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A new synthesis of tricyclic sesquiterpene (±)-sterpurene

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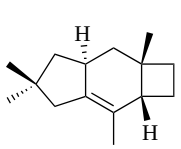
Abstract—A new synthesis of tricyclic sesquiterpene, sterpurene **1** is reported. An intermolecular [2+2]-photocycloaddition **14**→**15** serves as a key step, which is promoted through the stabilisation of the enone excited state through a β-carbomethoxy substituent on the α,β-unsaturated enone moiety. A tricyclo[6.3.0.$0^{3,6}$]undecane based advanced intermediate **19** en route to **1**, has been fragmented to the bicyclo[6.3.0]undecane system **27** present in the asteriscane-type sesquiterpenoids.

The fungus *Chondrostereum purpureum*, responsible for the so-called 'silver leaf disease' (recognised through the metallic lustre of the foliage), is widespread in North American forests and fruit orchards. *C. purpureum* when grown in malt extract liquid culture produces a complex mixture of sesquiterpene metabolites of a new structural type. From the culture filtrates of this fungal source, Ayer in the early 1980's and subsequently others, have reported the isolation of several novel 5-6-4 ring fused sesquiterpenes **1**–**9** named sterpuranes.[1a–f] More recently, this skeleton has also been encountered as a metabolite **10** from *Gloeophyllum* sp. 97022, a conspicuous fungus causing intensive brown rot of the colonised wood.[1g] The novel architecture of sesquiterpenes **1**–**10** has aroused considerable synthetic and biosynthetic interest and in particular, sterpurene **1**, the parent hydrocarbon of this family has been a target of many synthetic endeavours.[2] While the first synthesis of sterpurene **1** was along a biomimetic route[2a] from humulene, others have followed routes that test a particular synthetic methodology.[2b–j] Herein, we report a new synthesis of sterpurene **1** from a diquinane precursor **11**.

We have recently described a ready and simple access to the *cis*-diquinane ketone **11** from commercially available 1,5-cyclooctadiene (1,5-COD).[3] α-Carbomethoxylation followed by alkylation with methylene bromide in **11** furnished **12** as a mixture of diastereomers. Exposure of **12** to TBTH resulted in radical mediated one carbon ring expansion to **13**,[4] which was further elaborated to the *cis*-hydrindane-enone **14** via phenylselenation–selenoxide elimination steps (Scheme 1).[5] The β-carbomethoxy–cyclohexenone moiety in **14** was strategically deployed to promote the installation of the four-membered ring present in the target structure **1** through an intermolecular [2+2]-photocycloaddition.[6] Delightfully, irradiation of **14** in the presence of excess of *trans*-dichloroethylene led to **15** (mixture of *cis*- and *trans*-1,2-dichloro isomers) in a near quantitative yield (Scheme 1). Protection of the carbonyl group in **15** and DIBAL-H reduction furnished the tricyclic hydroxy-



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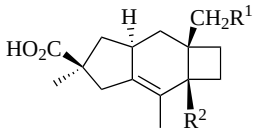
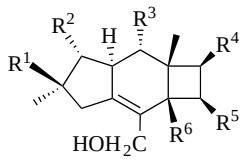


2: R^1=H, R^2=OH

3: R^1, R^2=OH

4: R^1, R^2=-OC(H)(Me)O-



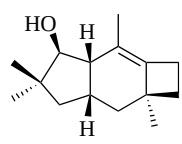
5: R^2, R^3, R^4, R^5=H; R^1=CH_2OH, R^6=OH

6: R^1, R^3, R^4, R^5, R^6=H; R^2=OH

7: R^1, R^2, R^4, R^5, R^6=H; R^3=OH

8: R^1, R^2, R^3, R^5, R^6=H; R^4=OH

9: R^1, R^2, R^3, R^4, R^6=H; R^5=OH



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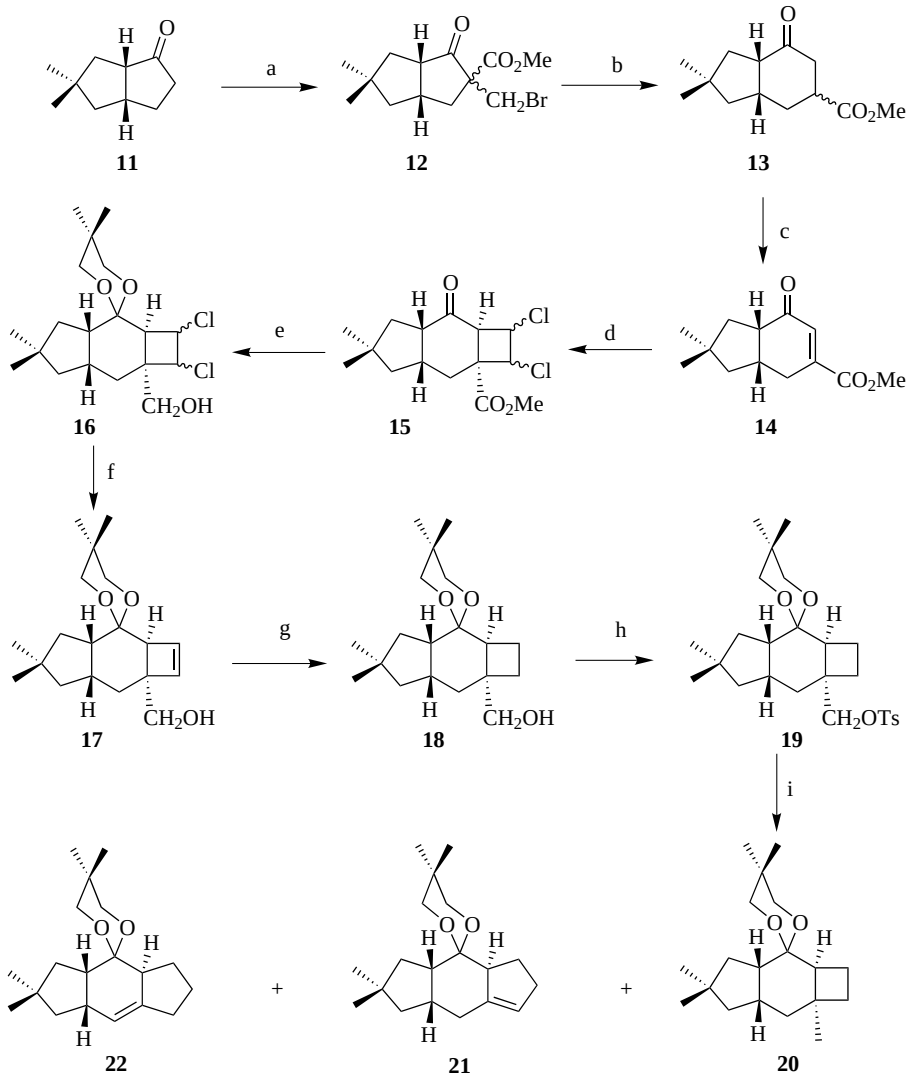
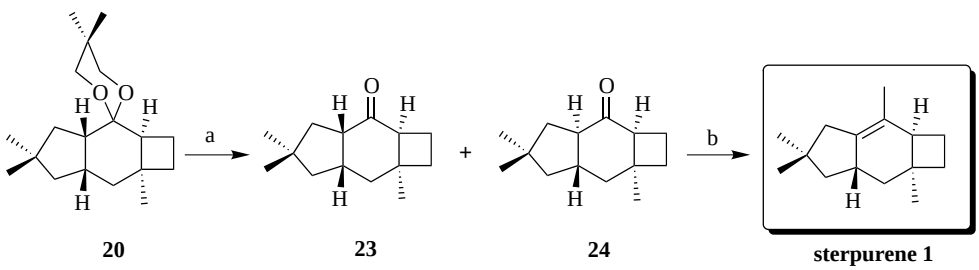
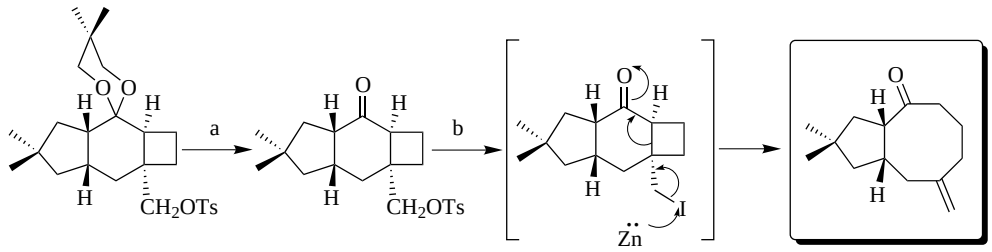
methyl compound **16**.[5] Sodium naphthalenide mediated eliminative dehalogenation in **16** gave *cis*,*anti*,*cis*-tricyclic cyclobutene **17**[5] as a single diastereomer, indicating that the [2+2]-photocycloaddition was completely stereoselective. Catalytic hydrogenation of the cyclobutene double bond led to **18** and further tosylation of the primary hydroxyl group furnished **19**,[5] in which the tosylate functionality needed to be reductively displaced to generate the requisite quaternary methyl group. After many trials, it was observed that exposure of **19** to



Scheme 1. *Reagents and conditions*: (a) (i) NaH, $(MeO)_2CO$, C_6H_6, 78%, (ii) K_2CO_3, CH_2Br_2, acetone, 70%; (b) *n*-tributyltinhydride (TBTH), AIBN, C_6H_6, 63%; (c) (i) LHMDS, PhSeCl, THF, −78°C, (ii) 30% H_2O_2, DCM, 0°C, 50%; (d) *trans*-1,2-dichloroethylene, C_6H_{12}, *hv*, 95%; (e) (i) 2,2-dimethyl-1,3-propanediol, PTSA, C_6H_6, (ii) DIBAL-H, DCM; (f) sodium naphthalenide, DME, 70% (three steps); (g) H_2, PtO_2, EtOAc, 96%; (h) *p*-toluenesulfonylchloride, pyridine, 90%; (i) $NaBH_4$, DMSO, 70°C, 80% (**20**:**21**:**22** = 3:1:1).



Scheme 2. *Reagents and conditions*: (a) Amberlyst-15, Me_2CO, 85% (**23**:**24** = 95:5); (b) (i) MeLi, Et_2O, (ii) $SOCl_2$, pyridine (Ref. 2b,g,j).



Scheme 3. *Reagents and conditions*: (a) Amberlyst-15, acetone, 85%; (b) NaI, Zn, acetone, reflux, 50%.

sodium borohydride in DMSO led to the desired tricyclic compound **20**[5] and the novel ring expanded 5,6,5-fused tricycles **21**[5] and **22**[5] in 3:1:1 ratio, in decent yield (Scheme 1). Deprotection of the carbonyl group in **20** readily furnished the ketone **23** (95:5)[2b,g,j,5] and a minor epimerised *trans*-isomer **24**. Both, **23** and **24** have been previously transformed[2b,g,j] to sterpurene **1** in a simple two-step sequence involving methyl lithium addition and dehydration, thus constituting a synthesis of the natural product (Scheme 2).

The availability of **19**, en route to sterpurene **1**, provided an opportunity for an interesting deviation. Carbonyl deprotection in **19** yielded keto-tosylate **25** which on exposure to sodium iodide in the presence of zinc metal was transformed to the *cis*-bicyclo[6.3.0]undecane derivative **27** in a single pot reaction through the intermediacy of the iodo-ketone **26** (Scheme 3). While cyclobutane fragmentation reactions have been previously employed for the syntheses of eight-membered rings and bicyclo[6.3.0]undecane system,[8,9] the fragmentation of **26**, bearing a tricyclo[6.3.0.0^{3,6}]undecane system, to **27** is a new variant.[8] It is interesting to note that the bicyclic keto-olefin **27** has been recently prepared by us[10] following an entirely different route and further transformed in a few steps to an asteriscane-type sesquiterpene natural product (asterisca-3(15),6-diene)[10,11] based on the bicyclo[6.3.0]undecane framework.[8]

In short, we have outlined a new synthesis of the tricyclic sesquiterpene hydrocarbon sterpurene **1** from a readily available diquinane precursor **11**. Our approach employs a tactic in which an electron withdrawing β-substituent on the α,β-unsaturated enone moiety promotes intermolecular [2+2]-photocycloadditions and this may find further applications in synthesis. As a bonus in these endeavours, tricyclo[6.3.0.0^{3,6}]undecane based intermediate **19**, en route to the synthesis of sterpurene **1**, has been fragmented to the bicyclo[6.3.0]undecane system **27** present in the asteriscane sesquiterpenoids.[8]

Acknowledgements

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5. All new compounds reported here are racemic and were duly characterised on the basis of spectral (IR, ^{1}H and ^{13}C NMR) and mass spectral/analytical data. Selected data for **14**: IR (neat) ν_{max} 1725, 1675 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.76 (s, 1H), 3.83 (s, 3H), 2.80–2.68 (m, 3H), 2.58–2.49 (m, 1H), 2.02 (dd, J=13.2, 6.0 Hz, 1H), 1.78–1.53 (m, 2H), 1.35 (dd, J=12.9, 8.1 Hz, 1H), 1.05 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 202.1, 167.2, 145.7, 132.1, 52.6, 49.4, 46.4, 43.1, 37.5, 37.3, 31.2, 31.1, 26.7; EIMS (70 eV) m/z 222 (M^+).
Compound **17**: IR (neat) ν_{max} 3408, 3040, 1112 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.22–6.18 (m, 2H), 3.80 (d, J=8.4 Hz, 1H), 3.77 (d, J=8.4 Hz, 1H), 3.68 (s, 1H), 3.59 (1/2 ABq, J=10.5 Hz, 1H), 3.54 (1/2 ABq, J=10.5

Hz, 1H), 3.36–3.28 (m, 2H), 2.48–2.30 (m, 2H), 1.98–1.88 (m, 1H), 1.67 (dd, $J=12.9$, 5.2 Hz, 1H), 1.60–1.40 (m, 5H), 1.16 (s, 3H), 1.07 (s, 3H), 0.90 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 141.3, 137.6, 102.6, 70.3, 70.0, 68.2, 54.4, 49.3, 43.4, 41.4, 39.0, 38.2, 33.7 (2C), 29.7, 29.0, 26.8, 23.1, 22.1; EIMS (70 eV) m/z 306 (M^+).

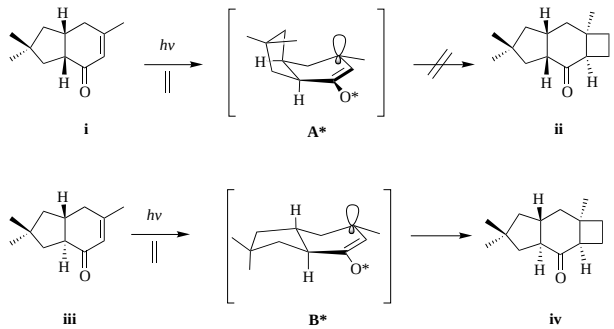
Compound **20**: IR (neat) ν_{max} 1463, 1103 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.67 (d, $J=11.4$ Hz, 1H), 3.59 (d, $J=11.4$ Hz, 1H), 3.28 (dd, $J=10.8$, 2.4 Hz, 1H), 3.20 (dd, $J=11.1$, 2.7 Hz, 1H), 3.14–3.09 (m, 1H), 2.60–2.50 (m, 2H), 1.92–1.55 (series of m, 4H), 1.49 (dd, $J=12.6$, 6.9 Hz, 1H), 1.30 (dd, $J=13.2$, 5.1 Hz, 1H), 1.20–1.01 (m, 4H), 1.14 (s, 3H), 1.11 (s, 3H), 1.09 (s, 3H), 0.97 (s, 3H), 0.69 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 102.2, 70.0, 69.7, 49.5, 42.9, 39.6, 39.0, 38.2, 38.0, 35.4, 34.0, 30.9, 29.5, 29.2, 28.0, 27.2, 23.2, 22.2, 15.7; EIMS (70 eV) m/z 292 (M^+).

Compound **21**: IR (neat) ν_{max} 3041, 1663 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.35 (br s, 1H), 3.78 (d, $J=11.1$ Hz, 1H), 3.69 (d, $J=11.1$ Hz, 1H), 3.41 (dd, $J=11.4$, 2.1 Hz, 1H), 3.30 (dd, $J=11.1$, 2.1 Hz, 1H), 3.21–3.12 (m, 1H), 2.98–2.88 (br m, 1H), 2.40–2.20 (m, 4H), 2.10–1.90 (m, 3H), 1.75–1.52 (m, 2H), 1.45–1.20 (m, 2H), 1.21 (s, 3H), 1.16 (s, 3H), 1.07 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 142.2, 122.4, 100.6, 70.1, 69.8, 49.9, 47.2, 40.5, 38.9, 38.2, 36.9, 32.7, 32.6, 31.6, 30.8, 29.6, 23.3, 22.4, 21.6; EIMS (70 eV) m/z 290 (M^+).

Compound **22**: IR (neat) ν_{max} 1676, 1114, 802 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.37 (br s, 1H), 3.77 (d, $J=10.8$ Hz, 1H), 3.70 (d, $J=10.8$ Hz, 1H), 3.40–3.25 (m, 3H), 2.80–2.70 (br m, 1H), 2.60–2.40 (br m, 1H), 2.35–2.28 (m, 2H), 2.00–1.15 (series of m, 8H), 1.18 (s, 3H), 1.04 (s, 6H), 0.74 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 138.7, 121.3, 101.4, 70.1, 70.0, 48.0, 45.0, 39.7, 37.4, 35.6, 30.9, 30.5, 29.8, 29.3 (2C), 24.9, 23.9, 23.1, 22.2; EIMS (70 eV) m/z 290(M^+).

Compound **23**: IR (neat) ν_{max} 1697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.26 (q, $J=9.7$ Hz, 1H), 3.18–3.03 (m, 1H), 2.64 (dd, $J=8.7$, 5.7 Hz, 1H), 2.30–2.13 (m, 2H), 2.10–1.80 (series of m, 3H), 1.70–1.55 (m, 3H), 1.16 (s, 3H), 1.07 (s, 3H), 1.00 (s, 3H), 1.11–0.99 (m, 1H), 0.91 (t, $J=13.2$ Hz, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 52.6, 49.0, 47.8, 42.5, 42.2, 40.7, 38.0, 37.2, 30.3, 29.0, 28.4, 27.6, 17.2; EIMS (70 eV) m/z 206 (M^+).

6. It has been reported that *cis* bicyclic α,β-unsaturated enones like (**i**), related to **14**, do not undergo photochemical [2+2]-cycloadditions with olefins like ethylene to furnish (**ii**).[2b] On the other hand, *trans* compound (**iii**) readily furnishes the [2+2]-photocycloaddition product (**iv**). The failure of (**i**)→(**ii**) photocycloaddition has been attributed to the energy raising steric interaction **A*** (cf. **B***) during the [2+2]-cycloaddition excited state.[2b,g] However, it is also known that in the excited state of α,β-unsaturated ketones, the β-carbon is charged negatively with respect to the α-carbon.[7] Thus, any stabilisation of the negative charge on the β-carbon of the α,β-unsaturated ketones should promote the excited state for the [2+2]-photocycloaddition. This consideration led us to install the β-carbomethoxy substituent in the α,β-unsaturated *cis*-enone **14** and gratifyingly the [2+2]-photoaddition now worked quite efficiently.



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