A stereoselective total synthesis of the novel triquinane sesquiterpene cucumín E

Goverdhan Mehta* and Jayant D. Umuye

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

Abstract—A total synthesis of cucumín 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.

During the past few decades, the linearly-fused triquinane sesquiterpeneoids 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. 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.).

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.

Pentacyclic dione 8, readily available from 1,2,3,4-tetra-chloro-5,5-dimethoxycyclopentadiene and benzoquinone in two steps, 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 quite satisfactorily,

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* Corresponding author. E-mail: gm@orgchem.iisc.ernet.in
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. 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. 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 on 15 delivered 16. The next task en-route to the cucumin skeleton was the introduction of the angular methyl group to generate the complete C15-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) considerations and 18 was obtained as the major product, Scheme 2. The enone moiety in ring-A of 18 was established through allylic oxidation following the Sharpless catalytic selenium dioxide oxidation to give 19 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.

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.

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Scheme 1. Reagents and conditions: (a) i. Li, liq. NH₃, THF, H₂O, 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. H₂, 10% Pd/C, 1 atm, EtOAc, rt, 1 h, quant.; ii. PPh₃, CH₂Br₂, 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.), CS₂, imidazole (cat.), MeI, THF, 5 h, Δ, 80%. ii. TBTH–AIBN, toluene, Δ, 10 min, 70–80%.
References


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.

6. 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).