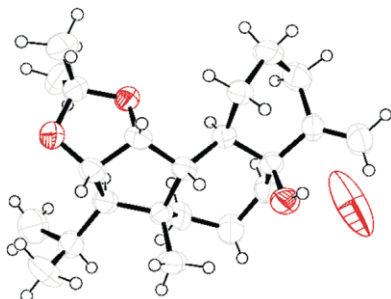


**Scheme 1.** Reagents and conditions: (i) 10% Pd/C, H<sub>2</sub>, EtOAc, 98%; (ii) DIBAL-H, DCM, 98%; (iii) MCPBA, DCM, 92%; (iv) pyridine, TMSOTf, DMAP, 75–80%; (v) DMP, acetone, PPTS, 95%; (vi) 3,5-dimethylpyrazole, CrO<sub>3</sub>, DCM, 50%; (vii) 10% Pd/C, H<sub>2</sub>, EtOAc, 80%; (viii) LDA, THF, HMPA, I(CH<sub>2</sub>)<sub>3</sub>CCTIPS, -78°C–rt, 12 h, 30%; (ix) TBAF, moist THF, rt, 95%; (x) Na-naphthalenide, THF, 90%.



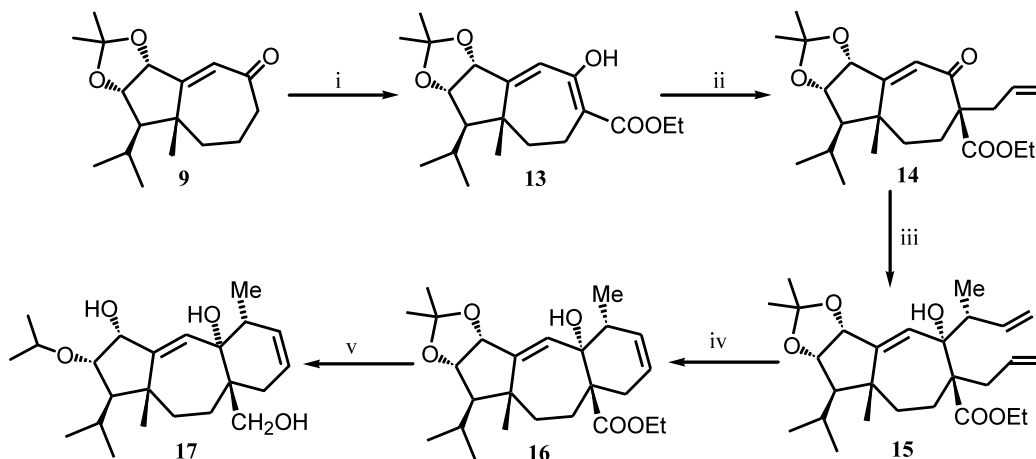
**Figure 1.**

Our first foray was targeted towards the construction of the tricyclic guanacastepane skeleton by annulation of a six-membered ring onto a hydroazulenenic precursor following the earlier<sup>3b</sup> model study that led to the realization of **3**. However, the implementation of the projected reaction sequence resulted in a regiochemical deviation and led to the novel isoguanacastepane skeleton. Hydroazulenenic enone **5**, readily available through a short sequence<sup>3a</sup> from tricyclic enone **4** was elaborated to **6** through selective catalytic hydrogenation of the isolated double bond and stereoselective enone reduction (Scheme 1). This stereoselective reduction is somewhat anomalous with hydride addition exclusively from the same face as the  $\beta$ -isopropyl and  $\beta$ -methyl groups and is in accordance with earlier observations in similar systems.<sup>3a,4</sup> Stereoselective epoxidation of **6** led to **7** and TMSOTf mediated epoxide opening furnished the *cis*-enediol **8** (Scheme 1).<sup>5</sup> Acetonide protection of the

*cis*-diol in **8** and allylic oxidation<sup>6</sup> furnished **9**<sup>5</sup> in which we had a versatile precursor that had in place the key oxy-functionalization in the A-ring and the olefinic bond in the B-ring as required in the natural product **1**. Therefore the main task ahead was the annulation of the six-membered C-ring and for this purpose several strategies (vide infra) were explored.

Repeated efforts to alkylate **9** at the desired C-8 position with *tris*-isopropylsilyl protected 5-iodo-1-pentyne or other alkylating agents to set-up the planned six-ring annulation<sup>3b</sup> proved abortive. While this effort was in progress others also reported similar observations.<sup>2,4</sup> Recourse was then taken to the reduced product **10** of **9**, which could be alkylated regioselectively with *tris*-isopropylsilyl protected 5-iodo-1-pentyne to furnish **11**<sup>5</sup> via C-2 alkylation rather than at the required C-8 position (Scheme 1). Silyl deprotection of **11** and sodium naphthalenide mediated intramolecular alkyne-ketone cyclization<sup>3b</sup> proceeded with excellent stereoselectivity and in high yield to furnish **12** (Scheme 1). A single crystal X-ray structure determination<sup>7</sup> of **12** confirmed the site of alkylation in **10** and consequent acquisition of the new 5,7,6-fused tricyclic (*iso*-guanacastepane) skeleton (Fig. 1).

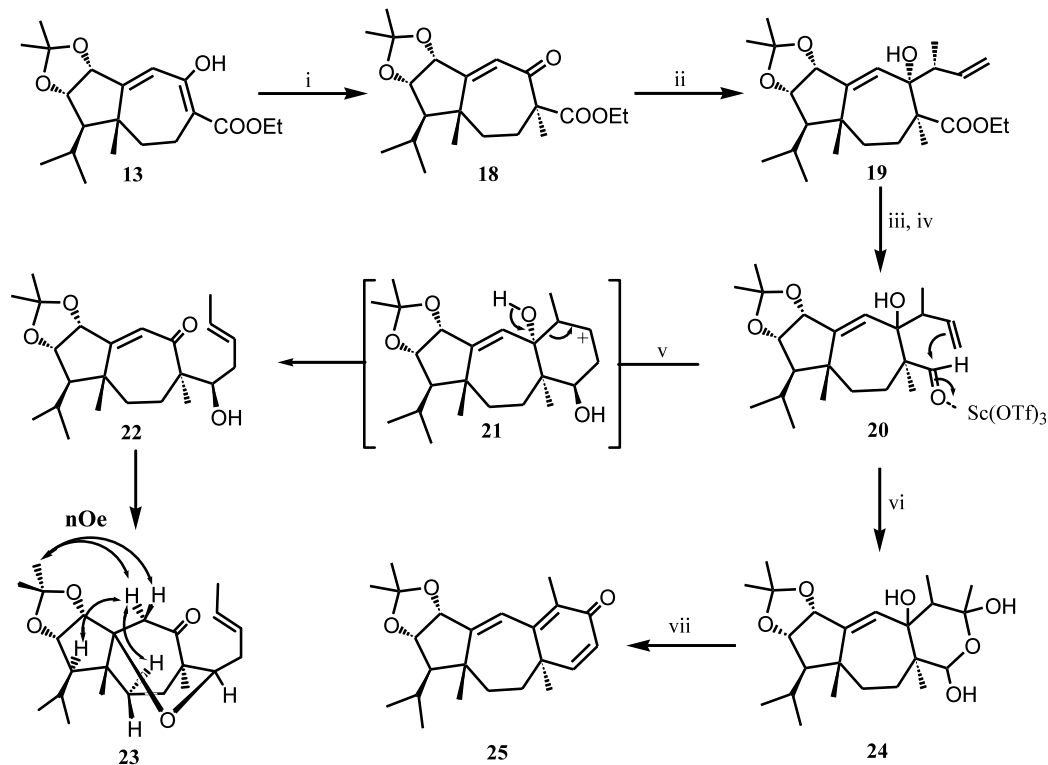
Attention was now turned to address the crucial issue of alkylation of the enone **9** at the C-8 position. It was observed that **9** could be  $\alpha$ -carboethoxylated at the C-8 position employing Mander's reagent<sup>8</sup> to yield **13**, which could be further allylated stereoselectively (vide infra) and in good yield to **14** (Scheme 2). Addition of



**Scheme 2.** Reagents and conditions: (i) LDA, THF–HMPA, CNCOOEt,  $-78^{\circ}\text{C}$ , 75%; (ii) NaH, THF, allyl bromide, rt, 95%; (iii) Mg, 3-chloro-1-butene,  $\text{CeCl}_3$ , THF, 60%; (iv) Grubbs' catalyst (10 mol%), benzene,  $\Delta$ , 96%; (v) DIBAL-H, DCM, 65%.

the Grignard reagent prepared from 3-chloro-1-butene to **14** in the presence of cerium(III) chloride<sup>9</sup> proceeded stereoselectively to furnish **15**<sup>5</sup> and set the stage for the contemplated RCM protocol for the construction of the six-membered C-ring of guanacastepene (Scheme 2). Indeed, exposure of **15** to Grubbs' catalyst resulted in smooth conversion to the tricyclic compound **16** in high yield (Scheme 2).<sup>5</sup> Reduction of **16** with DIBAL-H resulted not only in the reduction of the ester functionality to a primary alcohol but quite unexpectedly also

reductively cleaved the acetonide moiety to yield **17** (Scheme 2). An X-ray crystal structure determination<sup>7</sup> of **17** firmly established its stereochemistry and indicated that it was epimeric at C-8 with respect to the natural guanacastepenes and that the allylation of **13** had preferentially occurred from the less hindered  $\alpha$ -face. However, in a short sequence it was possible to transform the bicyclic ketone **9** into the  $\text{C}_{20}$ -skeleton corresponding to *epi*-guanacastepene with a rich complement of functionalities in all the three rings (Fig. 2).



**Scheme 3.** Reagents and conditions: (i) NaH, THF, MeI, 85–90%; (ii) Mg, 3-chloro-1-butene,  $\text{CeCl}_3$ , THF, 70%; (iii) LAH, THF, rt, 75%; (iv) TPAP, NMMO, 4 Å MS, 70%; (v)  $\text{Sc}(\text{OTf})_3$  (catalytic), DCM, 60–70%; (vi)  $\text{PdCl}_2$ , CuCl,  $\text{O}_2$ , DMF– $\text{H}_2\text{O}$ , 85%; (vii) NaOEt, EtOH, rt, 40–50%.

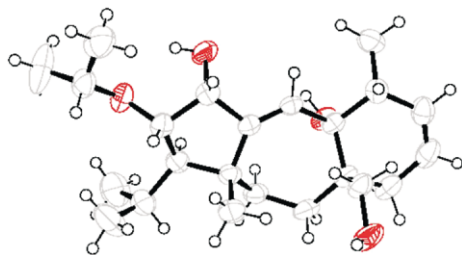


Figure 2.

The epimeric nature of **17** at C-8 indicated that the way to generate the correct stereochemistry present in the natural guanacastepanes was to harness the carboethoxy group in **13** in the C-ring forming protocols. Towards this end **13** was methylated to furnish **18** and correctly install the C-8 quaternary centre with the methyl group in the  $\alpha$ -orientation and *trans* with respect to the pre-existing C-11 angular methyl group (Scheme 3). Addition of the Grignard reagent derived from 3-chloro-1-butene to **18** in the presence of cerium(III) chloride was chemoselective and furnished **19**.<sup>5</sup> The ester group in **19** was now elaborated via LAH reduction and *n*-tetrapropylammonium per-ruthenate (TPAP) oxidation to aldehyde **20**,<sup>5</sup> in preparation for its integration into the proposed six-membered ring. For this purpose, an intramolecular Prins-type cyclization in **20** with several Lewis acids was explored but without much success. We therefore turned to a recent report where Sc(OTf)<sub>3</sub> had been found to be effective in inducing aldehyde-ene cyclization.<sup>10</sup> Consequently, **20** was exposed to Sc(OTf)<sub>3</sub> and the reaction took an interesting course. We found that **22**, a *seco*-guanacastepane derivative, was formed first via the fragmentation of the initially generated aldehyde-ene cyclization intermediate **21**. Continued exposure of **22** to the reaction milieu resulted in further intramolecular cyclization to the interesting bridged ether **23**,<sup>5</sup> whose stereostructure was secured through detailed 2D NMR (COSY, NOE) studies (Scheme 3). As a consequence of this unanticipated albeit interesting deviation, we had to alter our strategy. Wacker oxidation of the terminal olefinic bond in **20** led to the hydrate **24**, an appropriate candidate for effecting aldol cyclization to generate the C-ring of guanacastepanes. In the event, stirring **24** with sodium ethoxide in ethanol led to the desired cyclization and concomitant dehydration to yield an extremely interesting cross conjugated trienone **25**<sup>5</sup> with the complete guanacastepane framework and a high level of functionalization (Scheme 3). It is to be noted that the cross-conjugated trienone functionality present in **25** is quite unique and may impart some useful biological attributes to this molecule.

In summary, we have achieved a synthesis of the 5,7,6-fused tricyclic framework of guanacastepane diterpenes, replete with requisite stereochemical features and extensive functionalization, from a hydroazulenenic precursor with the focus on the exploration of different six-ring annulation strategies. Our efforts have also provided

access to new tricyclic structural variants (*iso*-guanacastepane and *epi*-guanacastepane) of the biologically promising guanacastepene **A 1**.

## Acknowledgements

J.D.U. and K.S. thank CSIR for the award of a research fellowship. We also acknowledge the help from SIF at the IISc towards obtaining high field NMR spectral data. X-ray data were collected at the CCD facility at IISc.

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- All new compounds reported here are racemic and were duly characterized on the basis of spectral (IR, <sup>1</sup>H and <sup>13</sup>C NMR) and analytical data. Selected spectral data: **Compound 12**: IR (cm<sup>-1</sup>): 3449, 1645; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  4.99 (s, 1H), 4.77 (s, 1H), 4.42–4.31 (m, 2H), 2.24–2.07 (m, 4H), 1.90–1.84 (m, 2H), 1.72–1.50 (series of m, 8H), 1.49 (s, 3H), 1.27 (s, 3H), 1.27–1.25 (m, 1H), 1.16–1.08 (m, 1H), 1.02–1.00 (brs, 9H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  158.6, 109.5, 107.0, 82.2, 82.1, 60.7, 51.8, 46.7, 43.4, 42.9, 39.3, 29.5, 28.8, 26.4, 26.2, 26.0, 25.4, 24.3, 23.5, 21.2, 19.2. **Compound 16**: IR (cm<sup>-1</sup>): 3519, 1730; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  5.84 (d, *J*=1.5 Hz, 1H), 5.63–5.58 (m, 1H), 5.35 (brd, *J*=10.2 Hz, 1H), 4.87 (d, *J*=7.2 Hz, 1H), 4.37 (dd as t, *J*=7.2 Hz, 1H), 4.05 (q, *J*=7.5 Hz, 2H), 2.84–2.82 (m, 1H), 2.51–2.41 (m, 2H), 2.34 (dd, *J*=18.6, 3.0 Hz, 1H), 2.67–2.20 (m, 1H), 1.85–1.82 (m, 1H), 1.78 (brs, 1H), 1.74–1.66 (m, 1H), 1.48 (s, 3H), 1.43–1.36 (m, 1H), 1.36 (s, 3H), 1.20 (t, *J*=7.5 Hz, 3H), 1.12 (d, *J*=7.2 Hz, 3H), 1.04 (d,

$J=6.6$  Hz, 3H), 0.98 (d,  $J=6.6$  Hz, 3H), 0.86 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  175.8, 150.6, 131.6, 125.5, 123.6, 112.4, 82.8, 80.2, 72.6, 61.6, 60.2, 54.1, 49.5, 40.2, 37.0, 36.7, 33.8, 28.1, 27.9, 26.2, 23.6, 22.4, 18.8, 14.0, 13.9; HRMS calcd for:  $\text{C}_{25}\text{H}_{38}\text{O}_5\text{Na}$  ( $\text{MNa}^+$ ): 441.2671. Found: 441.2629. **Compound 20**: IR ( $\text{cm}^{-1}$ ): 3494, 1713;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.78 (s, 1H), 5.78–5.66 (m, 1H), 5.52 (s, 1H), 5.09–5.02 (m, 2H), 4.79 (d,  $J=6.9$  Hz, 1H), 4.42 (dd as t,  $J=7.2$  Hz, 1H), 2.89–2.79 (m, 1H), 2.53 (s, 1H), 2.04–1.99 (m, 2H), 1.90–1.85 (m, 1H), 1.80–1.68 (m, 2H), 1.64–1.59 (m, 1H), 1.49 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H), 1.08 (d,  $J=6.0$  Hz, 3H), 1.07 (d,  $J=6.6$  Hz, 3H), 1.04 (d,  $J=6.6$  Hz, 3H), 1.00 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  207.9, 145.3, 141.1, 134.4, 117.7, 111.8, 82.0, 81.9, 81.8, 63.2, 53.3, 49.3, 47.0, 34.5, 28.3, 26.7, 26.1, 25.1, 24.6, 21.8, 20.4, 17.4, 16.6; HRMS calcd for  $\text{C}_{23}\text{H}_{36}\text{O}_4\text{Na}$  ( $\text{MNa}^+$ ): 399.2511. Found: 399.2500; **Compound 23**: IR ( $\text{cm}^{-1}$ ): 1720, 970;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.54–5.43 (m, 2H), 4.50 (d,  $J=8.0$  Hz, 1H), 4.24 (dd,  $J=8.4$ , 5.6 Hz, 1H), 3.76 (dd,  $J=7.6$ , 4.0 Hz, 1H), 2.71 (1/2ABq,  $J=19.6$  Hz, 1H), 2.40 (1/2ABq,  $J=19.6$  Hz, 1H), 2.22–2.15 (m, 1H), 2.00–1.88 (m, 3H), 1.72–1.67 (m, 1H), 1.65 (d,  $J=4.4$  Hz, 3H), 1.62–1.58 (m, 1H), 1.47 (s, 3H), 1.37 (dt,  $J=14.8$ , 4.0 Hz, 1H), 1.30 (s, 3H), 1.27–1.23 (m, 1H), 1.03 (s, 6H), 0.99 (d,  $J=6.4$  Hz, 3H), 0.92 (d,  $J=6.4$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  212.1, 128.1, 127.1, 112.7, 85.3, 84.6, 82.7, 82.0, 60.3, 52.5, 51.0, 42.2, 38.7, 38.3, 34.9, 29.5, 25.9, 24.7, 22.7, 22.4, 20.4, 18.0, 16.0; HRMS calcd for:  $\text{C}_{23}\text{H}_{36}\text{O}_4\text{Na}$  ( $\text{MNa}^+$ ): 399.2511. Found: 399.2526. **Compound 25**: IR ( $\text{cm}^{-1}$ ): 1658, 1625;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.71 (d,  $J=9.6$  Hz, 1H), 6.33 (s, 1H), 6.23 (d,  $J=9.6$  Hz, 1H), 4.88 (d,  $J=6.4$  Hz, 1H), 4.44 (dd as t,  $J=6.8$  Hz, 1H), 2.00–1.92 (m, 1H), 1.85 (s, 3H), 1.78–1.64 (m, 5H), 1.53 (s, 3H), 1.37 (s, 3H), 1.27 (s, 3H), 1.06 (d,  $J=6.4$  Hz, 3H), 1.01 (d,  $J=6.4$  Hz, 3H), 0.86 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  186.1, 157.2, 152.5,

132.3, 126.6 (brd), 124.4, 112.0, 82.8, 81.4 (brd), 34.5 (brd), 31.9 (brd), 29.7, 28.3, 27.4, 26.1, 24.2, 21.9, 11.5; HRMS calcd for  $\text{C}_{23}\text{H}_{32}\text{O}_3\text{Na}$  ( $\text{MNa}^+$ ): 379.2249. Found: 379.2268.

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7. **Crystal data for compound 12**: Structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares using SHELXL-97. Crystal system: monoclinic, space group:  $C2/c$ , cell parameters:  $a=9.882$  (1),  $b=21.732$ (3),  $c=20.003$  (3) Å;  $\beta=102.709$ (3)°;  $V=4190.98$  Å<sup>3</sup>,  $Z=8.0$ ,  $F(000)=1568.0$ ,  $\mu=0.07$  mm<sup>-1</sup>,  $D_{\text{calcd}}=1.13$ ,  $\lambda=0.7107$  Å. Total number of l.s. parameters=375,  $R_1=0.0874$  for 1517  $F_o>4\sigma(F_o)$  and 0.2519 for all 4213 data. GOF ( $S$ )=0.972, restrained GOF=0.972 for all data. An ORTEP diagram (with trapped water molecule) with 50% ellipsoidal probability of compound **12** is shown in Figure 1, CCDC No. 205947. **Crystal data for compound 17**: Structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares using SHELXL-97. Crystal system: monoclinic, space group:  $P2(1)/c$ , cell parameters:  $a=7.1824$  (7),  $b=17.096$  (1),  $c=17.994$  (1) Å;  $\beta=92.759$  (2)°;  $V=2207.03$  Å<sup>3</sup>,  $Z=4.0$ ,  $F(000)=832.0$ ,  $\mu=0.08$  mm<sup>-1</sup>,  $D_{\text{calcd}}=1.139$ ,  $\lambda=0.7107$  Å. Total number of l.s. parameters=396,  $R_1=0.0530$  for 3070  $F_o>4\sigma(F_o)$  and 0.0664 for all 3731 data. GOF ( $S$ )=1.105, restrained GOF=1.105 for all data. An ORTEP diagram with 50% ellipsoidal probability of compound **17** is shown in Figure 2, CCDC No. 205714.
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