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Synthesis of the hydroazulene portion of guanacastepene A using a [2.3]sigmatropic sulfoxide rearrangement: observations on silyl enol ether electrophilic chemistry for the introduction of the C-13 hydroxyl group

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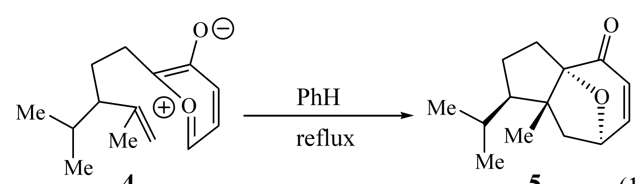
Abstract—The intermediate **6** can be converted into enone **13** using a [2.3]sigmatropic sulfoxide rearrangement as the key transformation. The C-13 hydroxylation of **13** was studied, and found to give **14** (epimeric to guanacastepene A). Examination of silyl enol ethers of **13** demonstrated the ready isomerization of the kinetic silyl enol ether into the more stable thermodynamic silyl enol ether under mild electrophilic reaction conditions.

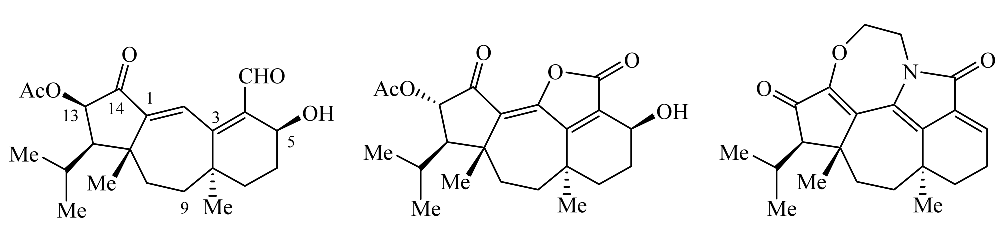
The structure of guanacastepene A **1** was reported recently (Scheme 1).[1] The compound was isolated from an extract of a fungus from the branch of a *Daphnopsis americana* tree, and the extract showed antibiotic activity against drug-resistant strains of *Staphylococcus aureus* and *Enterococcus faecalis*. It appears that **1** is but one member of a structurally diverse group of similar metabolites produced by an endophytic fungus.[2] Representative examples of other metabolites include **2**, which is also epimeric at C-13, and **3**, which is oxidized at C-13.

Recently, Danishefsky and coworkers have completed the synthesis of **1**.[3,4] The groups of Snider,[5] Mehta[6] and others[7] have reported their respective approaches to the synthesis of **1**. Our own approach is based upon the cyclization of the pyrylium–ylide **4** to the hydroazulene **5** (Eq. (1)).[8]



(1)

In this letter we report the use of new methodology to open the 1,9-oxido bridge, followed by a sulfoxide–sulfenate–allylic alcohol rearrangement,[9] and introduction of the C-13 secondary alcohol functionality.



Scheme 1.

Keywords: guanacastepene; [2.3]sigmatropic rearrangement; silyl enol ethers.
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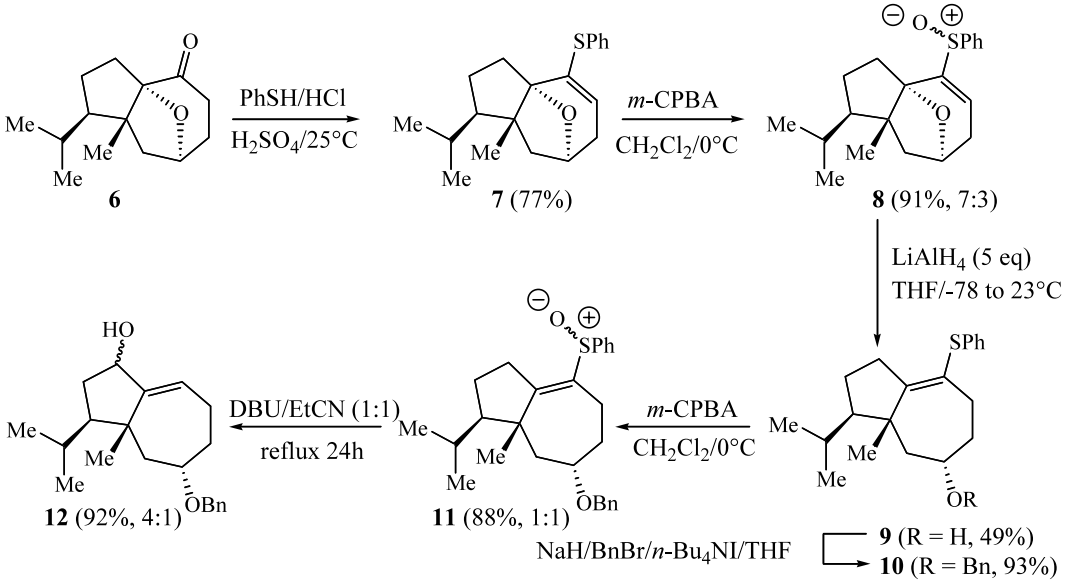
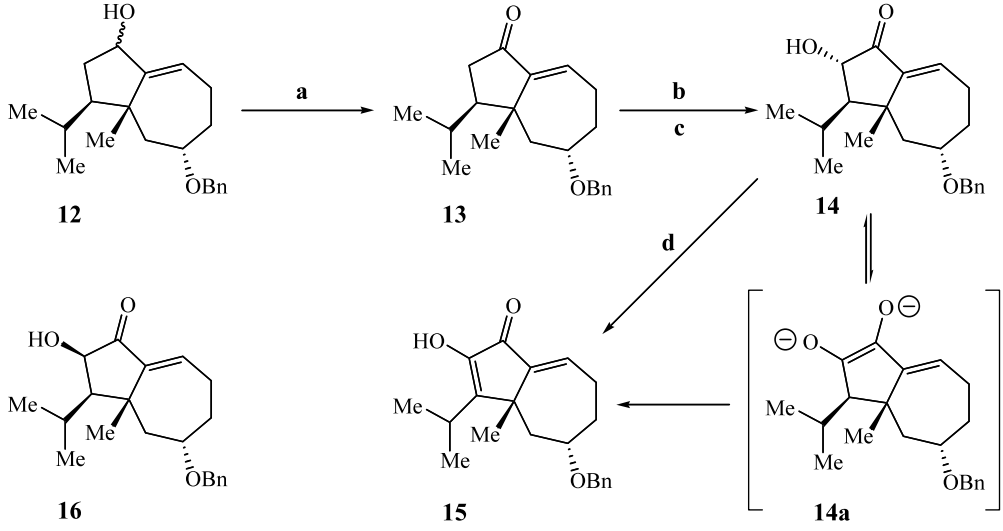
Treatment of **6** with thiophenol/HCl/H_2SO_4 gave the vinyl sulfide **7** directly (Scheme 2). The derived sulfoxide **8** was exposed to an excess of $LiAlH_4$/THF, which resulted in conjugate reduction with concomitant cleavage of the oxido-bridge and formation of the vinyl sulfide **9**.[10] The derived benzyl ether **10** was converted into the sulfoxide **11**, and treated with DBU/EtCN heated at reflux, which resulted in sulfoxide–sulfenate rearrangement[9] to give **12** (92%) as a 4:1 mixture of epimeric secondary alcohols. Oxidation of the mixture of alcohols **12** with the Dess–Martin periodinane reagent[11] gave **13** (Scheme 3).

Introduction of the C-13 hydroxyl group into **13** was attempted by treatment of **13** with $KN(SiMe_3)_2$/THF followed by (10-camphorsulfonyl)oxaziridine[12] which gave **14**[13] and **15** (78%, 93:7). The stereochemical outcome (as expected) at C-13 corresponds to that required for **2**. All attempts to epimerise C-13 via the enediolate **14a** resulted in the formation of **15** (X-ray) due to presence of adventitious oxygen. Indeed treatment of **13** with the classical autoxidations reaction conditions gave **14** which was further oxidized to **15**.[14] We were not able to find any evidence for the formation of **16**.

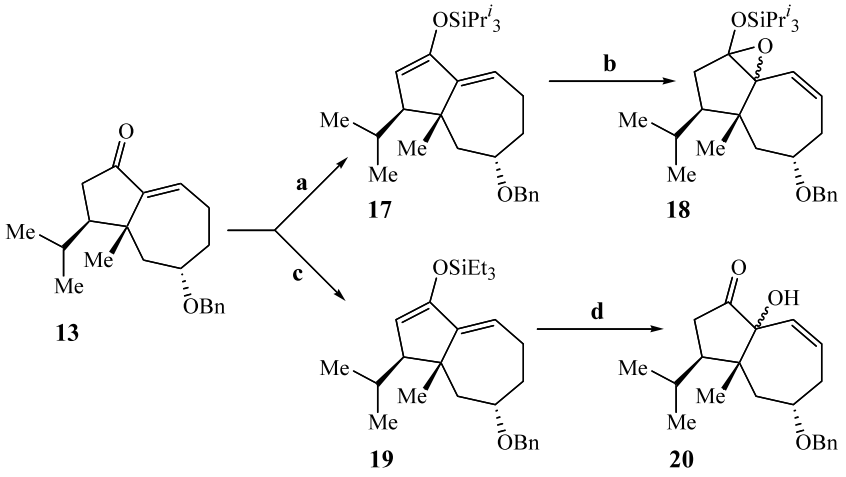
Examination of the Rubottom-type[15] oxidation of silyl enol ethers of **13** gave the following results (Scheme 4). Treatment of **17** with *m*-chloroperoxybenzoic acid (MCPBA) gave **18**.[16] Correspondingly, treatment of **19** with dimethyldioxirane followed by camphor sulfonic acid in aqueous acetone gave **20**.[17]



Scheme 2.



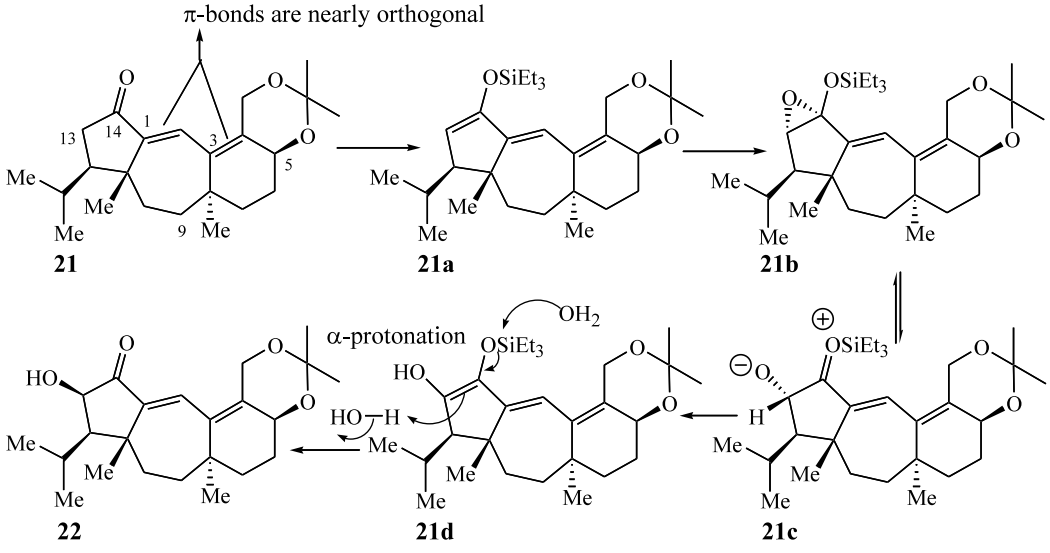
Scheme 3. *Reagents and conditions*: (a) Dess–Martin periodinane reagent (1.5 equiv.)/CH_2Cl_2/23°C, **13** (83%); (b) (i) $KN(SiMe_3)_2$ (1.5 equiv.)/THF degassed/−78°C/2.5 h, (ii) (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine (1.8 equiv.)/1.5 h, **14**/**15** (78%, 93:7); (c) *t*-BuOK (10.0 equiv.)/THF/O_2/$P(OEt)_3$/−78°C/3 h, **14**/**15** (46%, 3:7); (d) *t*-BuOK (10.0 equiv.)/*t*-BuOH/O_2/THF (1:5)/23°C/2.5 h, **15** (89%).



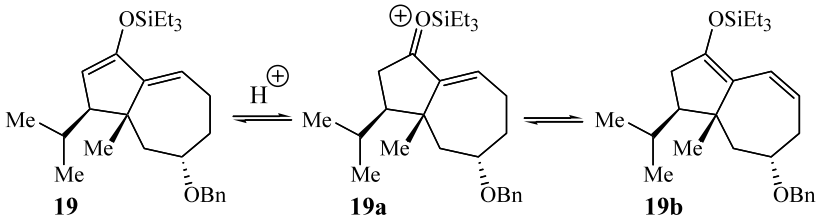
Scheme 4. *Reagents and conditions*: (a) ^{i}Pr$_3$SiOTf/Et$_3$N/CH$_2$Cl$_2$/23°C; (b) MCPBA (1.0 equiv.)/CH$_2$Cl$_2$/−78 to 0°C, followed by Me$_2$S, **18** (61%, after purification on silica); (c) Et$_3$SiOTf/Et$_3$N/CH$_2$Cl$_2$; (d) (i) dimethyldioxirane (1.1 equiv.)/CH$_2$Cl$_2$/−78°C, followed by Me$_2$S, **20** (47% from **13**), (ii) camphor sulfonic acid (0.3 equiv.) in wet acetone at reflux.

These results suggest that acid catalyzed equilibration of the kinetic silyl enol ether (for example) **19** to give the thermodynamic (extended conjugation) silyl enol ether **19b** via **19a** is more rapid than epoxidation of the silyl enol ether double bond in **19** (Eq. (2)). Consequently, the only product that was detected after acid hydrolysis, namely **20**, was the result of epoxidation of **19b**.

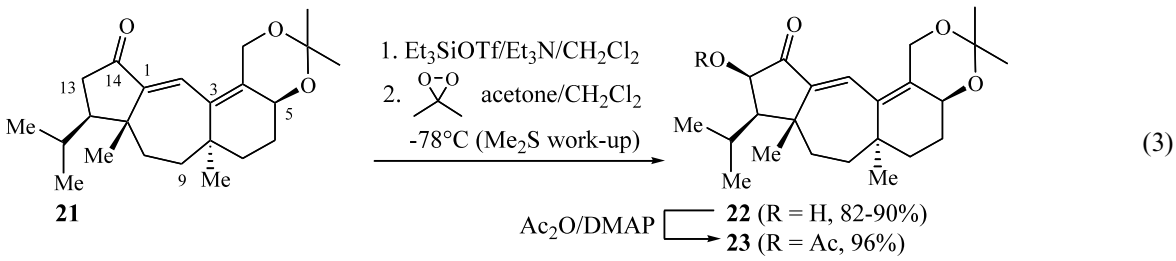
In contrast to these results, Danishefsky reported that treatment of the triethyl silyl enol ether derived from **21** (**21a**, Scheme 5) with dimethyldioxirane gave **22**, which was acetylated to provide **23** (Eq. (3)).[3] The surprising, and unexplained facet of this transformation, is the stereochemical outcome (cf. **14**, Scheme 3). In the light of the above results and rationalizations (Scheme 4 and Eq. (2)) a plausible reason for the stereochemical result in Eq. (3) is as follows.



Scheme 5.



(2)



(3)

The silyl enol ether **21a** is epoxidized from the least hindered face to give **21b** (Scheme 5). Isomerization of **21a** to the thermodynamic silyl enol ether is not possible because the C-1 and C-3 double bonds are orthogonal. The epoxide **21a** undergoes ring opening to the onium ion **21c**, which on proton loss gives **21d**. Desilylation of **21d** with protonation from the least hindered face (α-face) gives **22**.

It is clear from the above results that silyl enol ethers can equilibrate under mild reaction conditions[18] that perturb the 'normal' regio- and sterochemical predictions, and caution should be exercised with respect to structural assignments in the light of these possibilities.

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13. Compound **14**: crystals (recrystallized in hexane (slow evaporation)); mp 86–88°C; IR (neat): 3421, 1720, 1683, 1645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.37–7.26 (m, 5H), 6.99 (dd, $J=4.5$, 9.0 Hz, 1H), 4.62 (d, $J_{AB}=11.7$ Hz, 1H, part A of the AB system), 4.56 (d, $J_{AB}=11.7$ Hz, 1H, part B of the AB system), 4.20 (d, $J=12.3$ Hz, 1H), 3.71–3.63 (m, 1H), 2.76–1.99 (m, 5H), 1.51–1.24 (m, 4H), 1.13 (d, $J=5.7$ Hz, 3H), 1.11 (d, $J=5.7$ Hz, 3H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.9, 145.1, 138.5 (2C), 128.4 (2CH), 127.6 (2CH), 77.2, 76.8, 75.9, 70.5, 57.4, 45.1, 40.6, 33.1, 25.7, 25.2, 23.6, 19.8, 18.9; HRMS for $C_{21}H_{29}O_3$ [MH^+]: 329.2116, found: 329.2107. Structure confirmed by single-crystal X-ray crystallography.
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17. Compound **20**: crystals (not recrystallized); mp 102–110°C; IR (neat): 3357, 1745, 1698, 1653, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.39–7.22 (m, 5H), 6.09 (d, $J=11.4$ Hz, 1H), 5.86 (td, $J=5.4$, 11.4 Hz, 1H), 4.57 (d, $J_{AB}=11.4$ Hz, 1H, part A of the AB system), 4.43 (d, $J_{AB}=11.4$ Hz, 1H, part B of the AB system), 4.03 (s, 1H), 3.79–3.74 (m, 1H), 2.76 (dd, $J=9.0$, 19.5 Hz, 1H), 2.47–2.12 (m, 4H), 1.87 (dd, $J=9.0$, 19.5 Hz, 1H), 1.56–1.70 (m, 2H), 1.02 (d, $J=6.6$ Hz, 3H), 0.92 (d, $J=6.6$ Hz, 3H), 0.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.9, 137.6, 128.8, 128.8, 128.4 (2CH), 127.8, 127.7 (2CH), 81.6, 74.5, 70.3, 49.5, 47.7, 42.9, 38.7, 32.5, 29.9, 23.4, 22.9, 17.5; HRMS for $C_{21}H_{29}O_3$ [MH^+]: 329.2116, found: 329.2111.
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