Towards a total synthesis of guanacastepene A: construction of fully functionalized AB and BC ring segments

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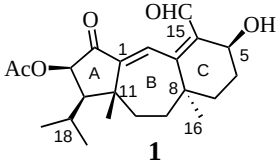
Abstract—Studies directed towards the total synthesis of the diterpene antibiotic, guanacastepene A, of current interest and displaying promising biological activity against drug-resistant pathogens, has led to the acquisition of fully functionalized AB and BC ring segments of the natural product.

Isolation and structure determination of a novel diterpene, guanacastepene A **1**, from an unidentified endophytic fungus growing on the tree *Daphnopsis americana* has been recently reported by Clardy et al.[1a] and shown to exhibit impressive activity against methicillin-resistant *Staphylococcus aureus* and vancomycin resistant *Enterococcus faecium*. In further biological studies **1** exhibited moderate activity against Gram-positive bacteria, poor activity against Gram-negative bacteria and hemolytic activity against human RBC.[1b]



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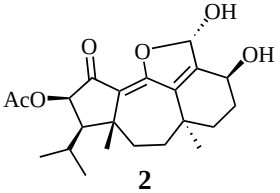

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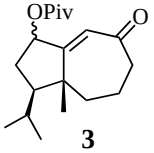
While these latter attributes undermine the therapeutical potential of **1**, its analogues may offer good chances of harnessing the antibiotic activity of this system against drug-resistant pathogens. Thus, an intensive world-wide quest for synthetic and naturally occurring analogues of **1** is on. More recently, several additional guanacastepenes B–O have been isolated from the same fungus but among them only guanacastepene I **2** shows moderate biological activity.[1c] A total synthesis of guanacastepene A **1** has not been accomplished so far although this target has attracted widespread attention and during the past year several model studies have been reported.[2–6]

Considering the synthetic challenge posed by the 5, 7, 6-fused tricarbocyclic framework of **1**, replete with complex stereochemical and functionalization pattern, initial attention has been focussed on the hydroazulenic



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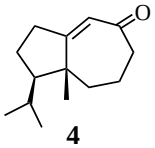

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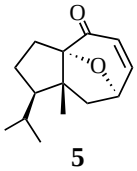

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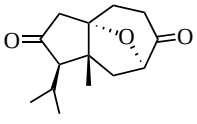

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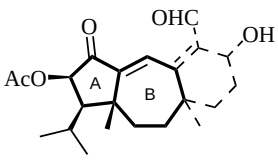

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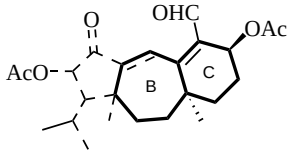

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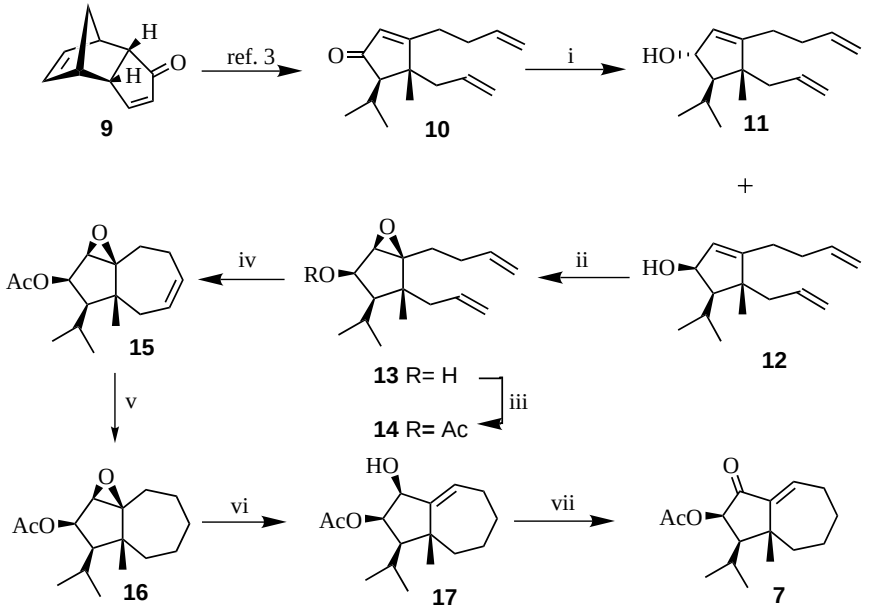
AB-ring substructure present in it. Preliminary reports from the research groups of Snider,[2a] Danishefsky[2b,c] and Magnus[2d] have outlined strategies leading to the AB ring models **3**, **4** and **5**, respectively. Our approach to **1** has led to **6**.[3] An approach towards the BC ring model of guanacastepene A **1** has also been described.[4] The AB ring hydroazulenic models **3**–**6** reported so far en route to **1** are well short of the requisite functionalization required in the natural product and no solution is available thus far for generating the sensitive α,β-unsaturated aldehyde–allylic alcohol functionality present in ring C of guanacastepene A **1**.[2–6] We report here the acquisition of the AB and BC ring segments **7** and **8** of **1**, with full complement of functionality and stereochemistry present in the natural product. The access to bicyclic structures **7** and **8** delineated here should pave the way for the total synthesis of **1** and enable access to a range of model compounds and analogues for biological screening.

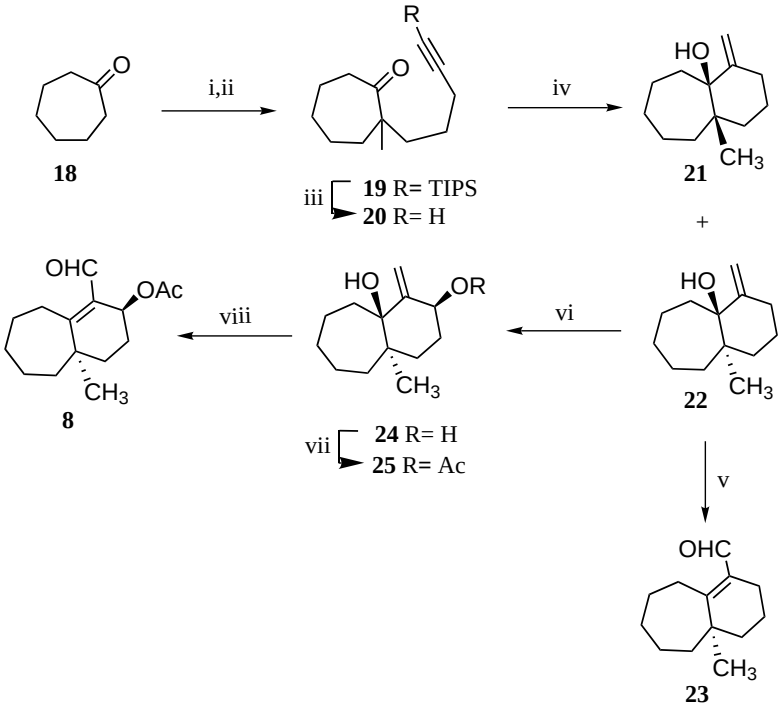
We have recently described the transformation of the readily available tricyclic enone **9** into cyclopentenone **10** through a short sequence.[3] Sodium borohydride reduction of **10** led to a mixture of allylic alcohols **11** (α-OH) and **12** (β-OH) in an 85:15 ratio (Scheme 1).[7] Directed epoxidation[8] of allylic alcohol **12** led to the epoxy–alcohol **13** as a single diastereomer and was further converted to the acetate **14**.[7] Ring-closure metathesis in **14** in the presence of Grubbs' catalyst[9] delivered the bicyclic hydroazulene derivative **15** and the cycloheptene double bond was reduced to give **16**.

TMSOTf-mediated[10] opening of the epoxide ring in **16** proceeded as planned to give, after the removal of the TMS protecting group, allylic alcohol **17** (Scheme 1).[7] Oxidation of the allylic hydroxy group in **17** delivered the desired AB ring segment **7** of guanacastepene A **1** with exact functionality and stereochemistry (Scheme 1).[11] Although, the reduction of **10** was non stereoselective and only the minor isomer **12** was the required one, the redeeming feature was that the unwanted isomer **11** could be recycled through oxidation to **10**.

Attention was next turned towards the BC ring fragment **8** of **1**. Sequential alkylation of cycloheptanone **18** with methyl iodide and tris-isopropyl protected 5-iodo-1-pentyne furnished **19** (Scheme 2). Removal of the TIPS protective group in **19** and titration of the resulting acetylenic ketone **20** with a solution of sodium naphthalenide resulted in intramolecular reductive cyclization to furnish a separable mixture (40:60) of *cis*-**21** and *trans*-bicyclic alcohol **22** (Scheme 2).[12–14] Both the allylic alcohols **21** and **22** underwent a smooth oxidative transposition reaction in the presence of PCC to furnish **23** having the unsaturated aldehyde functionality present in guanacastepene A **1**. To complete the full complement of functionality in the C ring of the natural product, the *trans*-allylic alcohol **22** was subjected to catalytic selenium dioxide oxidation to furnish a single crystalline diol **24** (Scheme 2).[7] X-Ray single-crystal structure[15] (Fig. 1) determination on **24** confirmed the stereoselective nature of the allylic hydroxylation reaction to install the correct relative stereochemistry at the angular methyl group and the secondary hydroxyl group. Selective acetylation of the hydroxyl group in **24** to give **25** and PCC mediated oxidative allylic transposition yielded the BC ring segment **8** of guanacastepene A **1** in a short sequence from commercially available cycloheptanone **18** (Scheme 2).



Scheme 1. *Reagents and conditions*: (i) $NaBH_4$, $CeCl_3$, MeOH 90%, **11**:**12** = 85:15; (ii) *m*-CPBA, CH_2Cl_2, 0–15°C, 65%; (iii) Ac_2O, DMAP, CH_2Cl_2, 0°C–rt, 90%; (iv) Grubbs' catalyst, C_6H_6, Δ, 5 h, 92%; (v) H_2, 10% Pd/C, EtOAc, quant.; (vi) (a) TMSOTf, DMAP, Py, rt, 2 days (b) 5% HCl, THF, 0°C, 75% for the two steps; (vii) MnO_2, CH_2Cl_2, rt, 5 h, 98%.



Scheme 2. *Reagents and conditions*: (i) (a) LDA, HMPA, −78°C, 20 min, (b) CH_3I, −78°C–rt, 62%; (ii) (a) KH, 0°C, 3 h, (b) $I(CH_2)_3CCTIPS$, 0°C–rt, 18 h, 66%; (iii) TBAF, THF, rt, quant.; (iv) $C_{10}H_8$, Na, THF, rt, 30% (**21**/**22**:40/60); (v) PCC, CH_2Cl_2, 0°C–rt, 4 h, 90%; (vi) SeO_2, ^tBuOOH, salicylic acid, CH_2Cl_2, rt, 24 h, 40%; (vii) Ac_2O, DMAP, CH_2Cl_2, 0°C–rt, 3 h, quant.; (viii) PCC, CH_2Cl_2, 0°C–rt, 8 h, 80%.

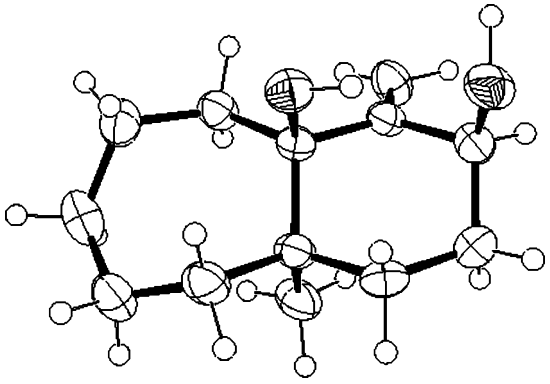


Figure 1. ORTEP diagram of **24**.

In summary, we have outlined short and simple approaches to fully functionalized bicyclic AB and BC ring segments of guanacastepene A **1** which augur well for the synthesis of the natural product and for accessing new potent analogues and libraries.

Acknowledgements

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5. Since the preparation of this manuscript, the following additional studies directed towards the synthesis of guanacastepene A have come to our attention. See: (a) Shipe, W. D.; Sorensen, E. J. *Org. Lett.* **2002**, *4*, 2063; (b) Nguyen, T. M.; Lee, D. *Tetrahedron Lett.* **2002**, *43*, 4033.
6. During the review process of this paper, a total synthesis of guanacastepene A by Danishefsky and co-workers has appeared. See: (a) Tan, D. S.; Dudley, G. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2185; (b) Lin, S.; Dudley, G. B.; Tan, D. S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2188.
7. All new compounds reported here are racemic and were duly characterized on the basis of spectral (IR, ^1H and ^{13}C NMR) and analytical data. Selected spectral data: Compound **7**: ^1H NMR (300 MHz, $CDCl_3$): δ 7.00 (dd,

$J=8.4$, 3.9 Hz, 1H), 5.43 (d, $J=6.3$ Hz, 1H), 2.50–2.41 (m, 1H), 2.35–2.20 (m, 2H), 2.10 (s, 3H), 2.04–1.96 (m, 1H), 1.90–1.78 (m, 3H), 1.54 (dd, $J=9.6$, 6.0 Hz, 1H), 1.35–1.22 (m, 2H), 1.31 (s, 3H), 1.10 (d, $J=6.6$ Hz, 3H), 0.93 (d, $J=6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.8, 169.5, 148.6, 141.1, 74.6, 55.1, 46.5, 39.8, 28.2, 27.1, 25.4, 24.8, 23.4, 23.0, 20.8, 18.1. Compound **12**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.92–5.81 (m, 1H), 5.66 (s, 1H), 5.44–5.36 (m, 1H), 5.10–4.97 (m, 4H), 4.48 (brs, 1H), 2.35–2.26 (m, 4H), 2.08–1.94 (m, 3H), 1.55 (dd, $J=11.1$, 5.7 Hz, 1H), 1.12 (s, 3H), 1.07 (d, $J=6.0$ Hz, 3H), 1.06 (d, $J=6.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2, 138.3, 135.5, 125.1, 117.5, 114.8, 75.8, 53.9, 50.3, 41.7, 31.3, 25.8, 25.4, 24.2, 22.8, 21.9. Compound **21**: IR (neat, cm^{-1}): 3489, 1640; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.90 (s, 1H), 4.71 (s, 1H), 2.31–2.17 (m, 2H), 2.12–2.00 (m, 2H), 1.9–1.83 (m, 3H), 1.60–1.10 (m, 9H), 0.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 155.7, 105.1, 79.1, 42.0, 37.8, 36.6, 35.3, 33.7, 26.8, 23.9, 22.4, 20.7, 20.6; Mass (EI) $M^+=194$. Compound **22**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.83 (s, 1H), 4.73 (s, 1H), 2.60–2.48 (m, 2H), 2.17–2.00 (m, 2H), 1.80–0.95 (m, 12H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.1, 108.3, 78.1, 41.8, 37.6, 36.9, 34.3, 32.2, 26.6, 22.9, 21.6, 20.5, 19.0. Compound **24**: IR (neat, cm^{-1}): 3363, 1634; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.09 (s, 1H), 4.97 (s, 1H), 4.31 (s, 1H), 3.62 (s, 2H), 2.22–2.04 (m, 2H), 1.92–1.30 (m, 10H), 1.06–0.93 (m, 2H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.8, 112.9, 78.7, 75.5, 41.9, 36.6, 34.1, 32.2, 29.9, 26.5, 21.6, 19.6, 18.8; Mass (EI) (M^+-H_2O, 192) ($M^+-H_2O-CH_3$, 177). Compound **8**: IR (neat, cm^{-1}): 1734, 1672, 1615; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.08 (s, 1H), 5.68 (s, 1H), 3.24 (dd, 1H, $J=13$, 6.4 Hz, 1H), 2.22–2.16 (m, 2H), 2.04 (s, 3H), 1.90–1.60 (m, 9H), 1.40–1.10 (m, 2H), 1.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 190.7, 172.9, 170.2, 130.7, 63.6, 40.7, 40.4, 31.4, 30.7, 30.6, 26.5, 26.3, 24.6, 23.3, 21.3; Mass (EI) ($M^+-H-OAc$, 190).

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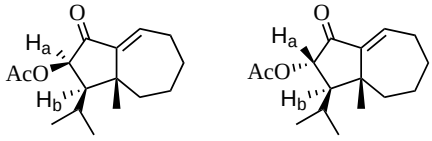
11. The diastereomeric allylic alcohol **11** (α-OH) was also elaborated to the bicyclic hydroazulenic stereoisomer (**i**) of **7**, essentially following the synthetic sequence described in Scheme 1. The two diastereomers **7** and (**i**) could be readily distinguished on the basis of the *cis* and *trans* vicinal coupling constants, $J_{Ha-Hb}=6.3$ Hz in **7** and $J_{Ha-Hb}=12.6$ Hz in (**i**), respectively.[6] The *cis* vicinal coupling constant for these protons in the guanacastepene A **1** is $J=7.5$ Hz.[1a] Spectral data for (**i**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.97 (dd, $J=9.0$, 4.2 Hz, 1H), 5.50 (d, $J=12.6$ Hz, 1H), 2.51–2.36 (m, 1H), 2.30–2.18 (m, 1H), 2.16 (s, 3H), 2.07–1.94 (m, 2H), 1.90–1.71 (m, 4H), 1.33–1.24 (m, 2H), 1.15 (s, 3H), 1.03 (d, $J=6.9$ Hz, 3H), 0.98 (d, $J=6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.4, 170.0, 145.4, 139.6, 77.0, 54.1, 44.2, 39.0, 28.3, 27.4, 25.7, 25.2, 24.9, 20.9, 19.8, 18.1



7 **(i)**

12. Contrary to the observations reported here, reductive cyclization of the acetylenic ketone **20** has been earlier shown[13] to give only a single product assigned the *cis* bicyclic structure **21**. However, this product is actually *trans*-**22** as shown by the X-ray crystal structural determination of the diol **24**.[15] Similarly, diol **24** was incorrectly[13] formulated earlier as having the all *cis* arrangement of the two hydroxyl groups as well as the angular methyl group. As it turns out now the secondary hydroxyl group and the angular methyl group have the requisite *trans* relationship present in the natural product.
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14. See also: (a) Mehta, G.; Krishnamurthy, N. *Tetrahedron Lett.* **1987**, *28*, 5945; (b) Mehta, G.; Krishnamurthy, N.; Karra, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 5765.
15. *Crystal data for the compound **24***: Structure was solved by direct methods (SIR-92) on an APEX SMART instrument. Refinement was by full-matrix least-squares using SHELXL-97. Crystal system: monoclinic, space group: $P2(1)/n$, cell parameters: $a=6.9065(8)$, $b=6.7739(8)$, $c=24.755(3)$ Å; $\beta=95.276(2)°$; $V=1153.2(2)$ Å^3; cell formula units (Z)=4; temperature=273 K; R-factor=0.0492 for $1704F_o>4\sigma(F_o)$ and 0.0718 for all 2335 data. Crystallographic data has been deposited in the Cambridge Crystallographic Data Center, CCDC 183724.