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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☆

A. Srikrishna* and Dattatraya H. Dethe

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, India

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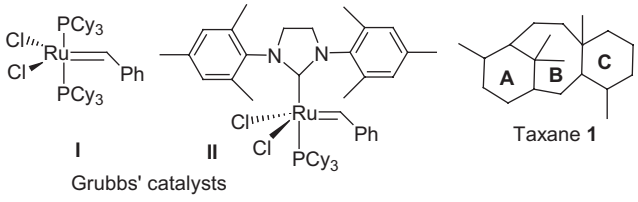
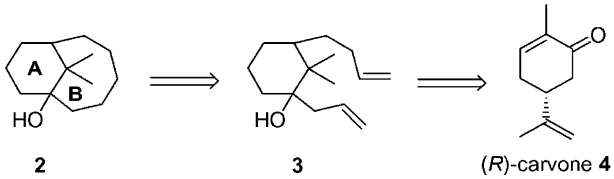
Abstract—A sequence of highly regio- and stereoselective intermolecular metatheses followed by ring-closing metathesis of an 1-allyl-3-(3-butenyl)cyclohexanol led to a C_3-symmetric head to tail cyclic trimer; a 24-membered macrocycle containing three inward directed hydroxyl groups creating a hydrophilic 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. reported[2] 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 reported[5] 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.

* Corresponding author. Tel.: +91 80 22932215; fax: +91 80 23600683; e-mail: ask@orgchem.iisc.ernet.in

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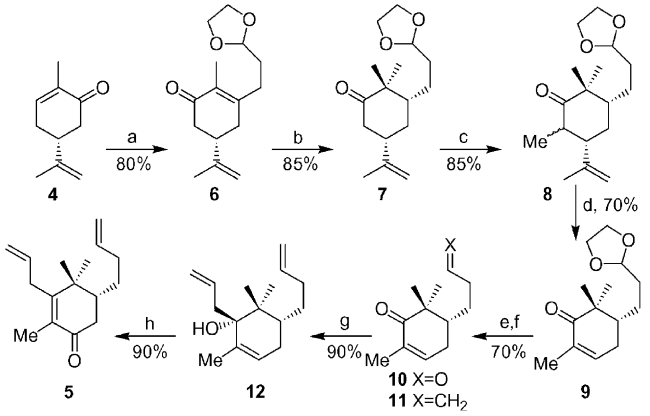
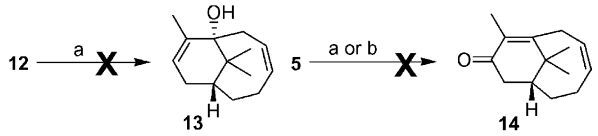


Scheme 1. Reagents and conditions: (a) i. Li, (–OCH_2CH_2O–)-$CHCH_2CH_2Br$, THF, 1 h; ii. PCC, silica gel, CH_2Cl_2, 4 h; (b) Li, liq. NH_3, THF; MeI; (c) LDA, THF, MeI, −70 °C→rt, 15 h; (d) O_3/O_2, MeOH:CH_2Cl_2 (1:5), −70 °C; Ac_2O, Et_3N, DMAP, C_6H_6, reflux, 6 h; (e) AcOH, H_2O, 60 °C, 1 h; (f) $Ph_3P^+CH_3I^-$, $K^{+t}AmO^-$; C_6H_6, 0–5 °C, 5 min; (g) Zn, CH_2=$CHCH_2Br$, THF, 20 min; (h) PCC, silica gel, CH_2Cl_2, 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 fragmentation[6] 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, C_6H_6 or CH_2Cl_2 reflux.
(b) Grubbs' second generation catalyst, PhMe, C_6H_6 or CH_2Cl_2 (0.005 M) reflux.

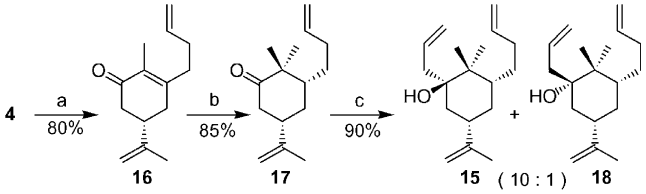
The *trans*-orientation of the two side chains in the alcohol **12** and the substantial increase in strain for the formation of a bicyclo[5.3.1]undecane with a bridgehead double bond are perhaps responsible for the failure of the RCM reactions of the alcohol **12** and the enone **5**. Hence, we contemplated 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 ^{13}C NMR, LRMS and HRMS) consistent with their structures. Selected spectral data for the minor alcohol **18**: $[\alpha]_D^{24}$ −26.7 (*c* 1.5, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3568, 910, 887. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.95–5.70 (2H, m, 2 × C*H*=CH_2), 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=CH_2), 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-CH_3), 1.65–1.45 (5H, m), 1.35–1.20 (2H, m), 1.04 (3H, s) and 1.02 (3H, s) [2 × *tert*-CH_3]. ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 150.1 (C, *C*=CH_2), 139.4 (CH, *C*H=CH_2), 134.1 (CH, *C*H=CH_2), 119.9 (CH_2, CH=*C*H_2), 114.4 (CH_2, CH=*C*H_2), 108.8 (CH_2, C=*C*H_2), 75.6 (C, C–OH), 46.9 (CH), 42.1 (CH_2), 39.6 (C), 38.4 (CH_2), 34.8 (CH), 34.0 (CH_2), 29.1 (CH_2), 28.8 (CH_2), 27.2 (CH_3), 22.3 (CH_3), 21.3 (CH_3). Mass: *m/z* 221 (M−C_3H_5, 35%), 203 (15), 163 (15), 137 (22), 123 (15), 121 (25), 109 (28), 107 (25), 95 (70), 93 (28). HRMS: *m/z* for $C_{18}H_{30}ONa$ (M+Na), calcd: 285.2194. Found: 285.2189.

For the major isomer **15**: $[\alpha]_D^{24}$ −9.7 (*c* 6.0, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3572, 910, 887. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.96–5.70 (2H, m, 2 × C*H*=CH_2), 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=CH_2), 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-CH_3), 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*-CH_3]. ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 150.0 (C, *C*=CH_2), 139.2 (CH, *C*H=CH_2), 134.5 (CH, *C*H=CH_2), 119.5 (CH_2, CH=*C*H_2), 114.5 (CH_2, CH=*C*H_2), 108.8 (CH_2, C=*C*H_2), 75.6 (C, C–OH), 41.3 (CH), 41.2 (CH_2), 40.4 (C), 39.4 (CH), 37.7 (CH_2), 33.0 (CH_2), 32.5 (CH_2), 30.2 (CH_2), 21.0 (CH_3), 20.9 (CH_3), 17.5 (CH_3). Mass: *m/z* 221 (M−C_3H_5, 35%), 203 (10), 163 (12), 137 (18), 123 (15), 121 (25), 109 (28), 107 (25), 95 (65). HRMS: *m/z* for $C_{18}H_{30}ONa$ (M+Na), calcd: 285.2194. Found: 285.2186.

For the trimer **20**: mp 174–176 °C $[\alpha]_D^{24}$ +67.5 (*c* 0.8, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3435, 884. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.55–5.25 (6H, m, CH=CH), 4.65–4.55 (6H, m, C=CH_2), 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-CH_3), 0.95 (9H, s) and 0.75 (9H, s) [6 × *tert*-CH_3]. ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 150.3 (C), 135.6 (CH), 126.3 (CH), 108.6 (CH_2), 75.3 (C), 40.1 (C), 39.7 (CH_2), 39.4 (CH), 38.3 (CH), 37.9 (CH_2), 30.8 (CH_2), 30.0 (CH_2), 27.4 (CH_2), 21.2 (CH_3), 21.1 (CH_3), 17.8 (CH_3). Mass: *m/z* 667 [M−H_2O−OH, 15], 413 (20), 217 (45), 175 (30), 161 (30), 147 (25), 135 (30), 121 (60), 107 (75), 95 (80). HRMS: *m/z* for $C_{48}H_{78}O_3Na$ (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. $C_{48}H_{78}O_3{\cdot}H_2O$; MW 721.18; crystal system: orthorhombic, space group: $P2_12_12_1$, cell parameters: *a* = 13.306(3) Å, *b* = 18.294(4) Å, *c* = 18.972(4) Å, *V* = 4618.2(17) Å^3, *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 $F_0 > 4\sigma$ (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, CH_2=$CHCH_2CH_2Br$, 40 min; ii. PCC, silica gel, CH_2Cl_2, 4 h; (b) Li, liq. NH_3, THF, MeI; (c) Zn, CH_2=$CHCH_2Br$, THF, 20 min.

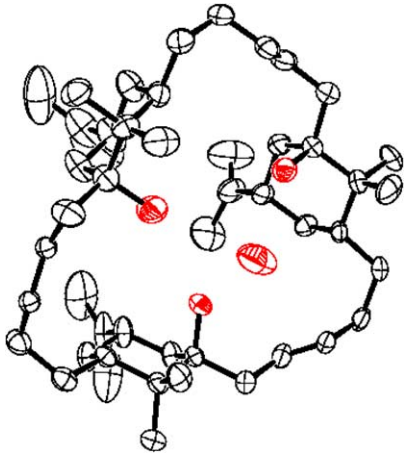


Figure 1. ORTEP diagram of the trimer **20** (hydrogen atoms were not included for clarity).

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.

Acknowledgements

We thank Professor Blechert for exchanging information.

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