# A stereoselective total synthesis of the novel triquinane sesquiterpene cucumin E

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**Abstract**—A total synthesis of cucumin E, a recently isolated triquinane natural product with a new carbon framework, has been achieved. The key step is the flash vacuum pyrolysis (FVP)-induced cyclobutane fragmentation in a readily available pentacyclic caged dione to deliver the triquinane skeleton with functionalization in all the three five-membered rings suitable for further elaboration to the natural product. © 2001 Published by Elsevier Science Ltd.

During the past few decades, the linearly-fused triquinane sesquiterpenoids have been encountered in increasing numbers among diverse natural sources. Notable examples of the various tricyclo[6.3.0.0$^{2,6}$]undecane framework based triquinane skeleta, differing in methyl group disposition and level of functionalization, are hirsutic acid **1** (hirsutane type), capnellene **2** (capnellane type), ceratopicanol **3** (ceratopicane type) and pleurotellol **4** (pleurotellane type). The presence of an unusual tricarbocyclic core with skeletal, stereochemical and functional group diversity have sustained a high level of synthetic interest in this family of natural products.[1] In 1998, research groups of Steglich and Anke have reported the isolation and structure determination of a new type of triquinane sesquiterpenes named cucumins E-G **5**–**7** from the mycelial cultures of agaric *Macrocystidia cucumis* (Pers ex Fr.).[2] The stereostructures of cucumins E–G were determined through incisive high-field NMR studies and these sesquiterpenes bear a close biogenetic relationship to the hirsutanes from which they are derived through a methyl group migration. Herein, we report the **first** total synthesis of cucumins, particularly of cucumin E **5**, following an interesting variant of the photo-thermal metathetic approach to linear triquinanes delineated by us sometime ago.[3]

Pentacyclic dione **8**, readily available from 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene and benzoquinone in two steps,[4] on reductive dehalogenation and oxidation furnished **9**, which we had identified as our key starting material. After some trials, it was possible to devise flash vacuum pyrolysis (FVP) conditions under which **9** underwent [2+2]-cycloreversion of the cyclobutane ring to furnish the triquinane bis-enone **10**[5] quite satisfactorily,
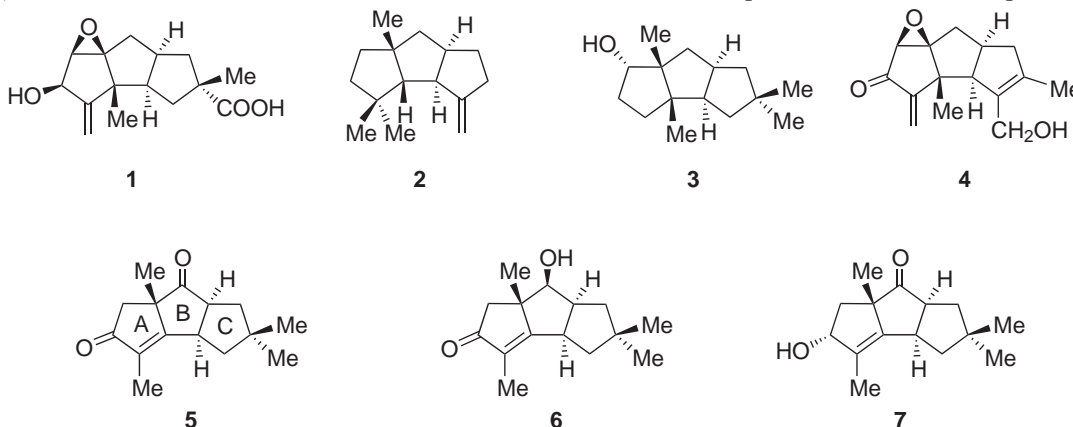


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Scheme 1. The important outcome was that the dimethyl acetal group of **9**, necessary for our projected synthesis, was retained during the FVP conditions. Exposure of **10** to base established an equilibrium through back and forth double bond isomerizations and resulted in the desired epimerization at the ring junction to furnish a readily separable mixture (4:1) of the isomerized bis-enone **11** and the epimerized *cis,anti,cis*-bis-enone **12**.[5] The bis-enone **11** could be further equilibrated in the presence of base to furnish **12**, ensuring preparative access to the required *cis,anti,cis*-isomer.

Attention was now turned towards the installation of the four methyl groups on the triquinane **12** and relevant functional group adjustments. Catalytic hydrogenation of **12** and selective mono-Wittig olefination led to the ketone **13** (Scheme 1). Methylation of **13** was effected regioselectively and efficiently to furnish the *gem*-dimethylated ketone **14**.[5] The carbonyl group was sought to be removed at this stage and, as direct deoxygenation methods were unsuccessful, **14** was reduced with lithium aluminum hydride to furnish **15** (5:1, *exo:endo*), Scheme 1. The Barton deoxygenation sequence[6] on **15** delivered **16**.[5] The next task en-route to the cucumin skeleton was the introduction of the angular methyl group to generate the complete $C_{15}$-carbon framework. For this purpose, the ketal moiety in **16** was deprotected to furnish **17**. Angular methylation in **17** exhibited fair regioselectivity (2:1 in favour of C7 versus C9), an outcome that we had anticipated on account of the steric (methylation at C9

would lead to relative crowding in the *gem*-dimethyl bearing ring-C) and electronic (the deprotonation at C7 leads to a homoallylic carbanion)[7] considerations and **18**[5] was obtained as the major product, Scheme 2. The enone moiety in ring-A of **18** was established through allylic oxidation following the Sharpless[8] catalytic selenium dioxide oxidation to give **19**[5] and further PDC oxidation to the enone **20** (Scheme 2). Rh(III)-mediated isomerization of the exocyclic double bond in **20** delivered cucumin E **5**, whose spectral characteristics were exactly identical to the natural product as established through direct comparison.[2]

In short, we have accomplished a total synthesis of the tricyclic natural product cucumin E **5**, with good regio- and stereochemical control, following a tactical modification of the photo-thermal metathesis based strategy that provides direct and rapid access to the ring-B functionalized triquinane framework.
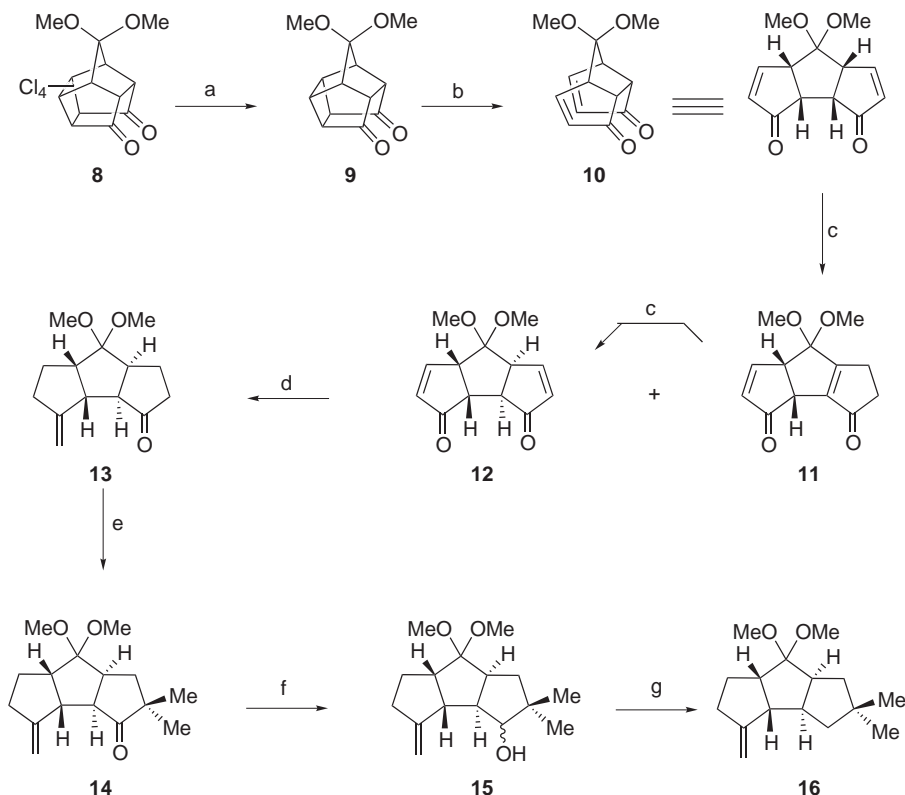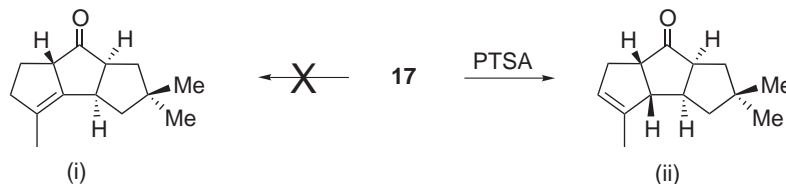
**Scheme 1.** *Reagents and conditions*: (a) i. Li, liq. NH$_3$, THF, H$_2$O, 55%; ii. PCC, NaOAc, DCM, 3 h, 50%; (b) FVP, 590–610°C, $10^{-2}$ mmHg, 65%; (c) DBU, DCM, 24 h, Δ, quant. **11**:**12** (4:1); (d) i. H$_2$, 10% Pd/C, 1 atm, EtOAc, rt, 1 h, quant.; ii. PPh$_3^+$CH$_3$Br$^-$, $^t$BuO$^-$K$^+$, benzene, 5°C, 95% at 60% conversion; (e) NaH (5 equiv.), MeI (10 equiv.), THF, 8–10 h, 85–90%; (f) LAH (excess), THF, 0.5 h, 90%; (g) i. NaH (8 equiv.), CS$_2$, imidazole (cat.), MeI, THF, 5 h, Δ, 80%. ii. TBTH–AIBN, toluene, Δ, 10 min, 70–80%.
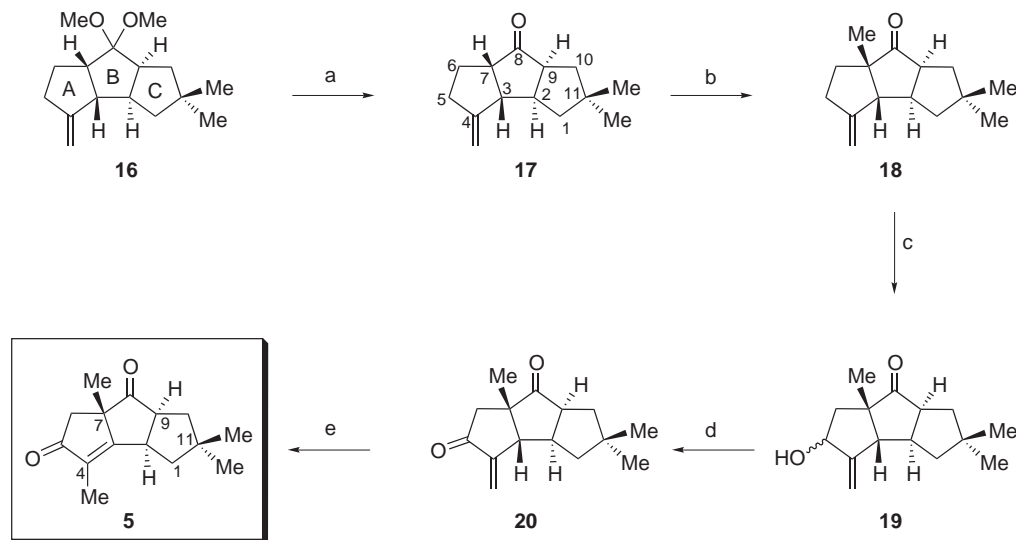
**Scheme 2.** *Reagents and conditions*: (a) Amberlyst-15, aq. acetone, quant.; (b) LDA (3 equiv.), MeI (10 equiv.), THF, −10°C, 10 min, (2:1, mixture of regioisomers), 70%; (c) SeO₂, TBHP, DCM, rt, 4 h, 90%; (d) PDC, DCM, rt, 3 h, 70%; (e) RhCl₃, EtOH (degassed), Δ, 1 h, 80%.

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5. All new compounds reported here were racemic and characterized on the basis of spectroscopic data (IR, ¹H and ¹³C NMR, mass) and elemental analyses. Selected spectral data. **10**: mp 149°C; ¹H NMR (300 MHz, CDCl₃): δ 7.5 (dd, J = 5.8, 1.8 Hz, 2H), 5.97 (dd, J = 5.8, 2.4 Hz, 2H), 3.54 (br s, 2H), 3.4 (s, 3H), 3.3 (s, 3H), 3.2 (br s, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 207.1, 161.7, 135.2, 106.7, 54.2, 51.2, 49.6, 48.6; MS: m/z 233 (M⁺−1). **12**: mp 148°C; ¹H NMR (300 MHz, CDCl₃): δ 7.56 (dd, J = 5.4, 3.3 Hz, 2H), 6.21 (dd, J = 5.7,

(s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 158.4, 110.4, 103.9, 54.2, 52.2, 50.5, 50.1, 49.4, 48.7, 48.0, 42.0, 40.5, 33.4, 29.3, 28.2, 26.8; MS: m/z 249 (M⁺−1). **18**: ¹H NMR (300 MHz, CDCl₃): δ 4.96 (br s, 1H), 4.92 (br s, 1H), 2.98–2.89 (m, 1H), 2.62–2.5 (m, 1H), 2.5 (br s, 1H), 2.4–2.34 (m, 2H), 1.93–1.83 (m, 2H), 1.76 (ddd, J = 13.2, 9.9, 1.5 Hz, 1H), 1.5–1.6 (m, 2H), 1.16 (dd, J = 12.3, 8.7 Hz, 1H), 1.17 (s, 3H), 1.04 (s, 3H), 0.96 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 225.2, 157.1, 106.3, 58.8, 58.3, 52.2, 48.9, 46.5, 43.3, 41.1, 37.58, 32.5, 29.0, 28.2, 22.8; MS: m/z 217 (M⁺−1). **20**: ¹H NMR (300 MHz, CDCl₃): δ 6.11 (d, J = 2.3 Hz, 1H), 5.5 (d, J = 2.3 Hz, 1H), 3.1 (ddd, J = 10 Hz, 1H), 2.86 (m, 1H), 2.66 (m, 1H), 2.57 (d, J = 19 Hz, 1H), 2.24 (d, J = 19 Hz, 1H), 1.97 (ddd, J = 13, 8, 1.5 Hz, 1H), 1.84 (ddd, J = 13, 9.9, 1.5 Hz, 1H), 1.64 (dd, J = 12.9, 7.5 Hz, 1H), 1.46 (dd, J = 12.9, 7.5 Hz, 1H), 1.26 (s, 3H), 1.07 (s, 3H), 0.99 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 221.7, 204.1, 148.6, 119.2, 55.7, 52.2, 51.5, 48.5, 47.8, 46.3, 43.4, 41.7, 28.8, 28.0, 23.1; MS: m/z 232 (M⁺).

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7. In order to ensure regioselectivity during the key angular methylation reaction, it was proposed to isomerize the



exocyclic double bond in **17** to endocyclic position as in (i) to promote the formation of the delocalized carbanion. However, efforts to relocate the double bond in **17** led only to (ii).

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1.8 Hz, 2H), 3.5 (m, 2H), 3.28 (s, 6H), 2.88 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 208.3, 161.3, 134.2, 108.2, 53.6, 50.0, 49.2; MS: m/z 234 (M⁺). **16**: ¹H NMR (300 MHz, CDCl₃): δ 4.76 (br s, 2H), 3.21 (s, 3H), 3.14 (s, 3H), 2.8–2.76 (m, 2H), 2.55–2.4 (m, 3H), 2.29–2.2 (m, 1H), 1.89 (dd, J = 12.6, 9 Hz, 1H), 1.76–1.6 (m, 3H), 1.34–1.23 (m, 2H), 1.07 (s, 3H), 0.9