6 (CH), 143.5 (CH), 143.7 (CH), 144.9 (C), 145.3 (C), 216.7 (CO), 217.6 (CO); HRMS (ESI) calcd for $C_{20}H_{30}O_2Na$ $(M+Na)^+$, 325.2144; found 325.2144. Compound **16**: IR (neat): 1693, 3533 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (3H, d, J = 6.3 Hz), 1.21–1.38 (2H, m), 1.64–1.70 (1H, m), 1.77 (3H, br s), 1.83–1.88 (2H, m), 2.09–2.15 (3H, m), 2.36–2.47 (3H, m), 2.58–2.82 (3H, m), 2.92–2.97 (1H, m), 4.25–4.27 (1H, m), 4.71 (1H, br s), 4.80 (1H, Br s), 5.17–5.22 (1H, m), 5.41 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) (for the major diastereomer): δ 14.5 (CH_3), 19.5 (CH_3), 28.9 (CH_2), 32.0 (CH_2), 35.5 (CH_2), 36.9 (CH_2), 37.7 (CH), 38.0 (CH), 41.5 (CH), 42.0 (CH), 45.3 (CH), 59.6 (CH), 71.8 (OCH), 104.6 (CH_2), 113.9 (CH), 131.1 (CH), 151.1 (C), 211.5 (CO); HRMS (ESI) calcd for $C_{18}H_{26}O_2Na$ $(M+Na)^+$, 297.1830; found 297.1834.

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