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Synthesis of a highly functionalized tricyclic ring system related to guanacastepene via a tandem ring-closing metathesis reaction

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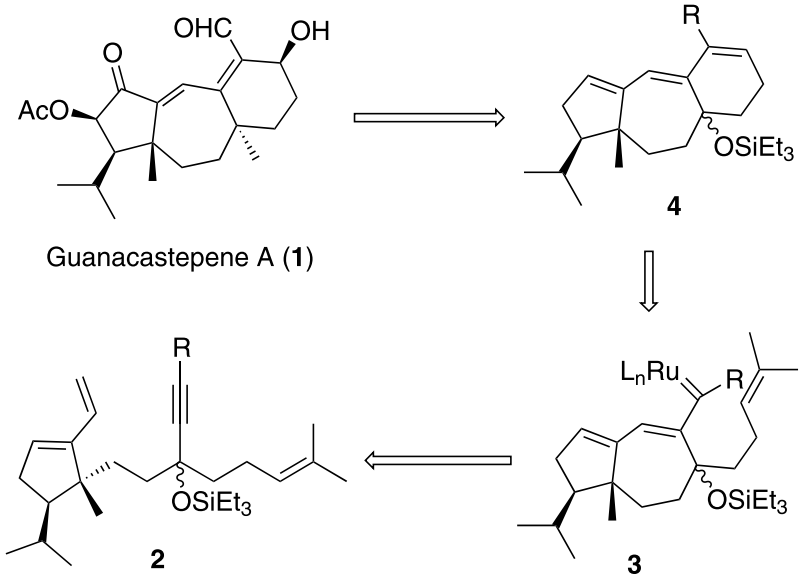
Abstract—A new approach to a highly functionalized 5,7,6-tricyclic core structure of guanacastepene has been developed using the tandem ring-closing metathesis reaction of dienynes as the key step.

Guanacastepene A (**1**) is a novel 5,7,6-ring fused diterpene, originally isolated from a fungus collected in the Guanacaste Conservation Area in Costa Rica. It exhibits excellent activity against both methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis*.[1] Further biological studies indicated that **1** has a moderate activity against Gram-positive bacteria, a poor activity against Gram-negative bacteria and a hemolytic activity against human red blood cells.[2] Despite these drawbacks, guanacastepene could be considered as a potential lead compound in the development of new antibacterial agents. The biological activity combined with the novel carbon skeleton of this product has served to stimulate an important synthetic activity by a number of groups[3–8] which culminated in the first total synthesis of guanacastepene A, recently published by Danishefsky and co-workers.[4c,d]

The tandem ring-closing metathesis (RCM) reaction of dienynes has proved to be a useful tool to produce polycyclic polyenes with various ring systems.[9,10] In a



Scheme 1.

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previous report, we described the application of this technique for the preparation of polyoxygenated fused bicyclic systems containing medium-sized rings from carbohydrates.[11] Our interest in the synthesis of guanacastepene was therefore stimulated by the possibility that the 5,7,6 tricyclic framework could be constructed by using a cascade of RCM reactions starting from a suitably functionalized trienyne such as **2**. We report herein the successful implementation of this strategy.

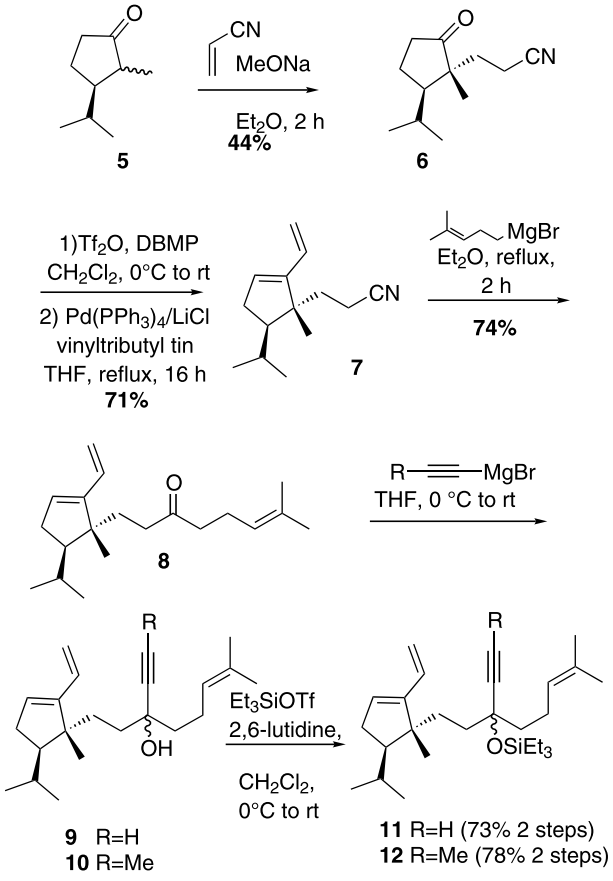
As shown in Scheme 1, our approach is based on the assumption that the formation of a metal carbene on **2** should first occur at the monosubstituted olefin which can cyclize to give the 5,7-bicyclic intermediate **3**. This tetraene could then undergo a second RCM reaction to give the desired 5,7,6-fused product **4**.

The synthesis started from 3-isopropyl-2-methylcyclopentanone **5**, readily prepared from 2-methylcyclopentanone.[12] Treatment of **5** with a catalytic amount of sodium methoxide in diethyl ether followed by the addition of acrylonitrile afforded ketone **6** as a single diastereomer and generated one of the quaternary centers of the target (Scheme 2). The stereochemical outcome of the alkylation reaction is controlled by the steric influence of the β-isopropyl group, and can be assigned by analogy to similar reactions.[4a,13] Treatment of cyclopentanone **6** with Tf_2O and 2,6-di-*tert*-butyl-4-methylpyridine (DBMP) afforded the corresponding enol triflate, which underwent the Stille coupling reaction with tributyl(vinyl)tin to deliver diene **7** in 71% overall yield. Addition of the Grignard reagent (10 equiv.), generated from 4-bromo-2-methylpent-2-ene,[14] to nitrile **7** furnished ketone **8** in 74% yield. Treatment of **8** with ethynylmagnesium bromide or propynylmagnesium bromide in THF at room temperature afforded tertiary alcohols **9** and **10**, respectively, as a ca. 1:1 mixture of diastereomers. These alcohols were then protected as their triethylsilyl ethers **11** and **12**.

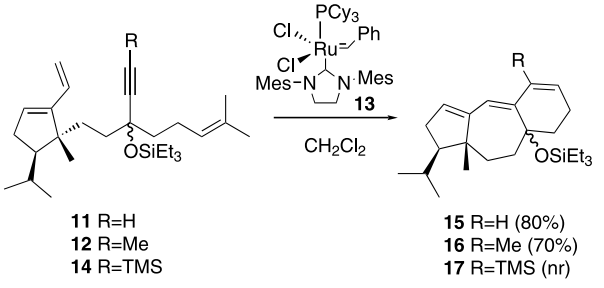
The trienynes prepared above were subjected to RCM conditions using the highly active Grubbs' catalyst **13**.[15,16] In a first attempt, treatment of **11** with 10 mol% catalyst in CH_2Cl_2 at reflux gave an intractable mixture of products. However, when this reaction was carried out at room temperature, the desired product **15** was produced (40–60%) along with remaining starting material (Scheme 3). In considering ways of improving the reproducibility and the efficiency of this transformation, we found that simply stirring the solution of **11** and the catalyst (7.5 mol%) in CH_2Cl_2 at room temperature overnight under a stream of nitrogen so that the solvent slowly evaporated, the reaction was completed and **15** was obtained in 78–81% yield.[17] Under the same conditions trienyne **12**, bearing a methyl group on the triple bond, afforded the tricyclic compound **16** in 70% yield. With the trimethylsilyl substituent (compound **14**) the dienyne cyclization was not observed.

Having established the feasibility of this approach, we turned next to the elaboration of the tricyclic core bearing conveniently positioned oxygen functionalities. We recognized that the methyl ester in **19** (Scheme 4) could serve as a suitable precursor to the required aldehyde in guanacastepene. Toward this end, dienyne **18**, readily prepared from ketone **8**, was selected as precursor for the tandem RCM reaction. When **18** was refluxed in CH_2Cl_2 in the presence of 10 mol% of catalyst **13** for 4 h, the metathesis product **19**[18] was obtained in 93% yield as a separable mixture of diastereomers. In contrast to **15**, this compound is sufficiently stable to be isolated by chromatography on silica gel.

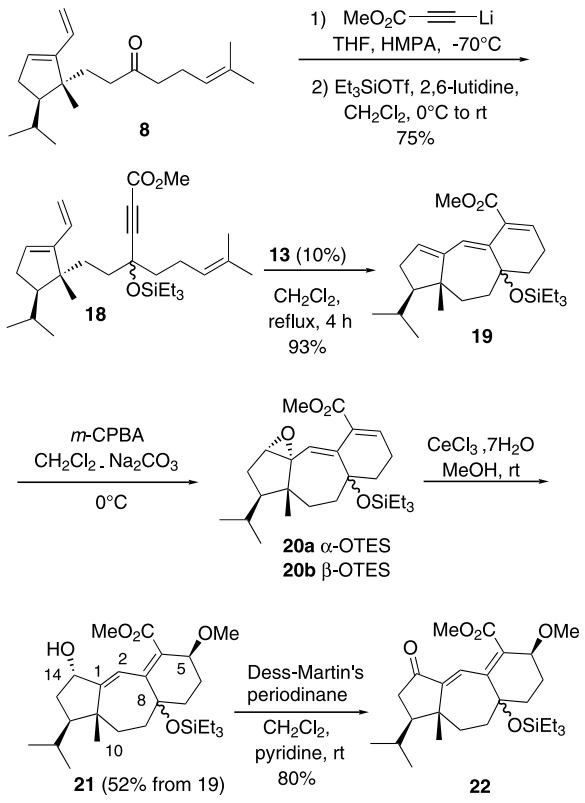
With the desired substrate in hand, we next undertook the introduction of oxygen functionalities at C14. Oxidation of **19** with *m*-CPBA at 0°C in CH_2Cl_2 and saturated aqueous $NaHCO_3$ was found to be chemo- and stereoselective producing a mixture of two diastereomeric epoxides **20a** and **20b** easily separable by



Scheme 2.



Scheme 3.



Scheme 4.

flash column chromatography. The stereochemical outcome of this reaction is controlled by the angular methyl group at C11 which blocks the β-face at C1.[19] The reductive epoxide-opening of **20** was next examined separately on each isomer. Attempts to achieve this reaction using Dibal-H in hexane at −70 to 0°C gave a complex mixture. However, when subjected to Luche's conditions ($NaBH_4$, $CeCl_3{\cdot}7H_2O$ in methanol), **20** was smoothly converted into a single product, identified as the unexpected alcohol **21**. Obviously, **21** resulted from the nucleophilic cleavage of epoxy diene **20** by methanol. Indeed, when both isomers (**20a** and **20b**) were stirred in methanol at room temperature in the presence of $CeCl_3$, $7H_2O$[20] for 3 h, alcohols **21a** and **21b** were isolated in 52% overall yield from **19**. This reaction probably proceeded via S_N2' type mechanism: the nucleophilic attack was assumed to occur on the β-face, *anti* to the epoxide ring.[21] This nucleophilic addition may also be assisted by the electron-withdrawing ester group. Oxidation of **21** using Dess–Martin's periodinane reagent[24] in the presence of pyridine furnished ketone **22**. This structure was confirmed by its spectral data (IR, NMR and mass spectrometry).[18,25] However, the assignment of the relative configuration of the OTES group at C8 in **22a** and **22b** has yet to be established.

In summary, we have developed a concise synthesis of the highly functionalized 5,7,6 tricyclic system **22** via tandem RCM reaction of dienynes. Efforts are currently underway to build up the remaining quaternary center at C8 in order to achieve the total synthesis of guanacastepene A.

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17. Trienes **15** and **16** are unstable. They were isolated as 1:1 mixture of diastereomers (^1H NMR) by rapid chromatography on Florisil using light petroleum ether as eluent.

18. Spectral data for key compounds: compound **19**: ^{1}H NMR (400 MHz): $\delta = 6.74$ (t, $J = 3.9$ Hz, 0.55H), 6.57 (br s, 0.55H), 6.51 (br s, 0.45H), 6.25 (s, 0.45H), 5.57 (br s, 0.55H), 5.44 (br s, 0.45H), 3.75 (s, 1.65H), 3.73 (s, 1.35H), 2.51–2.30 (m, 3H), 2.21–2.11 (m, 2H), 2.05–1.50 (m, 7H), 1.04–0.84 (m, 18H), 0.58 (q, $J = 7.7$ Hz, 3H), 0.52 (q, $J = 7.7$ Hz, 3H). ^{13}C NMR (100 MHz): $\delta = 168.1$ (C), 168.0 (C), 150.0 (C), 149.6 (C), 138.6 (CH), 137.4 (br C), 135.5 (C), 131.9 (C), 128.9 (CH), 124.1 (CH), 75.8 (C), 58.0 (CH), 56.5 (CH), 55.3 (C), 52.0 (C), 51.6 (CH_3), 38.2 (CH_2), 37.5 (CH_2), 37.1 (CH_2), 36.4 (CH_2), 35.9 (CH_2), 32.7 (CH_2), 32.6 (CH_2), 29.7 (CH), 29.4 (CH), 24.2 (CH_2), 23.2 (CH_2), 23.0 (CH_3), 22.9 (CH_3), 21.1 (CH_3), 7.3 (CH_3), 7.2 (CH_3), 6.7 (CH_2), 6.2 (CH_2). IR (CCl_4, cm^{-1}): 2954, 2874, 1720, 1456, 1254, 1077. Compound **22**: ^{1}H NMR (400 MHz): $\delta = 6.79$ (br s, 1H), 4.23 (t, $J = 5.4$ Hz, 1H), 3.77 (s, 3H), 3.37 (s, 3H), 2.48 (dd, $J = 18.0$, 7.6 Hz, 1H), 2.20–2.04 (m, 3H), 1.95–1.90 (br m, 1H), 1.82–1.73 (m, 5H), 1.62–1.55 (m, 2H), 1.07 (s, 3H), 1.05 (d, $J = 6.6$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 9H), 0.88 (t, $J = 7.7$ Hz, 9H), 0.51 (q, $J = 7.7$ Hz, 6H). ^{13}C NMR: $\delta = 205.0$ (C), 167.9 (C), 146.3 (br), 130.1 (C), 75.0 (br), 56.1 (CH_3), 51.9 (CH_3), 51.0 (br), 46.1 (C), 41.1 (CH_2), 38.1 (br), 32.8 (br), 29.7 (CH_2), 28.7 (CH_2), 27.2 (CH_3), 24.1 (CH_3), 22.3 (CH_3), 18.1 (br), 7.1 (CH_3), 6.5 (CH_2). IR (CCl_4, cm^{-1}): 2955, 2931, 2875, 1720, 1644, 1618, 1458, 1434, 1214, 1116. CI MS NH_3 m/z (%) 494 (M+ NH_4^+, 8), 477 (MH^+, 1), 445 (M–OMe, 100).

19. The stereochemical assignment at C14 was also based on extensive literature precedent (see for example Refs. 3a and 4c).

20. For the only example of the cerium chloride catalyzed 1,2-ring-opening of epoxides by amines see: Reddy, L. R.; Reddy, M. A.; Rao, K. R. *Synthesis* **2001**, 831–832.

21. Although the S_N2' displacement by organocopper reagents is well documented (Ref. 22), to our knowledge the ring-opening of vinyl oxiranes by alcohols in the presence of Lewis acid according to such a process is unprecedented.[23]

22. For a comprehensive review on S_N2' additions of organocopper reagents to vinyl oxiranes, see Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503–1511.

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25. Inspection of the ^{1}H NMR spectrum of **22** indicated a significant downfield shift of the vinylic proton from 5.95 ppm in **21** to 6.79 in **22**, and absence of the R_2C**H**OH signal at 4.38 ppm (together with absence of the O-H stretching band in the IR spectrum at 3610 cm^{-1}]. Furthermore, the Hα at C13 clearly exhibited an AB quartet at 2.48 ppm [$J_{(13H\alpha-13H\beta)} = 18$ Hz and $J_{(13H\alpha-12H)} = 7.6$ Hz] consistent with the observations reported by Danishefsky and co-workers for a similar system (Ref. 4c).