

An efficient construction of a C_3 -symmetric macrocycle by head to tail cyclotrimerization of an unsymmetrical diene via a sequence of highly regio- and stereoselective metathesis reactions[☆]

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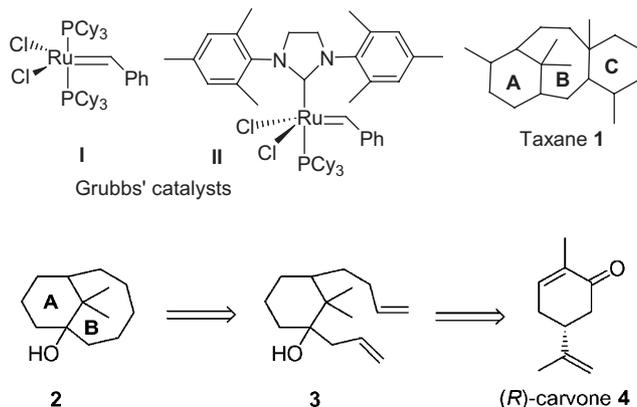
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Abstract—A sequence of highly regio- and stereoselective intermolecular metatheses followed by ring-closing metathesis of an 1-allyl-3-(3-butenyl)cyclohexanol led to a C_3 -symmetric head to tail cyclic trimer; a 24-membered macrocycle containing three inward directed hydroxyl groups creating a hydrophilic cavity.

The last decade has witnessed an exponential growth in the application of the ring-closing olefin metathesis (RCM) reaction in organic synthesis.¹ The catalytic nature of the reaction in combination with its operational simplicity and the remarkable tolerance of Grubbs' first (I) and second (II) generation catalysts to various functional groups and their stability to various conditions are key factors responsible for the increased use of the RCM reaction. A number of research groups have explored the RCM reaction for the construction of medium-ring and macrocyclic compounds.¹ However, during the construction of medium rings by RCM reactions, cyclic dimers have been encountered in a number of instances. For example, during their attempts to construct paddlanes by the RCM reaction of 9-thiabicyclo[4.2.1]nonane dioxides containing two identical alkenyl side chains at the two bridgehead positions, Paquette et al. reported² the isolation of several dimers (15–30%) and trimers (9–20%) depending on the length of the side chains.

Paclitaxel (Taxol) by virtue of its complex structure, coupled with its potent antitumour activity, has attracted the attention of a large number of synthetic

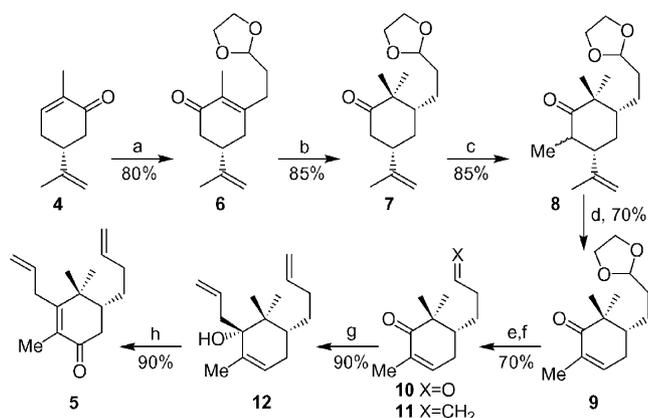
chemists.³ One of the most difficult tasks in the synthesis of the taxane (1) framework is the construction of the B-ring, because of the well known complications associated with the formation of an eight-membered ring.⁴ Recently, Blechert and co-workers reported⁵ the construction of the AB-ring system of taxanes by employing a RCM reaction of a substituted cyclohexane with two *cis*-oriented side arms at the 1- and 3-positions. Encouraged by this report, we have explored the RCM reaction of 1-allyl-3-(3-butenyl)cyclohexanes derived from the readily and abundantly available monoterpene (*R*)-carvone 4 to generate the AB-ring system of taxanes (e.g., 3→2) containing a hydroxy group at C-1 (as in taxol). However, this resulted in the generation of a symmetric cyclic trimer comprising of a 24-membered carbocyclic ring system, instead of the AB-ring system of taxanes, and is the subject of this communication.



Keywords: RCM reaction; Cyclotrimerization; AB-ring of taxanes; Enantiospecific synthesis.

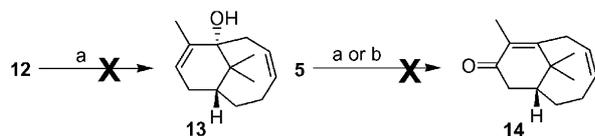
[☆]Chiral Synthons from Carvone, Part 68. For Parts 66 and 67, see Ref. 9.

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Scheme 1. Reagents and conditions: (a) i. Li, (–OCH₂CH₂O)–CHCH₂CH₂Br, THF, 1 h; ii. PCC, silica gel, CH₂Cl₂, 4 h; (b) Li, liq. NH₃, THF; MeI; (c) LDA, THF, MeI, –70 °C → rt, 15 h; (d) O₃/O₂, MeOH:CH₂Cl₂ (1:5), –70 °C; Ac₂O, Et₃N, DMAP, C₆H₆, reflux, 6 h; (e) AcOH, H₂O, 60 °C, 1 h; (f) Ph₃P⁺CH₃I[–], K⁺AmO[–]; C₆H₆, 0–5 °C, 5 min; (g) Zn, CH₂=CHCH₂Br, THF, 20 min; (h) PCC, silica gel, CH₂Cl₂, 4 h.

Initially, we explored the RCM reaction of diene **5**. Diene **5** was obtained from (*R*)-carvone **4** (Scheme 1). Alkylative 1,3-enone transposition transformed carvone **4** into the β-substituted enone **6**. Reductive alkylation of the enone **6** with lithium in liquid ammonia and methyl iodide furnished the cyclohexanone **7** in a highly stereoselective manner. Kinetic alkylation with LDA and methyl iodide followed by ozonolysis and Criegee fragmentation⁶ of **8** transformed the cyclohexanone **7** into the enone **9**. The acetal group in **9** was transformed into a terminal olefin via hydrolysis and Wittig reaction of **10** to generate the enone **11**. Addition of an allyl group to the enone **11** gave the tertiary alcohol **12**, which on oxidation furnished the enone **5**. RCM reactions of both the enone **5** and the alcohol **12** were explored with Grubbs' first and second generation catalysts. However, no detectable amounts of RCM products **13** or **14** were formed under a variety of conditions.



(a) Grubbs' first generation catalyst, C₆H₆ or CH₂Cl₂ reflux.
(b) Grubbs' second generation catalyst, PhMe, C₆H₆ or CH₂Cl₂ (0.005 M) reflux.

The *trans*-orientation of the two side chains in the alcohol **12** and the substantial increase in strain for the formation of a bicyclo[5.3.1]undecane with a bridgehead double bond are perhaps responsible for the failure of the RCM reactions of the alcohol **12** and the enone **5**. Hence, we contemplated the RCM reaction of the alcohol **15**, Scheme 2. Thus, 1,3-enone transposition of carvone **4** generated 3-(3-butenyl)carvone **16**, which on reductive methylation furnished the cyclohexanone **17** in a highly stereoselective manner. Reaction of the cyclohexanone **17** with allyl bromide and zinc furnished a 10:1 mixture of the *cis*- and *trans*-tertiary alcohols **15**

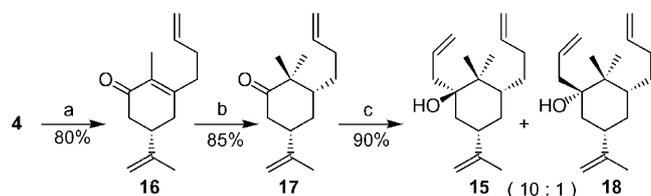
and **18**,[†] which were separated on a silica gel column. The RCM reaction of the *cis*-alcohol **15** under a variety of conditions using Grubbs' first generation catalyst did not furnish any products. However, refluxing a 0.05 M benzene solution of the alcohol **15** with 5 mol % of Grubbs' second generation catalyst for 1 h generated a

[†]All the compounds exhibited spectral data (IR, ¹H and ¹³C NMR, LRMS and HRMS) consistent with their structures. Selected spectral data for the minor alcohol **18**: [α]_D²⁴ –26.7 (*c* 1.5, CHCl₃). IR (neat): ν_{max}/cm^{–1} 3568, 910, 887. ¹H NMR (300 MHz, CDCl₃+CCl₄): δ 5.95–5.70 (2H, m, 2 × CH=CH₂), 5.18 (1H, dd, *J* 10.2 and 2.1 Hz), 5.09 (1H, d, *J* 18 Hz), 4.97 (1H, dd, *J* 17.1 and 1.8 Hz), 4.90 (1H, d, *J* 10.2 Hz), 4.68 (2H, s, C=CH₂), 2.45–2.30 (1H, m), 2.31 (1H, dd, *J* 13.2 and 8.1 Hz), 2.20–2.05 (2H, m), 1.90–1.65 (2H, m), 1.73 (3H, s, olefinic-CH₃), 1.65–1.45 (5H, m), 1.35–1.20 (2H, m), 1.04 (3H, s) and 1.02 (3H, s) [2 × *tert*-CH₃]. ¹³C NMR (75 MHz, CDCl₃+CCl₄): δ 150.1 (C, C=CH₂), 139.4 (CH, CH=CH₂), 134.1 (CH, CH=CH₂), 119.9 (CH₂, CH=CH₂), 114.4 (CH₂, CH=CH₂), 108.8 (CH₂, C=CH₂), 75.6 (C, C–OH), 46.9 (CH), 42.1 (CH₂), 39.6 (C), 38.4 (CH₂), 34.8 (CH), 34.0 (CH₂), 29.1 (CH₂), 28.8 (CH₂), 27.2 (CH₃), 22.3 (CH₃), 21.3 (CH₃). Mass: *m/z* 221 (M–C₃H₅, 35%), 203 (15), 163 (15), 137 (22), 123 (15), 121 (25), 109 (28), 107 (25), 95 (70), 93 (28). HRMS: *m/z* for C₁₈H₃₀ONa (M+Na), calcd: 285.2194. Found: 285.2189.

For the major isomer **15**: [α]_D²⁴ –9.7 (*c* 6.0, CHCl₃). IR (neat): ν_{max}/cm^{–1} 3572, 910, 887. ¹H NMR (300 MHz, CDCl₃+CCl₄): δ 5.96–5.70 (2H, m, 2 × CH=CH₂), 5.17 (1H, dd, *J* 9.9 and 1.8 Hz), 5.10 (1H, br d, *J* 18.6 Hz), 4.98 (1H, dd, *J* 17.1 and 1.8 Hz), 4.92 (1H, br d, *J* 11.1 Hz), 4.66 (2H, s, C=CH₂), 2.40 (1H, dd, *J* 13.8 and 8.1 Hz), 2.35–2.10 (2H, m), 2.13 (1H, dd, *J* 13.8 and 6.9 Hz), 2.05–1.85 (1H, m), 1.71 (3H, s, olefinic-CH₃), 1.75–1.50 (4H, m), 1.48 (1H, d, *J* 13.2 Hz), 1.44 (1H, d, *J* 13.2 Hz), 1.10–0.90 (2H, m), 0.97 (3H, s) and 0.79 (3H, s) [2 × *tert*-CH₃]. ¹³C NMR (75 MHz, CDCl₃+CCl₄): δ 150.0 (C, C=CH₂), 139.2 (CH, CH=CH₂), 134.5 (CH, CH=CH₂), 119.5 (CH₂, CH=CH₂), 114.5 (CH₂, CH=CH₂), 108.8 (CH₂, C=CH₂), 75.6 (C, C–OH), 41.3 (CH), 41.2 (CH₂), 40.4 (C), 39.4 (CH), 37.7 (CH₂), 33.0 (CH₂), 32.5 (CH₂), 30.2 (CH₂), 21.0 (CH₃), 20.9 (CH₃), 17.5 (CH₃). Mass: *m/z* 221 (M–C₃H₅, 35%), 203 (10), 163 (12), 137 (18), 123 (15), 121 (25), 109 (28), 107 (25), 95 (65). HRMS: *m/z* for C₁₈H₃₀ONa (M+Na), calcd: 285.2194. Found: 285.2186.

For the trimer **20**: mp 174–176 °C [α]_D²⁴ +67.5 (*c* 0.8, CHCl₃). IR (neat): ν_{max}/cm^{–1} 3435, 884. ¹H NMR (300 MHz, CDCl₃+CCl₄): δ 5.55–5.25 (6H, m, CH=CH), 4.65–4.55 (6H, m, C=CH₂), 2.34 (3H, dd, *J* 13.2 and 9.6 Hz), 2.30–1.85 (18H, m), 1.80–1.45 (12H, m), 1.15–0.75 (6H, m), 1.66 (9H, s, 3 × olefinic-CH₃), 0.95 (9H, s) and 0.75 (9H, s) [6 × *tert*-CH₃]. ¹³C NMR (75 MHz, CDCl₃+CCl₄): δ 150.3 (C), 135.6 (CH), 126.3 (CH), 108.6 (CH₂), 75.3 (C), 40.1 (C), 39.7 (CH₂), 39.4 (CH), 38.3 (CH), 37.9 (CH₂), 30.8 (CH₂), 30.0 (CH₂), 27.4 (CH₂), 21.2 (CH₃), 21.1 (CH₃), 17.8 (CH₃). Mass: *m/z* 667 [M–H₂O–OH, 15], 413 (20), 217 (45), 175 (30), 161 (30), 147 (25), 135 (30), 121 (60), 107 (75), 95 (80). HRMS: *m/z* for C₄₈H₇₈O₃Na (M+Na), calcd: 725.5849. Found: 725.5847.

Crystal data for the compound 20: X-ray data were collected at 293K on a SMART CCD-Bruker diffractometer with graphite-monochromated Mo–Kα radiation (λ = 0.7107 Å). Structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on *F*² using SHELXL-97. C₄₈H₇₈O₃·H₂O; MW 721.18; crystal system: orthorhombic, space group: *P*2₁2₁, cell parameters: *a* = 13.306(3) Å, *b* = 18.294(4) Å, *c* = 18.972(4) Å, *V* = 4618.2(17) Å³, *Z* = 4, ρ (calcd) = 1.034 g cm^{–3}, *F*(000) = 1592, μ = 0.063 mm^{–1}, λ = 0.71 Å. *R*1 = 0.089 for 5678 *F*₀ > 4σ(*F*₀) and 0.1258 for all 8448 data, *wR*2 = 0.2548, GoF = 1.020, Restrained GoF = 1.020 for all data. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre [CCDC 259490]. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223 336 033; email:deposit@ccdc.cam.ac.uk).



Scheme 2. Reagents and conditions: (a) i. Li, $\text{CH}_2=\text{CHCH}_2\text{CH}_2\text{Br}$, 40 min; ii. PCC, silica gel, CH_2Cl_2 , 4 h; (b) Li, liq. NH_3 , THF, MeI; (c) Zn, $\text{CH}_2=\text{CHCH}_2\text{Br}$, THF, 20 min.

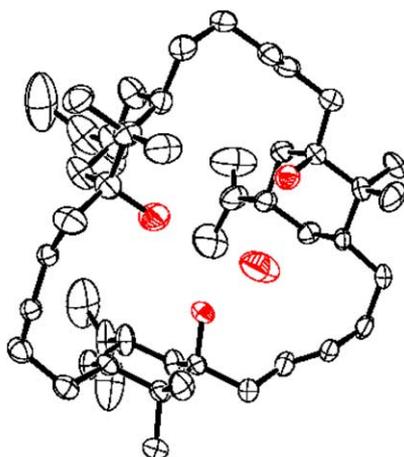
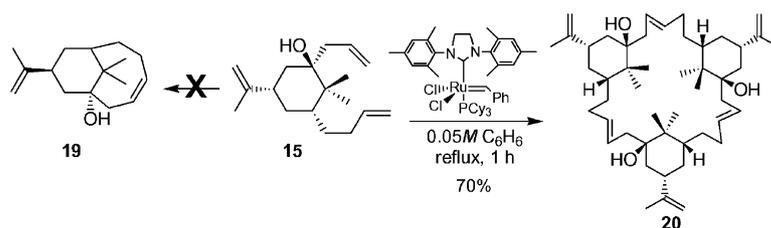


Figure 1. ORTEP diagram of the trimer **20** (hydrogen atoms were not included for clarity).

product, mp 174–176 °C, in an isolated yield of 70%, which exhibited ^1H and ^{13}C NMR spectral data matching for the RCM product **19**. However, mass spectroscopy failed to show the expected molecular ion, which prompted us to resort to X-ray analysis. Single crystal X-ray diffraction analysis revealed the structure of the product as the symmetric head to tail cyclic trimer **20**.[†] As depicted in Figure 1, the triol **20** accommodated one molecule of water as a guest via hydrogen bonding with the three inward pointing hydroxyl groups. Increasing the dilution of the reaction to 0.005 M only resulted in a decrease in the yield of the trimer **20**, and no detectable amount of either a monomeric or dimeric product was noticed. Formation of the structurally ordered trimer **20** from an unsymmetrical diene **15** is very intriguing. It requires a very highly planned reaction sequence, two cross-coupling metatheses and one RCM in a highly regio- (butenyl of one moiety couples with the allyl of the counterpart) and stereoselective manner to generate the C_3 -symmetric head to tail cyclic trimer,⁷ a 24-membered *E,E,E*-cyclotetracosatrienetriol **20**.



In conclusion, we have observed that the presence of appropriate side arms at the C-1 and C-11 positions of the A-ring of taxanes efficiently generated a C_3 -symmetric head–tail cyclic trimer in a highly regio- and stereoselective manner via metathesis reactions, instead of the expected AB-ring system of taxane. The present result is in contrast to the successful construction of the AB-ring of taxanes by Blechert and co-workers employing a similar approach,⁸ confirming that minor variations in substrates can lead to varying results in RCM reactions. The presence of one water molecule in the centre (cf. Fig. 1) as a guest reveals the potential of the cyclic triol **20** as a suitable chiral host molecule.⁷ Further investigations on the generality of this reaction as well as the binding ability of the triol **20** are currently under progress.

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