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A ring-closing metathesis approach to the bicyclo[4.3.1]decane core of caryolanes

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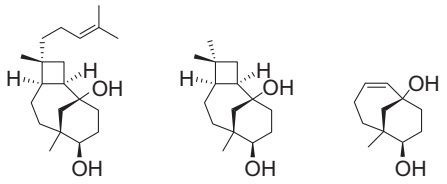
ABSTRACT

A synthesis of highly substituted and sterically congested bicyclo[4.3.1]decenes, a structure embedded in the core 4,7,6-tricyclic system of natural caryolanes, was successfully achieved via a ring-closing metathesis (RCM) reaction of *syn*-1,3-diene substituted cyclohexanols. The construction of the diene substrates, starting from 4-acetoxy-3-methyl-2-cyclohexen-1-one, employed diastereoselective copper-mediated conjugate addition and Grignard reactions. An X-ray crystal structure determination of a key synthetic intermediate confirmed the relative stereochemistry of the RCM bicyclic product.

The caryolane-based natural products, such as **1** and **2**, and the related isomers, have been isolated from a variety of natural sources from around the world, including the Japanese rootlets of *Panax ginseng*,[1] the flowers of Asian and European *Chrysanthemum indicum* L.,[2] the Egyptian herbal medicine *Cyperus longus*[3] and the Indonesian medicinal plant *Sindora sumatrana* M_{IQ}.[4] Many members of this family of natural compounds exhibit important anti-HIV, anti-tumour and anti-bacterial properties. Recently, Guo and co-workers reported the isolation of four related natural caryolanes, for example, excogallochaol A (**1**), from the Chinese mangrove shrub *Excoecaria agallocha* L.[5] The structural elucidation of this family of natural products was based, in part, on NMR data which identified a *cis*-fused 4,7-bicyclic unit embedded within these structures. In contrast, the 4,7-bicyclic unit found within many other natural caryolanes, and related structures, were reported to be *trans*-fused. These natural structures represent a synthetic challenge which lies in the assembly of the strained caryolane ring system, with the appropriate stereochemistry. The core 4,7,6-tricyclic structure of the caryolane ring system has been the subject of numerous synthetic studies on the rearrangement of caryophyllene,[6] and its derivatives.[7] However, we aimed to achieve a synthesis of this intriguing natural structure using a ring-closing metathesis (RCM) based approach to construct the bicyclo[4.3.1]decene core **3**.



The RCM reaction has proven to be a reliable method for the construction of strained carbo- and heterocyclic ring systems.[8] Following the first reports of bridged bicycloalkene formation via RCM,[9] this method was successfully employed in the total synthesis of natural products which possess strained ring systems.[10] In many of these cases the relative stereochemistry and substitution pattern of the bis-alkenyl substituted cyclic RCM substrates played a key role in either facilitating or hindering the progress of the reaction.[9,10b–g] In related studies, Martin[11] and later Mascareñas[12] employed *syn*-1,3-bis-alkenyl substituted six-membered substrates in the RCM formation of bridged bicyclic systems. In these cases the RCM cyclisation proceeded via a reactive conformation, favoured by strain or hydrogen-bonding effects.[13] However, the RCM construction of a related bridged bicyclic compound, which proceeded in the absence of these effects, suggested that other factors play a more significant role in the success of this reaction.[14]

In this Letter, a ring-closing metathesis based synthetic route to the bicyclo[4.3.1]decene core **3** of caryolane ring systems, such as **1** and **2**, which does not rely on a conformational bias of the diene substrate towards a reactive conformation, is described.

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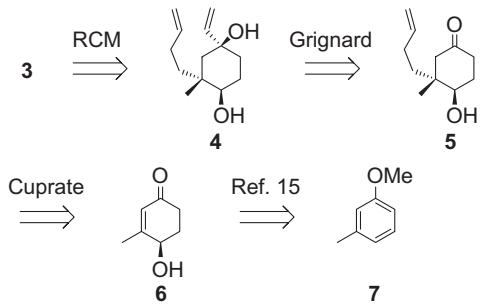
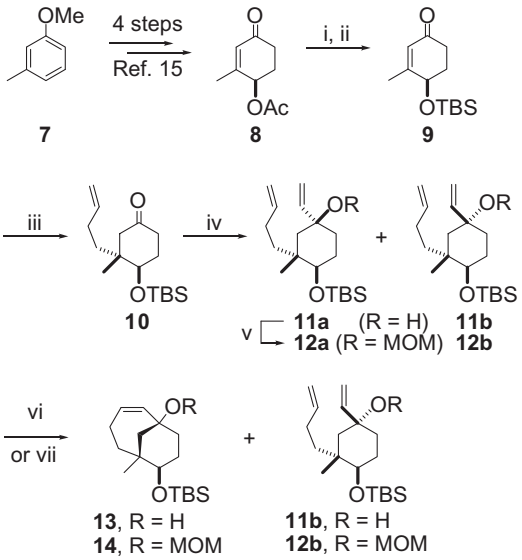
Our retrosynthetic analysis of the bicyclo[4.3.1]decene structure **3** revealed the RCM disconnection to **4**, shown in Scheme 1. Sequential Grignard and conjugate addition disconnections of the vinyl and 3-butenyl groups in **4**, respectively, led to the cyclohexenone **6**, via **5**. The conversion of commercially available 3-methylanisole (**7**) into the cyclohexenone **6** has been reported in the literature.[15] Based on this analysis, the planned forward synthesis demanded two diastereoselective reactions. The stereochemical course of the first, a copper-mediated conjugate addition step leading to **5**, was anticipated to proceed opposite to the protected secondary alcohol. The second was a selective vinyl Grignard addition step leading to **4**. Furthermore, the strategy required a compatible protecting group for the secondary hydroxy in **5** and **6**. The results of our synthetic studies based on this synthetic plan are described below.

The initial attempt towards a synthesis of the bicyclo[4.3.1]decene core **3** of the caryolanes began with the known conversion of commercially available 3-methylanisole (**7**) into the cyclohexenone **8** (Scheme 2).[15] This four-step sequence involved Birch reduction, enol ether hydrolysis, epoxidation and finally a one-pot elimination-epoxide opening sequence, which was followed by acetylation of the newly formed secondary alcohol. Transesterification of the acetate **8** using Na_2CO_3 in MeOH followed immediately by treatment of the resulting secondary alcohol with TBSCl in the presence of DMAP and triethylamine gave the silyl ether **9** in 57% yield over two steps. In our hands the intermediate alcohol was unstable, which necessitated its immediate use in the subsequent step. The copper-mediated conjugate addition reaction on **9** which led to the ketone **10** first involved the treatment of 4-bromobut-1-ene with magnesium, followed by the addition of CuBr·DMS and LiCl to give the corresponding cuprate to which was added the cyclohexenone **9** and TMSCl. The 1,4-addition product **10** was formed as a single diastereoisomer in 81% yield.[16] Based on the literature precedent,[15a] the 3-butenyl group was added onto the face of the enone **9** opposite to the TBS protected secondary alcohol, which was reflected in the relative *anti*-stereochemical relationship between these groups in the product **10**. Treatment of ketone **10** with vinylmagnesium bromide gave an inseparable 1.4:1 diastereoisomeric mixture of the dienes **11** in 85% combined yield. Attempts to separate the diastereoisomers using flash column chromatography were unsuccessful, and therefore this material was used as a mixture in all subsequent steps. Presumably, the major product **11a**, in which the 3-butenyl and vinyl groups are in a *syn*-relationship, resulted from equatorial attack of vinylmagnesium bromide on the ketone **10**. In an attempt to separate the tertiary alcohols **11** by chemical conversion, the diastereoisomeric mixture was treated with MOMCl, DIPEA and TBAI to give an inseparable 1.4:1 diastereoisomeric mixture of the MOM ethers **12** in 90% combined yield. Undeterred by this outcome, the mixture of diene diastereoisomers **11** was treated with 10 mol % of Grubbs' 1st generation pre-catalyst in refluxing CH_2Cl_2 to give the bicyclic product **13** in 66% yield,[17]



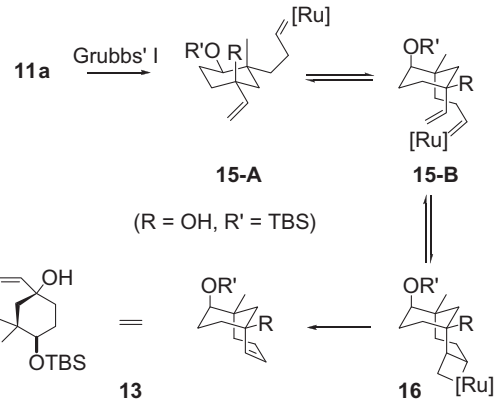
Scheme 1. Retrosynthetic analysis of bicyclo[4.3.1]decene **3**.



Scheme 2. Reagents and conditions: (i) Na_2CO_3, MeOH, rt, 88%; (ii) TBSCl, Et_3N, DMAP, CH_2Cl_2, rt, 65%; (iii) 4-bromobut-1-ene, Mg, I_2, THF, −78 °C; then CuBr·DMS, LiCl, TMSCl, THF, −78 °C, 81%; (iv) vinylmagnesium bromide, THF, rt, 85% combined yield (**11a**/**11b**, 1.4:1); (v) **11**, MOMCl, DIPEA, TBAI, CH_2Cl_2, rt, 90% combined yield (**12a**/**12b**, 1.4:1); (vi) **11**, Grubbs' I (10 mol %), CH_2Cl_2, 40 °C, 66% (**13**) and 14% (**11b**); (vii) **12**, Grubbs' I (10 mol %), CH_2Cl_2, 40 °C, 60% combined yield (**14**/**12b**, 2.2:1).

based on the amount of the *syn*-diene **11a** present in the starting mixture, together with the *anti*-diene diastereoisomer **11b** in 14% recovery. Finally, treatment of the mixture of diene diastereoisomers **12** under the RCM conditions described above led to an inseparable 2.2:1 mixture of the bicyclic product **14** and recovered *anti*-diene **12b** in 60% combined yield. In either case, we did not isolate any of the ruthenium alkylidene corresponding to **11b** or **12b**, cf. **15**; however it is likely that this unproductive intermediate could account for some of the remaining material balance.

The RCM reaction of the *syn*-diene **11a** to give the bicyclic product **13**, and the recovery of the *anti*-diene **11b**, suggested that the relative stereochemistry of the alkene units played a significant role in governing product formation. Furthermore, the conformation of the reactive intermediates of **11a** must also play an important role in the reaction. For example, treatment of the *syn*-diene **11a** with Grubbs' 1st generation pre-catalyst leads to the ruthenium alkylidene **15** which could adopt two possible chair conformations (Scheme 3). In the bis-equatorial conformation **15**-**A** the ruthenium alkylidene and alkene groups are unable to move into

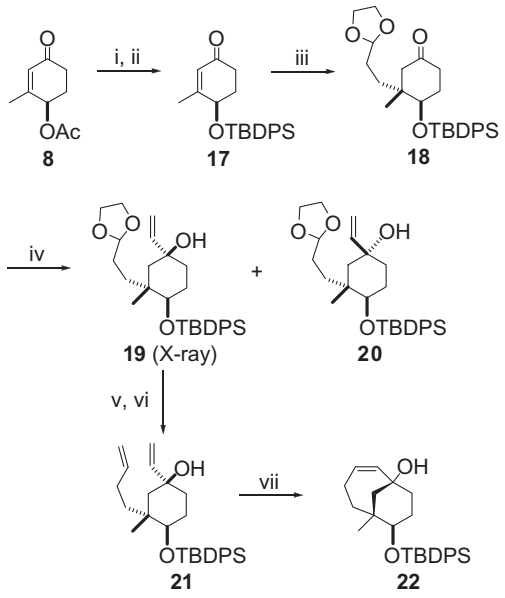


Scheme 3. Mechanism and conformational analysis of the RCM reaction of **11a**.

a reactive proximity. In contrast, the ruthenium alkylidene and alkene groups in the bis-axial conformation **15-B** are able to move into a reactive proximity, leading to the metallacyclobutane **16**. Finally, cycloreversion of **16** leads to the bicyclic product **13**.

Following the success of the synthetic studies which led to the bicyclo[4.3.1]decene **13**, we set out to construct the *syn*-diene **21**, cf. **11a**, in order to fully evaluate the potential of the synthetic route. The synthesis of **21** began with conversion of the acetate **8** into the silyl ether **17** in 62% yield, using a two-step sequence similar to the conditions described earlier, using TBDPSCl in place of TBSCl (Scheme 4). The copper-mediated conjugate addition reaction on **17**, using 2-(2-bromoethyl)-1,3-dioxolane under the conditions described by Piers and Oballa,[15a] gave the ketone **18** as a single diastereoisomer in 78% yield. The ketone **18** was treated with vinylmagnesium bromide to give the diastereoisomeric allylic tertiary alcohols **19** and **20** in 59% and 24% chromatographic yield, respectively. The major *syn*-diastereoisomer **19** was isolated as a colourless solid, and its structure and relative stereochemistry were confirmed based on a single crystal X-ray structure determination (Fig. 1).[18] Compound **19** possessed a *syn*-relationship between the vinyl and dioxolane groups and an *anti*-relationship between the dioxolane and silyl ether groups. Therefore, compound **19** possessed the correct stereochemistry for elaboration of the caryolane structure. Furthermore, we were confident that the relative stereochemistry of the ketone **10** was analogous to that of the ketone **18** based on the X-ray data recorded for **19**. It is important to note that the minor *anti*-diastereoisomer **20** could not be used to elaborate the caryolane structure **1**. Deprotection of the dioxolane **19** with $CeCl_3{\cdot}7H_2O$ and catalytic NaI in refluxing acetonitrile[19] gave the corresponding aldehyde in 87% crude yield, which was immediately treated with triphenylphosphonium bromide and *n*-BuLi in THF to give the *syn*-diene **21** in 44% yield. We were pleased to discover that treatment of the diene **21** with 10 mol % of Grubbs' 2nd generation pre-catalyst in refluxing CH_2Cl_2 gave the bicyclic product **22** in 90% yield.

The RCM reactions of the dienes **11a** and **21** did not rely on or benefit from strain or hydrogen-bonding effects which could bias



Scheme 4. Reagents and conditions: (i) Na_2CO_3, MeOH, rt, 88%; (ii) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, rt, 71%; (iii) 2-(2-bromoethyl)-1,3-dioxolane, Mg, I_2, THF, −78 °C; then CuBr·DMS, HMPA, TMSCl, THF, −78 °C, 78%; (iv) vinylmagnesium bromide, THF, rt, 59% (**19**) and 24% (**20**); (v) $CeCl_3{\cdot}7H_2O$, NaI, CH_3CN, 90 °C, 87% (from **19**); (vi) Ph_3PCH_3Br, *n*-BuLi, THF, 0 °C, 44%; (vii) Grubbs' II (10 mol %), CH_2Cl_2, 40 °C, 90%.

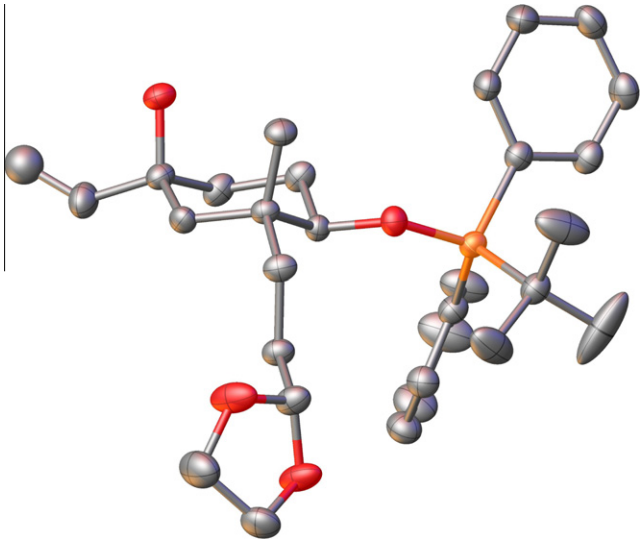


Figure 1. ORTEP representation of **19** at the 50% probability level. The disorder in the vinyl group was removed for clarity.

the conformation of the substrates towards, for example, the reactive bis-axial conformer **15-B**. In fact, analysis of the substitution pattern of these diene systems suggested that the unproductive bis-equatorial conformation, for example, **15-A**, was favoured. Therefore, these diene substrates were not predisposed to RCM; however the reactions were nonetheless successful.

In conclusion, a synthesis of the bicyclo[4.3.1]decene core **22**, found in natural caryolane structures such as **1** and **2**, was successfully achieved using a RCM based approach. The synthetic route employed diastereoselective copper-mediated conjugate addition and Grignard reactions for the construction of the *syn*-diene RCM precursor **21**. The relative stereochemistry of the bicyclic product was confirmed based on an X-ray crystal structure of the key synthetic intermediate **19**. The results of these synthetic studies suggested that the *anti*-diene substrates, such as **11b**, did not form the corresponding bicyclic product due to the relative stereochemistry of the alkene units, and therefore were not suitable substrates for RCM. We aim to exploit the results of these ongoing studies, which led to the bicyclic compound **22**, in a synthesis of caryolanes. This includes a direct approach to the 4,7,6-tricyclic caryolane system based on a photochemical [2+2]-cycloaddition reaction of a diene substrate, such as **21**. Our progress in these areas will be described in due course.

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16. The copper-mediated conjugate addition reaction leading to **10** was unreliable; however the highest yield recorded for this reaction was reported. In contrast, the related reaction which smoothly led to **18** was reliable and reproducible.
17. Satisfactory spectroscopic data were recorded for all synthesised compounds reported in this Letter. For example: *Data recorded for* **13**: ν_{max} (film)/cm^{-1} 3350, 3008, 2952, 2929, 2856, 1612, 1471 and 1258; δ_H (400 MHz, $CDCl_3$) 5.83 (1H, ddd, *J* 11.5, 8.9 and 3.4, CH_2CH=CH), 5.31 (1H, dt, *J* 11.5 and 2.6, CH_2CH=C*H*), 3.30–3.28 (1H, m, C*H*OTBS), 2.36–2.27 (1H, m, C*H*HC=C), 1.97–1.91 (1H, m, CH*H*C=C), 1.89–1.75 (3H, m, C*H*HCH$_2$C=C, CH(OTBS)C*H*H and C(4°)(OH)C*H*H), 1.68 (1H, dd, *J* 12.9 and 2.5, C(4°)(OH)CH*H*), 1.57–1.52 (2H, m, CH(OTBS)CH*H* and O*H*), 1.44–1.37 (1H, m, CH*H*CH$_2$C=C), 1.38 (3H, s, CH_3), 1.25 (1H, br s, C*H*H), 0.92–0.90 (1H, m, CH*H*), 0.91 (9H, s, SiC(CH_3)$_3$), 0.06 (3H, s, SiCH_3), 0.04 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$) 136.0, 130.8, 74.0, 73.6, 42.0, 38.1, 37.4, 32.4, 29.4, 27.4, 25.9, 22.8, 18.2, −4.4, −4.9; *m*/*z* (ES) 296.2180 (M$^+$, 2%, $C_{17}H_{32}O_2Si$ requires 296. 2172). *Data recorded for* **22**: ν_{max} ($CDCl_3$)/cm^{-1} 3594, 3073, 3053, 3014, 2932, 2858, 1601, 1469 and 1262; δ_H (400 MHz, $CDCl_3$) 7.72–7.68 (4H, m, Ar*H*), 7.45–7.33 (6H, m, Ar*H*), 5.79 (1H, ddd, *J* 11.4, 8.8 and 3.3, CH_2CH=CH), 5.27 (1H, ddd, *J* 11.4, 2.5 and 1.3, CH_2CH=C*H*), 3.46 (1H, dd, *J* 2.8 and 2.3, C*H*OTBDPS), 2.33–2.21 (1H, m, C*H*HC=C), 1.90–1.82 (4H, m, CH*H*C=C, CH_2 and C(4°)(OH)C*H*H), 1.65 (1H, tdd, *J* 14.3, 4.0 and 2.2, CH(OTBDPS)C*H*H), 1.46–1.40 (2H, m, CH(OTBDPS)CH*H* and O*H*), 1.37–1.32 (1H, m, C(4°)(OH)CH*H*), 1.27–1.23 (1H, m, C*H*HCH$_2$C=C), 1.24 (3H, s, CH_3), 1.10 (9H, s, SiC(CH_3)$_3$), 0.92–0.83 (1H, m, CH*H*CH$_2$C=C); δ_C (100 MHz, $CDCl_3$) 136.2, 136.1, 135.9, 134.8, 134.2, 130.8, 129.53, 129.48, 127.43, 127.42, 74.9, 73.9, 42.3, 38.6, 37.5, 32.6, 29.5, 27.4, 26.5, 22.7, 19.7; *m*/*z* (ES) 443.2366 (M$^+$+Na, 6%, $C_{27}H_{36}O_2SiNa$ requires 443.2382).
18. CCDC 796110 contains the supplementary crystallographic data recorded for the tertiary alcohol **19** reported in this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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