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Studies toward the Total Synthesis of Diterpene Antibiotic Guanacastepene A: Construction of the Hydroazulenic Core

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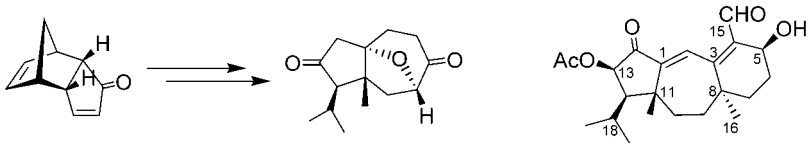
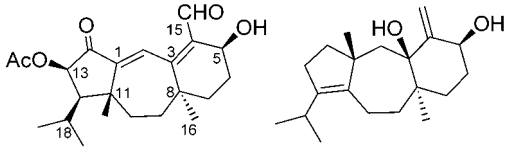
ABSTRACT



Guanacastepene A

As a part of studies aimed toward the total synthesis of biologically important natural product guanacastepene A of contemporary interest, a new and concise route to a fully functionally endowed hydroazulenic core is delineated. The strategy involves the building of the requisite stereochemical features on a *endo*-tricyclo[5.2.1.0^{2,6}]decane matrix and excision of the five-membered ring through a retro-Diels–Alder reaction. Generation of the seven-membered ring to access the hydroazulenic framework was achieved employing ring closure metathesis (RCM) reaction as the key step.

In 2000, a novel 5,7,6-ring fused diterpene guanacastepene A (**1**) was isolated from an unidentified fungus (CR 115) growing on the tree *Daphnopsis americana* by Clardy *et. al*. and its structure was elucidated through X-ray crystallography.[1a] More recently, a series of closely related metabolites guanacastepenes B−O have been isolated from the same source.[1b] Guanacastepene A (**1**), besides its structural novelty and interesting biosynthetic origin, exhibits impressive activity toward methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Entereococcus faecium*.[1c] These promising attributes identify **1** as a lead compound for developing a new family of antibacterials. Not surprisingly, **1** has evoked a great deal of attention from the synthetic community and as many as four reports directed toward the synthesis of **1** have appeared so far this year. These preliminary reports from the groups led by Snider,[2a] Magnus,[2b] and Danishefsky[2c,d] have focused on the synthesis of bicyclic hydroazulenic core present in **1**. A total synthesis of guanacastpene has not been achieved so far, and **1** continues to pose a formidable synthetic challenge.



1

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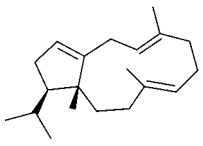

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We were attracted to undertake studies toward the synthesis of guanacastepene **1** on several counts: (1) The

(1) (a) Brady, S. F.; Singh, M. P.; Janso, J. E.; Clardy, J. *J. Am. Chem. Soc.* **2000**, *122*, 2116. (b) Brady, S. F.; Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900. (c) Singh, M. P.; Janso, J. E.; Luckman,. S. W.; Brady, S. F.; Clardy, J.; Greenstein, M.; Maiese, W. M. *J. Antibiot.* **2000**, *53*, 256.

(2) (a) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2001**, *3*, 569. (b) Magnus, P.; Waring, M. J.; Ollivier, C.; Lynch, V. *Tetrahedron Lett.* **2001**, *42*, 4947. (c) Dudley, G. B.; Danishefsky, S. *Org. Lett.* **2001**, *3*, 2399. (d) Dudley, G. B.; Tan, D. S.; Kim, G.; Tanski, J. M.; Danishefsky, S. *Tetrahedron Lett.* **2001**, *42*, 6789.

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biological activity profile, structural complexity, and contemporary interest made **1** a tempting target. (2) Our earlier synthetic strategy[3] toward a closely related 5,7,6 fused tricyclic marine diterpene isoamijiol **2** of dolastane-type could be adapted toward the synthesis of **1**. (3) Concurrent synthetic efforts underway in our group toward the marine diterpene **3**,[4] a possible biogenetic progenitor of **1** having a five-membered ring substitution pattern similar to guanacastepene A, suggested some useful synthetic leads. We report here a new, stereoselective approach to the hydroazulenic core of **1**, a notable feature of which is the generation of requisite level of functionalization in the five-membered ring.

In our approach to the hydroazulenic core of **1**, we recognized at the outset three essential requirements. These were the setting of the *cis* stereochemistry of the angular methyl group and the neighboring isopropyl group at C11 and C12, a desirable level of functionalization in the cyclopentane ring, and a functional group handle in the seven-membered ring to append the six-membered ring with the requisite functionality. Keeping these considerations in mind, readily available *endo*-tricyclo[5.2.1.$0^{2,6}$]deca-3,8-dien-5-one **4**[5] with well-established propensity toward reactivity on the *exo*-face was identified as the starting point. After considerable trials, it was possible to effect Cu(I)-promoted 1,4-addition of isopropylmagnesium iodide to **4** to furnish **5**[6,7] in good yield and with the stereoselective delivery of the isopropyl group exclusively from the *exo*-face. Sequential α-alkylation in the cyclopentanone moiety of **5** with allyl bromide (LDA base) and methyl iodide (NaH base) led to **6** as a single diastereomer.[8] While the first alkylation with allyl bromide furnished a mixture (~60:40) of *endo*- and *exo*-isomers along with some diallylated product, the second alkylation to our delight yielded only a single product with methyl addition exclusively from the *exo*-face.[9] Formation of both *exo*- and *endo*-allylated products from **5** in the initial allylation step is understandable in the presence of the bulky *exo*-isopropyl group and has precendence.[10a] Retro-Diels–Alder reaction in **6** under flash vacuum pyrolysis (FVP) conditions liberated the cyclopentenone **7**[8] and ejected a cyclopentadiene fragment.[10]

It was important to establish the *cis* disposition of the methyl and the isopropyl groups in **7** although predictable on the basis of the *exo*-proclivity of the tricyclodecane system **5**. The stereochemical assignment was secured through NOESY spectrum of **7**, which showed NOE interaction between the methine hydrogen attached to the isopropyl group and the allylic methylene of the allyl side chain, Scheme 1.

(3) (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.

(4) Bowden, B. F.; Coll, J. C.; Mitchell, S. J.; Stokie, G. J.; Blount, J. F. *Aust. J. Chem*. **1978**, *31*, 2039.

(5) (a) Rosenblum, M. *J. Am. Chem. Soc*. **1957**, *79*, 3179. (b) Woodward, R. B.; Katz, T. *Tetrahedron*. **1959**, *5*, 70.

(6) Initial efforts to effect 1,4-addition of isopropylmagnesium iodide to **4** were carried out in the presence of TMSCl[7a] or HMPA[7b] following the literature procedures for similar conjugate additions. However, a simple and straightforward procedure worked very well and consistently. Typical run: To a cold solution (0 °C) of isopropylmagnesium iodide (60 mL of 2 M solution in ether, 0.12 mol, further diluted with 100 mL of anhydrous ether), was added CuI (0.630 g, 3.3 mmol) in portions (four times) along with dropwise addition of compound **4** (8 g, 0.055 mol) in dry ether (100 mL) over a period of 1 h. The above mixture was stirred at 0 °C for 24 h and carefully quenched with saturated aqueous NH_4Cl solution (75 mL). The ethereal layer was separated and washed with water (3 × 50 mL) and brine (50 mL) and dried over sodium sulfate and concentrated. The residue was distilled (84 °C/0.1 mm) to provide **5** as a colorless oil, yield 9.4 g (90%): IR (cm^{-1}) 3060, 2960, 1732, 1467; ^1H NMR (300 MHz, $CDCl_3$) δ 6.19 (br s, 2H), 3.15 (br s, 1H), 3.00 (br s, 1H), 2.92 (ddd, J = 9.9, 4.8, 1.8 Hz, 1H), 2.70 (td, J = 9.0, 4.5 Hz, 1H), 2.16 (d 1/2ABq, J = 18.3, 9.3 Hz, 1H), 2.02 (dd 1/2ABq, J = 18.3, 7.8, 1.8 Hz, 1H), 1.66–1.43 (m, 4H), 0.94 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.7, 136.1, 135.3, 55.4, 52.3, 47.6, 46.5, 46.2, 45.8, 43.9, 34.3, 20.2, 20.1; Mass *m*/*z* 190 (M^+).

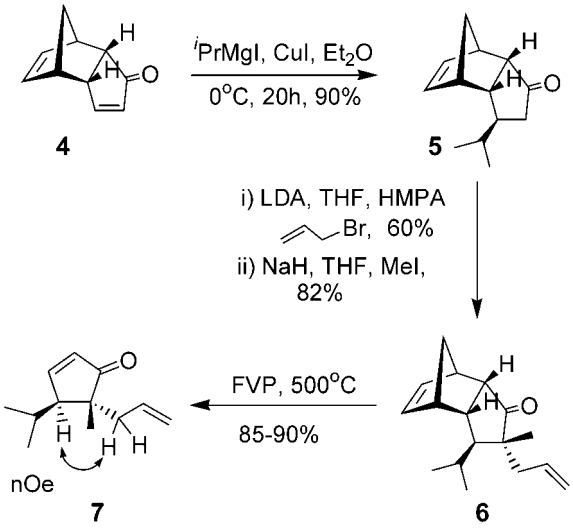
(7) (a) Piers, E.; Renaud, J.; Rettig, S. J. *Synthesis* **1998**, 590. (b) Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc*. **1975**, *97*, 107.

(8) All new compounds reported here are racemic and characterized on the basis of spectroscopic data (IR, ^1H and ^{13}C NMR, mass) and elemental analyses. Selected spectral data for **6**: IR (cm^{-1}) 3071, 2962, 1733, 1645, 912; ^1H NMR (300 MHz, $CDCl_3$) δ 6.08 (br s, 1H), 6.0 (br s, 1H), 5.52–5.38 (m, 1H), 4.95–4.87 (m, 2H), 3.12 (br s, 2H), 3.0 (br s, 1H), 2.6–2.5 (m, 2H), 1.99 (dd, J = 14.0, 9.3 Hz, 1H), 1.95–1.68 (m, 1H), 1.57 (1/2ABq, J = 8.4 Hz, 1H), 1.47 (1/2ABq, J = 8.4 Hz, 1H), 1.29 (t, J = 8.5 Hz, 1H), 1.08 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.7, 136.6, 135.7 (2C), 116.8, 57.4, 53.1, 52.4, 49.3, 47.7, 44.4, 44.3, 40.7, 30.8, 22.5, 22.3, 20.7; Mass *m*/*z* 244 (M^+). Data for **7**: IR (cm^{-1}) 3076, 2965, 1708, 1640, 1461, 836; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (dd, J = 6.0, 2.4 Hz, 1H), 6.15 (br d, J = 6 Hz, 1H), 5.66–5.52 (m, 1H), 5.05–5.00 (m, 2H), 2.53 (m, 1H), 2.32 (d 1/2 ABq, J = 13.5, 6.0 Hz, 1H), 2.13 (d 1/2 ABq, J = 13.5, 9 Hz, 1H), 1.92–1.81(m, 1H), 1.09 (d, J = 6.6 Hz, 3H), 1.09 (s, 3H), 0.90 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.3, 164.8, 134.1, 131.8, 118.3, 55.7, 50.2, 44.0, 27.7, 23.3, 20.6, 19.3; Mass *m*/*z* 178 (M^+). Data for **10**: IR (cm^{-1}) 3076, 2960, 1696, 1641, 995, 915; ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (s, 1H), 5.85–5.80 (m, 1H), 5.61–5.50 (m, 1H), 5.12–5.02 (m, 4H), 2.36 (br s, 4H), 2.31–2.10 (m, 3H), 2.01–1.98 (m, 1H), 1.19 (s, 3H), 1.17 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.7, 185.0, 137.0, 133.6, 128.6, 118.9, 115.7, 58.9, 49.9, 45.4, 30.9, 27.4, 27.3, 22.9, 20.3, 19.1; Mass *m*/*z* 232 (M^+). Data for **11**: IR (cm^{-1}) 2955, 1698, 1615, 1459; ^1H NMR (300 MHz, $CDCl_3$) δ 5.98–5.93 (m, 1H), 5.75 (s, 1H), 5.77–5.75 (m, 1H), 2.70–2.62 (m, 1H), 2.50–2.33 (m, 3H), 2.12–2.06 (m, 4H), 1.19 (s, 3H), 1.18 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.6, 187.9, 132.0, 129.0, 128.1, 62.9, 49.5, 40.4, 28.0, 27.2, 26.9, 23.4, 19.6, 19.4; Mass *m*/*z* 204 (M^+). Data for **12**: IR (cm^{-1}) 3446, 2956, 1462, 806; ^1H NMR (500 MHz, $CDCl_3$) δ 5.88 (d, J = 6.0 Hz, 1H), 5.70–5.61 (m, 1H), 5.54–5.49 (m, 1H), 5.44 (br d, J = 6.0 Hz, 1H), 2.35–2.21 (m, 3H), 2.14–1.92 (m, 3H), 1.73–1.63 (m, 1H), 1.11–1.08 (m, 1H), 0.99 (s, 3H), 0.95 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.2, 133.8, 131.3, 126.9, 88.2, 59.7, 53.0, 35.7, 28.0, 25.4 (2C), 22.9, 21.6, 18.4; Mass *m*/*z* 206 (M^+). Data for **13**: IR (cm^{-1}): 2967, 1697, 1615, 1459; ^1H NMR (300 MHz, $CDCl_3$) δ 5.72 (s, 1H), 3.24–3.18 (m, 1H), 3.08–3.01 (m, 1H), 2.71 (dd, J = 14.1, 6.0 Hz, 1H), 2.57–2.44 (m, 3H), 2.14–2.06 (m, 1H), 1.98 (d, J = 3.3 Hz, 1H), 1.40 (dd, J = 15.0, 7.8 Hz, 1H), 1.34 (s, 3H), 1.33–1.25 (m, 1H), 1.19 (d, J = 6.8 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2, 184.7, 128.9, 63.1, 54.2, 51.8, 49.7, 39.6, 27.8, 26.6, 26.3, 23.8, 19.9, 19.5; Mass *m*/*z* 178 (M^+ –42). Data for **14**: IR (cm^{-1}): 3395, 2832, 1737, 1649, 1073; ^1H NMR (500 MHz, $CDCl_3$) δ 4.33 (m, 1H), 3.96 (m, 1H), 2.56 (1/2 ABq, J = 19.5 Hz, 1H), 2.36 (1/2 ABq, J = 10.0 Hz, 1H), 2.32 (dd, J = 13.5, 10.0 Hz, 1H), 2.07 (1/2 ABq, J = 19.5 Hz, 1H), 2.04–1.98 (m, 1H), 1.97–1.90 (m, 2H), 1.89 (dd, J = 14.0, 6 Hz, 1H), 1.7 (dd, J = 14.0, 6.0 Hz, 1H), 1.64–1.54 (m, 1H), 1.18 (d J = 7.5 Hz, 3H), 1.09 (s, 3H), 1.07 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.7, 85.4, 78.5, 67.2, 65.3, 51.5, 45.6, 38.4, 29.5, 26.5, 25.5, 22.5, 21.4, 15.2; Mass *m*/*z* 238 (M^+). Data for **15**: IR (cm^{-1}) 2954, 1727, 1384, 1015; ^1H NMR (500 MHz, $CDCl_3$) δ 4.40 (d, J = 9.0 Hz, 1H), 2.76 (dd, J = 19.2, 1.2 Hz, 1H), 2.70 (dd, J = 14.0, 8.8 Hz, 1H), 2.64–2.56 (m, 1H), 2.48 (tdd, J = 18.0, 8.5, 1.6 Hz, 1H), 2.37 (dd, J = 8.4, 1.0 Hz, 1H), 2.34 (ddd, J = 14.2, 10.5, 8.5 Hz, 1H), 2.24 (d, J = 19.2 Hz, 1H), 2.14 (ddd, J = 14.2, 8.8, 1.6 Hz, 1H), 2.00–1.93 (m, 1H), 1.82 (dd, J = 14.0, 1.9 Hz, 1H), 1.22 (s, 3H), 1.20 (d, J = 6.6 Hz, 3H), 1.08 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.1, 205.8, 86.8, 82.0, 65.4, 51.4, 46.1, 43.1, 31.9, 29.9, 25.5, 22.4, 21.2, 17.7; Mass *m*/*z* 236 (M^+).

(9) It was not considered necessary to separate the diastereomers formed during the allylation of **5** as it was anticipated that the subsequent α-methylation would deliver the methyl addition from the *exo*-face, and this indeed turned out to be the case.

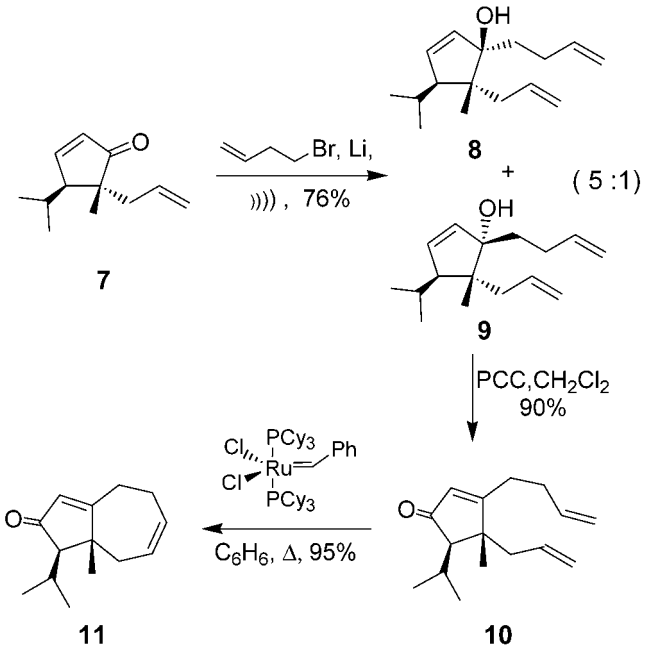
(10) (a) Stork, G.; Nelson, G. L.; Rouessac, F.; Gringore, G. *J. Am. Chem. Soc*. **1971**, *93*, 3091. (b) Wiel, J.-B.; Rouessac, F. *J. C. S. Chem. Comm*. **1976**, 446.(c) Review: Ogaswara, K. *Pure. Appl. Chem*. **1994**, *66*, 2119.

Scheme 1



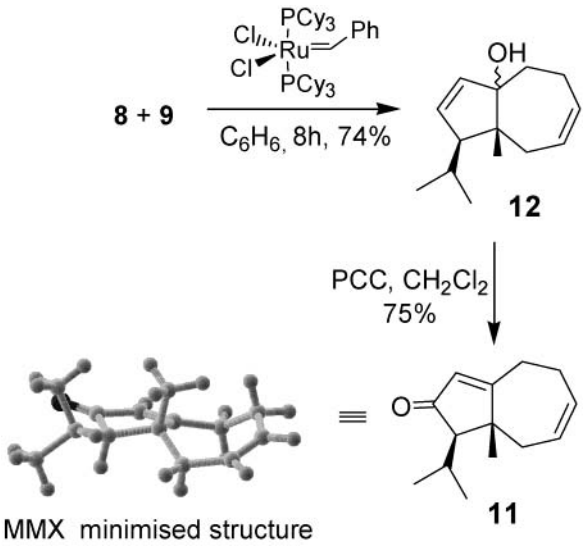
For the annulation of a seven-membered ring to cyclopentenone **7**, recourse was taken to a ring closing metathesis (RCM) based protocol. Barbier-type additions of 4-bromo-1-butene to **7** in the presence of lithium metal furnished a 5:1 mixture of diastereomeric carbinols **8** and **9** and were readily oxidatively transposed with PCC to the enone **10**, Scheme 2.[8] Predominance of the diastereomer **8** during the

Scheme 2



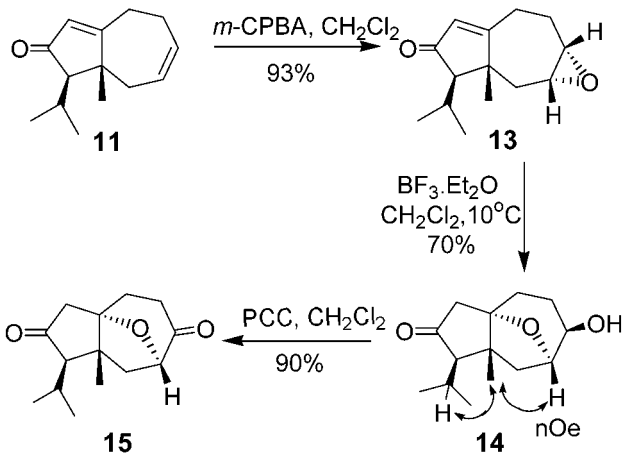
Barbier reaction of **7** can be attributed to the preferred addition of the butenyl group from the face opposite to the bulky isopropyl and methyl groups. On exposure to Grubbs' catalyst (~10 mol %),[11] **10** underwent smooth RCM reaction to deliver the hydroazulenic framework **11**, Scheme 2.[8] Structure of **11** was secured through incisive analyses of the spectral data[8] and had a full complement of functionality on the five-membered ring. Hydroazulene core **11** could also be accessed from the carbinol mixture **8** and **9** through RCM in the presence of Grubbs' catalyst[11] to **12**, followed by oxidative rearrangement, Scheme 3.

Scheme 3



To enhance the utility of the hydroazulenic substrate **11** for further evolution toward the natural product guanacastepene A (**1**), amplification of functionality in the seven-membered ring was considered desirable. Toward that objective, **11** was subjected to epoxidation to furnish a mixture of diastereomeric epoxides (90:10) in which the α-epoxide **13** predominated, Scheme 4. This outcome was

Scheme 4



to be expected as the β-face is hindered as a result of the presence of the bridgehead methyl group (see MMX minimized structure, Scheme 3). Stereostructure of **13** was

favored on steric considerations with the peracid reagent attacking from the bottom face opposite to the hindered face bearing methyl and isopropyl group and was secured through the detailed analysis of the NMR spectra (COSY, NOESY).[8] On exposure to BF_3-etherate in moist dichloromethane, **13** furnished the tricyclic ether **14**[8] through regioselective opening of the epoxide to the intermediate *trans*-diol and stereo- and regioselective transannular Michael addition to the cyclopentenone moiety, Scheme 4. Stereostructure of **14** was fully consonant with detailed NMR (COSY and NOESY) studies. The epoxide ring in **13** is opened from the β-face in a S_N2-type process. The regioselectivity of the epoxide ring opening in **13** is governed primarily by the steric congestion engendered on the β-face by the methyl and the isopropyl groups. Consequently, the epoxide ring opening is preferred at a distal site to avoid 1,3-interaction between the methyl group and the approaching nucleophile to furnish **14**. Oxidation of **14** led to **15**,[8] a fully endowed hydroazulenic precursor for further elaboration toward **1**. Formulation of **15** was fully secured through a single-crystal X-ray structure determination.[12]

In summary, we have outlined a short route to a functionally embellished hydroazulenic building block **15**, enroute to the biologically important natural product guanacastepene A (**1**), from a readily available tricyclo[5.2.1.$0^{2,6}$]deca-3,8-dien-5-one **4** precursor, employing RCM as a key step.

Acknowledgment. J.D.U. thanks CSIR for the award of a Research Fellowship. We thank SIF at IISc for timely help with high field NMR data.

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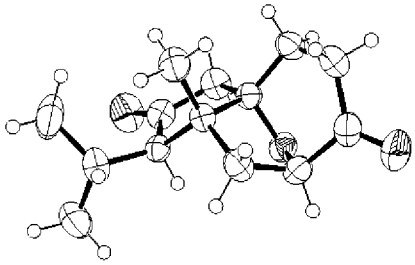
(11) Grubbs, R. H.; Chang, H. *Tetrahedron* **1998**, *54*, 4413.

(12) **Crystal data for the compound 15:** Structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares using SHELXL-97. Crystal system: triclinic, space group: *P*-1, cell parameters: $a = 6.209(1)$ Å, $b = 7.536(1)$ Å, $c = 15.002(3)$ Å; $\alpha = 82.819(3)°$, $\beta = 79.669\ (3)°$, $\gamma = 68.093(3)°$; $V = 639.55(9)$ Å^3. R-factor = 0.0555 for 2266 $F_o > 4\sigma(F_o)$ and 0.0637 for all 2732 data. Crystallographic data is being deposited with the Cambridge Crystallographic Data Center (CCDC 179048).



ORTEP diagram for **15**