Total synthesis of the bicyclo[6.3.0]undecane-based sesquiterpene (±)-asterisca-3(15),6-diene. Revision of the relative stereochemistry of the natural product

Goverdhan Mehta* and Jayant D. Umarye

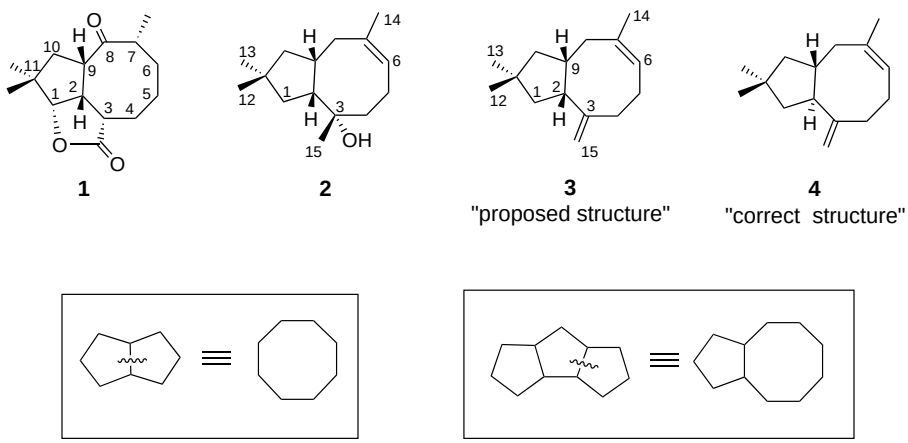
Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

Abstract—The first total synthesis of the novel bicyclic sesquiterpene hydrocarbon asterisca-3(15),6-diene is reported. As a consequence, the natural product is shown to possess structure **4** with a *trans*-5,8 ring fusion and not the previously assigned *cis*-asterisca-3(15),6-diene **3**.

In 1985, a novel 5,8-ring fused sesquiterpene asteriscanolide **1** was isolated from *Asteriscus aquaticus* L. (family *compositae*).[1a] Subsequently, two new natural products 3α-hydroxy-6-asteriscene **2**[1b] and asterisca-3(15),6-diene **3**[1c] from the essential oil of *Lippia integrifolia* (Griseb) were added in 1995 and 1999, respectively, to this rare bicyclo[6.3.0]undecane-based family of sesquiterpenes. While the stereostructure of asteriscanolide **1** was secured through a X-ray crystal structure determination,[1a] those of **2** and **3** were largely deduced from the analyses of their spectral data.[1b,c]

The absolute configuration of **2** and **3** remains unknown. All the three asteriscanes **1**–**3** were formulated as having a *cis*-fused 5,8-ring junction. Asteriscanolide **1**, being the first member of this new skeletal type among sesquiterpenes, has aroused considerable synthetic interest[2] and four total syntheses[3a–d] and several synthetic approaches[3e–g] have been reported. However, synthetic endeavours towards **2** and **3** have not been reported in the literature so far. We describe here the first synthesis of the natural product asterisca-3(15),6-diene and demonstrate that the stereostructure of the naturally occurring hydrocarbon needs to be revised to **4** with *trans*-ring fusion.

Our approach to the bicyclo[6.3.0]undecane system was based on the 'carbocyclic ring equivalency' concept.[4]



Scheme 1.

Keywords: terpenes; polyquinanes; cyclooctanes; Wittig reaction; stereochemistry.

* Corresponding author. E-mail: gm@orgchem.iisc.ernet.in

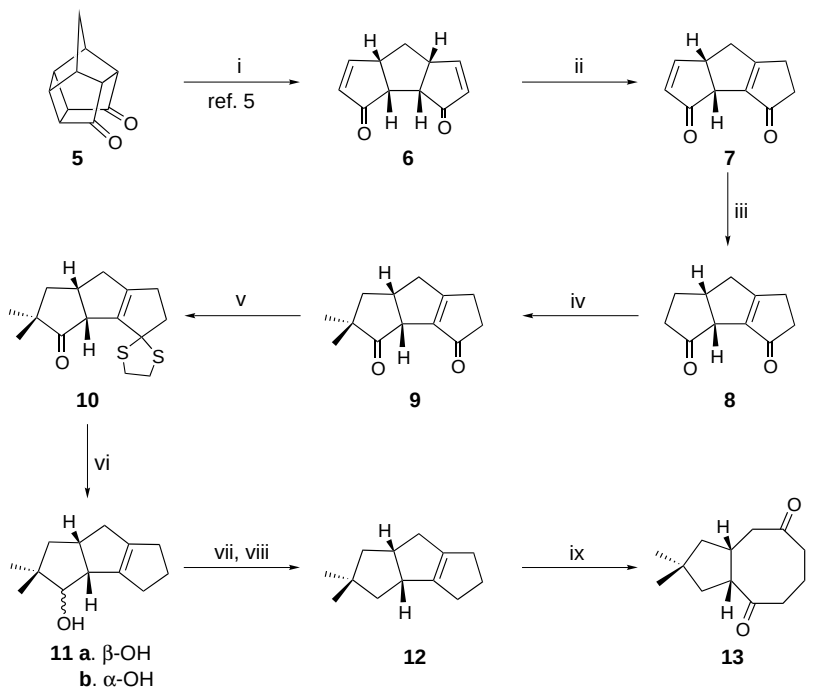
Thus, bicyclo[3.3.0]octane is an eight-membered ring equivalent and tricyclo[6.3.0.0^{2,6}]undecane (linear triquinane) is the latent form of the bicyclo-[6.3.0]undecane system (Scheme 1). In the backdrop of this theme, our synthesis of **3** (corresponding to the previously assigned[1c] *cis*-fused formulation) emanated from the *cis*,*syn*,*cis*-triquinane bis-enone **6**, readily and quantitatively available from the pentacyclic-caged dione **5** through flash-vacuum pyrolysis (FVP) as described by us many years ago.[5] Relocation of one of the enone moieties in **6** through thermal activation under static conditions led to the bis-enone **7** (Scheme 2). Controlled, selective catalytic hydrogenation to **8** and regioselective *gem*-dimethylation delivered **9**.[6] Chemoselective thioketalisation in **9** gave monothioketal **10**, which was subjected to reductive desulfurisation in metal–ammonia milieu to yield a diastereomeric mixture (2:1) of *exo*-**11a** and *endo*-**11b** alcohols (Scheme 2). The major alcohol **11a** was deoxygenated following the Barton protocol[7] and the resulting tricyclic tetrasubstituted olefin **12** on catalytic ruthenium oxidation afforded the 5,8-fused *cis*-bicyclic dione **13**[5] (Scheme 2).

Wittig olefination of *cis*-bicyclic dione **13** proceeded regioselectively at the carbonyl group distant from the ring junction and the *gem*-dimethyl group to furnish keto-olefin **14**.[6] Isomerisation of the exocyclic double bond to the desired endocyclic position in **14** proved to be difficult due to unwanted transannular cyclisations.[8] Consequently, the carbonyl group in **14** was reduced and the resulting hydroxyl compound was protected as a TMS–ether to give **15**. Rhodium-mediated olefin isomerisation in **15** led to a mixture of **16a** and **16b** (4:1) which could be readily separated. TMS–ether deprotection of the required isomer **16a** and PDC-oxidation yielded keto-olefin **17**[6] (Scheme 3). Finally, Wittig olefination of **17** furnished **3**, corresponding to the 'assigned structure' of the natural product[1c] (Scheme 3).

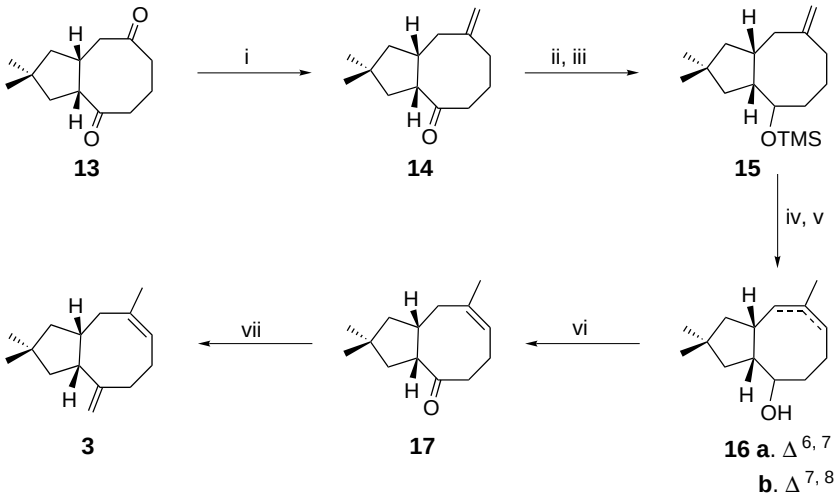
However, the spectral data (^{1}H and ^{13}C NMR)[6] of synthetic **3** was distinctly different from that reported for the natural product.[1c] Careful scrutiny of the spectral data led us to surmise that the natural product was the *trans*-isomer **4** and we undertook its synthesis.

cis-Bicyclic dione **13** on exposure to base could be readily equilibrated with its *trans*-isomer **18** in which the latter was the major product (4:1). Bicyclic *trans*-dione **18**, like its *cis* sibling **13**, also underwent a facile regioselective Wittig olefination to yield keto-olefin **19** (Scheme 4). $RhCl_3$-mediated double-bond isomerisation in **19** proceeded without any complications and gave a mixture of readily separable olefinic ketones **20a** and **20b** (40:60) (Scheme 4). Wittig olefination on the major compound **20b** proceeded smoothly to furnish the bicyclic hydrocarbon **4** whose spectral characteristics (^{1}H and ^{13}C NMR) exactly matched those reported for the natural product.[1c,6]

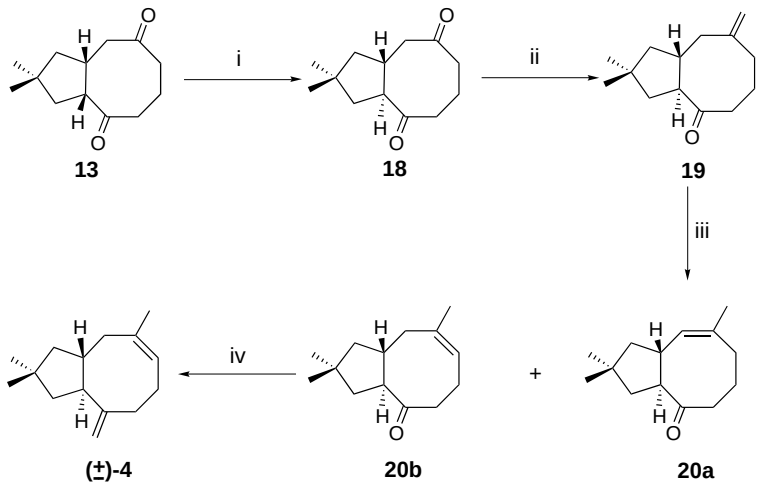
In short, we have accomplished the total synthesis of the natural product (±)-asterisca-3(15),6-diene and our synthetic efforts necessitates the revision of the earlier-assigned structure[1c] of the natural product from *cis*-**3** to *trans*-**4**. The synthetic methodology reported here is of general applicability and can be readily adapted for the synthesis of other asteriscane sesquiterpenes.



Scheme 2. *Reagents and conditions*: (i) 580°C, FVP, 0.1 torr, quantitative; (ii) diphenyl ether, 260°C, 30 min, 80%; (iii) H_2, 10% Pd/C, EtOAc, 1 h, 95%; (iv) NaH (2 equiv.), THF, MeI (2.5 equiv.), 5–12 h, 35–50%; (v) ethanedithiol, BF_3-etherate, MeOH, 0–10°C, 70%; (vi) Na–liq. NH_3, THF, 30 min, 85% (2:1 *exo*:*endo* epimers); (vii) NaH, THF, imidazole, CS_2, MeI, reflux, 95%; (viii) (*n*-Bu)$_3$SnH, benzene, reflux, 2 h; (ix) $RuCl_3$, $NaIO_4$, CCl_4–CH_3CN–H_2O, 4 h, 70% after two steps.



Scheme 3. *Reagents and conditions*: (i) $MePh_3P^+Br^-$, KO^{t}Bu, benzene, 40°C, 30 min, 75%; (ii) $NaBH_4$, MeOH, rt, 1 h, 75%; (iii) TMS–imidazole, TBAF (cat.), THF, 15 min, 95%; (iv) $RhCl_3 \cdot 3H_2O$, $NaHCO_3$, EtOH, reflux, 1 h; (v) 10% HCl, THF, 0°C, 15 min (1:4 mixture of **16a** and **16b**, respectively), 75% after two steps; (vi) PDC, 4 Å MS powder, DCM, rt, 3 h, 70%; (vii) $MePh_3P^+Br^-$, KO^{t}Bu, benzene, 40°C, 30 min, 95%.



Scheme 4. *Reagents and conditions*: (i) KO^{t}Bu, THF, ^{t}BuOH, 20 min (4:1 equilibrium mixture of **18** and **13**, respectively), quantitative; (ii) $MePh_3P^+Br^-$, KO^{t}Bu, benzene, 40°C, 30 min, 75%; (iii) $RhCl_3 \cdot 3H_2O$, $NaHCO_3$, EtOH, Δ, 1 h (2:3 mixture of **20a** and **20b**, respectively), 90%; (iv) $MePh_3P^+Br^-$, KO^{t}Bu, benzene, 40°C, 30 min, 95%.

Acknowledgements

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6. All new compounds reported here were racemic and characterised on the basis of spectroscopic data (IR, ^{1}H and ^{13}C NMR, mass) and elemental analyses. Selected spectral data: Compound **13**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.34 (dd, $J=16.5$, 7.8 Hz, 1H), 2.93–2.83 (m, 1H), 2.63–2.4 (m, 5H), 2.24 (dd, $J=13.8$, 3.6 Hz, 1H), 2.17–2.10 (m, 2H), 1.93 (dd, $J=13.2$, 7.5 Hz, 1H), 1.61 (dd, $J=12.6$, 6.3 Hz, 1H), 1.48 (dd, $J=13.5$, 7.5 Hz, 1H), 1.33 (dd, $J=12.3$, 10 Hz, 1H), 1.14 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.0, 213.5, 52.4, 48.0, 44.6, 44.2, 43.6, 42.0, 40.6, 37.6, 29.4, 29.3, 22.5. Compound **18**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.9 (dt, $J=10.8$, 7.8 Hz, 1H), 2.60–2.20 (m, 8H), 2.10–2.03 (m, 1H), 1.88–1.80 (m, 2H), 1.59 (dd, $J=12.9$, 7.2 Hz, 1H), 1.30 (dd as t, $J=12.1$ Hz, 1H), 1.10 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.7, 211.8, 56.4, 49.6, 46.9, 44.5, 43.4, 42.8, 42.6, 36.6, 31.4, 30.9, 21.6. Compound **3**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.38 (t, $J=7.2$ Hz, 1H), 4.92 (s, 1H), 4.77 (s, 1H), 2.66 (q, $J=7.5$ Hz, 1H), 2.5–1.9 (series of m, 6H), 1.7 (s, 3H), 1.68 (m, 1H), 1.62 (dd, $J=15.0$, 6.6 Hz, 1H), 1.56 (m, 1H), 1.45–1.27 (series of d, 2H), 1.11 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.6, 138.5, 123.1, 112.4, 47.6, 47.3, 47.2, 41.9, 40.9, 37.0, 36.2, 30.6, 30.0, 27.8, 24.3. Compound **4**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.20 (m, 1H), 4.80 (s, 1H), 4.66 (s, 1H), 2.43 (m, 1H), 2.32–2.26 (m, 1H), 2.22–2.05 (m, 3H), 1.98–1.94 (m, 1H), 1.83 (dd, $J=13.2$, 2.4 Hz, 1H), 1.68 (m, 1H), 1.68 (s, 3H), 1.59 (d, $J=9.6$ Hz, 2H), 1.56–1.48 (m, 1H), 1.17 (dd as t, $J=11.7$ Hz, 1H), 1.08 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.9, 137.1, 123.4, 109.3, 50.0, 49.6, 49.4, 47.7, 39.4, 37.4, 35.0, 31.8, 31.7, 25.1, 24.5.
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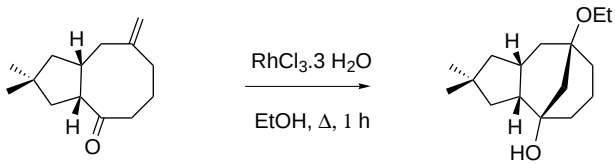
8. On exposure to $RhCl_3{\cdot}3H_2O$, the keto-olefin **14** exclusively furnished the transannularly cyclised product (**i**), which proved quite unserviceable for further elaboration towards the natural product.



14 (**i**)