Synthesis of the naturally occurring [3.3.3]propellane (±)-modhephene featuring a photocycloaddition–reductive fragmentation diquinane construction

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Modhephene has been synthesized in 11 steps and 21% overall yield from cyclopentadiene, by a stereoselective route that features a photocycloaddition–fragmentation sequence for the construction of the diquinane core.

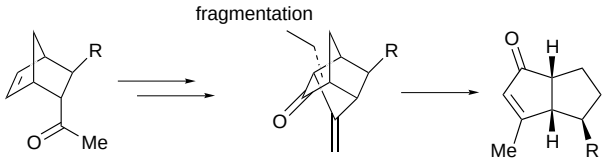
The fascinating realm of the polyquinane sesquiterpenes, recently reviewed,[1] has stimulated the development of new methodologies for the construction of fused five-membered rings. Previously we reported a route to di- and tri-quinanes that takes advantage of the connectivity gained when acylnorbornyl derivatives, obtained *via* the Diels–Alder reaction, are subjected to the Paterno–Büchi reaction (Scheme 1).[2] This expeditious assembly of a [3.3.0]bicyclic array is well suited for the synthesis of many members of the polyquinane class of natural products. We have completed concise, high-yielding syntheses of natural products having linear[2d] and angular triquinane[2b,e] frameworks using the photocycloaddition–fragmentation sequence. We report here a concise synthesis of naturally occurring propellane, modhephene **1**,[3] further extending the utility of our general strategy.

The propellane skeleton, the three contiguous quaternary centers, and the angular methyl group combine to make modhephene an attractive synthetic challenge, one taken on by several research groups.[4] We have examined two routes to modhephene, outlined retrosynthetically in Scheme 2. Appealing at first was a route that took advantage of enone **3**, a late-stage intermediate in our isocomene synthesis, wherein the methyl group stereochemistry was controlled through a Diels–Alder reaction.[2b,e] While it was possible to form the third ring by an alkylative cyclization of the terminal iodide derived from **3**,[5] the resulting enone **2** could not be converted to modhephene.[2h,l] An alternate route to the propellane framework of modhephene hinged on formation of the ring containing the angular methyl group, potentially by a radical cyclization.[6] The requisite diquinane precursor **6** was expected to be readily available through the photocycloaddition–reductive fragmentation sequence.

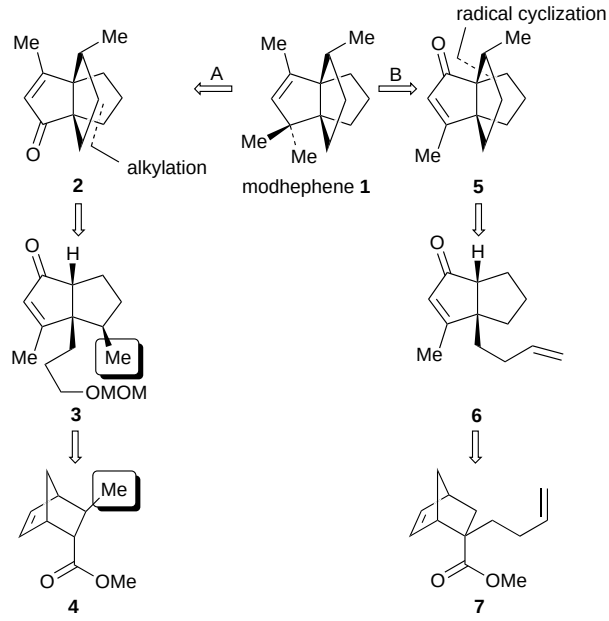
Diquinane **6** was prepared in high overall yield as described in Scheme 3. Norbornene **8**, obtained from cyclopentadiene and methyl acrylate (H_2O, room temp., 100%), was alkylated selectively on the *exo* face with 4-bromobut-1-ene using LDA in THF with 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (DMPU). The resulting ester **7** was converted into methyl ketone **9** by a one-pot modification of Corey's procedure,[7] affording the Paterno–Büchi precursor in 94% yield for the two steps. Irradiation of ketone **9** with Corex-filtered light provided oxetane **10** (89%), which possesses the connectivity required for a diquinane. Initially a three step sequence was used to convert oxetane **10** to a diquinane. Treatment of **10** with Pr^i_2NMgI gave alcohol **11**, which on oxidation with pyridinium dichromate (PDC) gave keto alkene **12** in good overall yield. Reductive fragmentation of **12** afforded the expected diquinane, **6**, in 80% yield.

The hidden diquinane unit was also liberated by a novel, direct fragmentation of the strained oxetane precursor, which shortened the sequence by one step (Scheme 4). Treatment of oxetane **10** with LDBB (2.0 equiv.), the radical anion of 4,4′-di-*tert*-butylbiphenyl, in the presence of Et_3Al (2.1 equiv.)[8] promoted the simultaneous scission of the oxetane C–O bond and the back-bond of the norbornane skeleton, affording diquinane moiety **13** in 86% yield.[9] The resulting allylic alcohol was then oxidized to enone **6** under standard conditions.

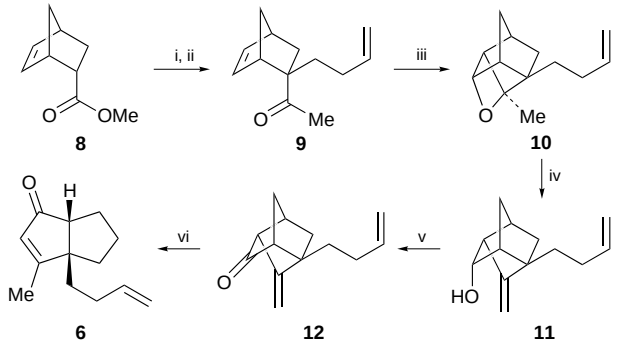
In preparation for closure of the final propellane ring, a suitable radical precursor was introduced α to the carbonyl group of **6** (Scheme 5). Selenation of the kinetic enolate of **6** afforded the desired phenyl selenide in 61% yield, provided inverse quenching conditions were employed. The bridgehead radical derived from **14** was expected to undergo 5-*exo*-*trig* cyclization onto the butenyl side-chain, concurrently setting the angular methyl group stereochemistry.[4m] Subjection of selenide **14** to standard radical conditions gave an excellent yield of the propellane (95%), albeit with a disappointing 2 : 1 ratio of inseparable diastereomers. This ratio was increased to a useful 6 : 1 level (69%) by carrying out the cyclization in toluene at −78 °C using Et_3B–air to initiate the radical chain.[10]



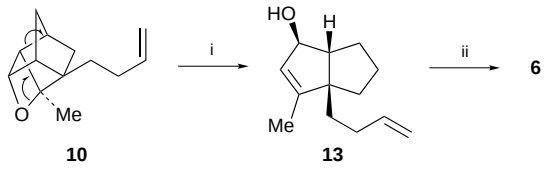
Scheme 1



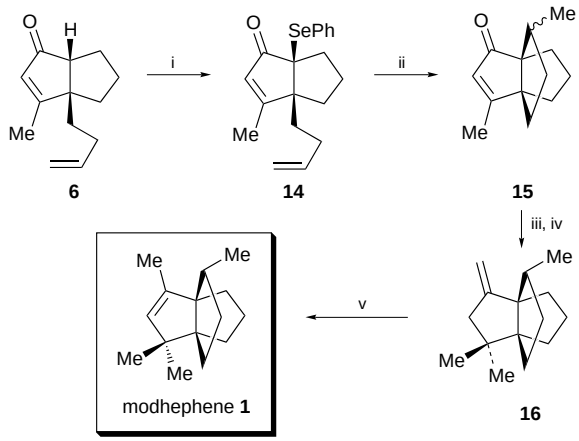
Scheme 2



Scheme 3 *Reagents and conditions*: i, LDA, THF, DMPU, 4-bromobut-1-ene; ii, $MeS(O)CH_2Li$, THF; Zn, aq. NaOH, $PhCH_3$ (94% overall); iii, *hν*, PhH, corex filters (89%); iv, Pr^i_2NMgI (2.6 equiv.) in THF (1.0 M), room temp., 1.5 days (87%); v, PDC (2.9 equiv.), DMF, room temp., 1 day (91%); vi, LDBB (3 equiv.) in THF (0.1 M), −78 °C (80%)



Scheme 4 *Reagents and conditions:* i, LDBB, THF, Et_3Al, −78 °C, 4 h, warm to room temp., 12 h (86%); ii PDC, DMF, room temp., 16 h (91%)



Scheme 5 *Reagents and conditions*: i, LDA, THF, −78 °C to room temp.; PhSeCl, −78 °C, inverse quench (61%); ii, Bu_3SnH, AIBN, PhH, reflux (2:1, 95%) (6:1 at −78 °C); iii, $Me_2CuLiCN$, THF, $Et_2O{\cdot}BF_3$; iv, $Ph_3P{=}CH_2$, THF (85% overall), MPLC separation; v, TsOH (cat.), CH_2Cl_2, 3 h (~100%)

The final two carbons were appended as previously described. Introduction of the geminal dimethyl unit to the hindered enone **15** requires a Lewis acid to assist the 1,4-addition of the higher order cuprate.[4b,l] Wittig olefination of the keto group with triphenylphosphonium methylide[4d] put in place the final carbon. The major diastereomer from the radical cyclization was separated at this stage by MPLC and then treated with a catalytic amount of TsOH, which isomerized the double bond to the endocyclic position, affording modhephene **1**. The minor diastereomer was similarly converted to epimodhephene.

The modhephene synthesis described here was accomplished in 11 steps from cyclopentadiene, with an overall yield of 21%, the highest to date. The synthesis illustrates the direct fragmentation of the cage-like oxetane **10** to diquinane **13** as well as the stereocontrolled formation of the propellane skeleton.

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Footnote and References

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