Tandem radical cyclization reaction of *N*-aziridinyl imines to [3.3.3]propellanes: formal total syntheses of *dl*-modhephene

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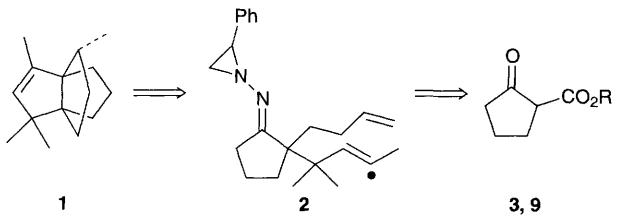
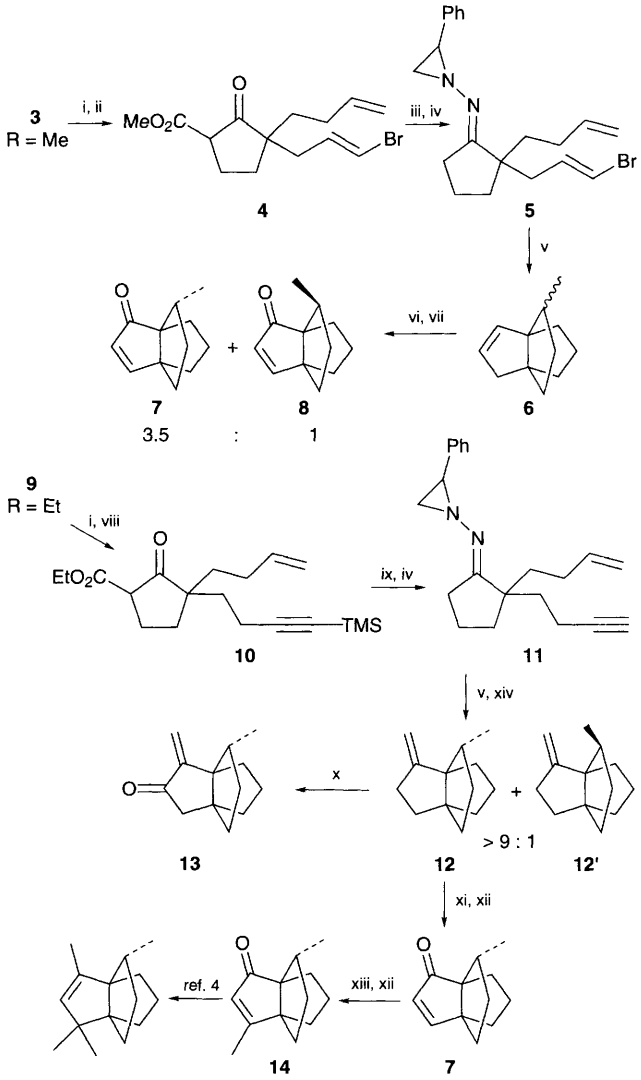
Tandem radical cyclization reaction of 5 and 11 produces [3.3.3]propellanes and leads to the total synthesis of *dl*-modhephene.

Modhephene, which belongs to the only naturally occurring propellane class of compounds,[1] has attracted considerable interest from synthetic organic chemists over the last 15 years.[2–6] Synthetic approaches based on radical cyclization methods[3] have synthesised propellanes by constructing two five membered rings on a pre-existing ring in two separate radical cyclization reaction steps. Ideally, the construction of two cyclopentane rings onto the pre-existing cyclopentane ring through radical mediated cyclization could be accomplished simultaneously or successively in a single operation. If a suitable synthon which can serve as a *gem*-diradical species is used, preparation of propellanes from a cyclopentane ring in a single operation could be realized. The tandem generation of radicals from *gem*-dibromo compounds has been reported[7] and several examples of carbon centres reacting as radical donors and acceptors simultaneously have also been reported.[8] Carbon monoxide,[8b] isonitriles,[9] acylsilanes[10] and *N*-aziridinyl imines[11] have been used as radical donors–acceptors in organic synthesis. Conceptually, *N*-aziridinyl imines are the carbene equivalents which react as diradicals, and can be used for the tandem radical reactions on the same carbon atom to produce tertiary or quaternary carbon centres. Thus the *N*-aziridinyl imines can serve as the ideal synthon for the synthesis of propellanes from cyclopentanes in one step.

Here we report the first successful synthesis of propellane rings *via* tandem radical cyclization reactions, and the application of this strategy to the synthesis of modhephene. The key intermediate contains a vinyl radical precursor, an *N*-aziridinyl imine and an alkene for the construction of two cyclopentane rings. The vinyl radical addition to the *N*-aziridinyl imine will generate the second radical at the same carbon centre and cyclization will produce a propellane ring system.[6,12] Here we report the preparation of two propellane compounds both of which were converted to the known intermediates of the total synthesis of modhephene. The first propellane compound was prepared from **3** in five steps. The ketoester **3** was alkylated successively with 4-bromobutene and 1,3-dibromopropene to produce **4**. After the decarboxylation, *N*-aziridinyl imine **5** was prepared. The pivotal radical cyclization reaction underwent smoothly to produce a mixture of isomeric propellane compounds which was purified after the epoxidation of **6**. For the synthesis of modhephene, the mixture of epoxides was rearranged into the corresponding allylic alcohols[13] and then the allylic alcohols were oxidized to a separable mixture of unsaturated ketones **7** and **8**. The major product **7** possessed the correct stereochemistry of the methyl group of modhephene. The confirmation of the stereochemistry of the methyl group of **7** came from the comparison of spectral data of **7** with that of the



Scheme 1



Scheme 2 *Reagents and conditions*: i, (*a*) LDA (2.4 equiv.), HMPA (3 equiv.)–THF, −78 → 0 °C; (*b*) 4-bromobutene, 87%; ii, (*a*) LDA (2.4 equiv.), HMPA (3 equiv.)–THF; (*b*) 1,3-dibromopropene, 45%: iii, LiCl–H_2O–Me_2SO, 120 °C, 86%; iv, *N*-amino-2-phenylaziridine, AcOH(cat.)–MeOH, 0 °C, 7 d, 75%: v, Bu_3SnH, AIBN, syringe pump (8 h)–C_6H_6: vi, (*a*) MCPBA–CH_2Cl_2, 73% from **5**; (*b*) Et_2NLi–HMPA, 45 °C, 74%: vii, (*a*) MnO_2–Et_2O, 84%; viii, (*a*) LDA (2.4 equiv.); HMPA (3 equiv); (*b*) 4-iodo-1-trimethylsilylbutyne, 48%: ix, KOH–MeOH, 60 °C, 75%: x, (*a*) SeO_2–*tert*-butylhydroperoxide; (*b*) $(COCl)_2$–Me_2SO; Et_3N, 61%: xi, O_3; Ph_3P, 55%: xii, (*a*) LDA; PhSeBr; (*b*) H_2O_2–pyridine, 43%: xiii, CuBr.Me_2S, MeMgBr, HMPA, 56% to **14**, xiv, SiO_2, 74% from **11**

same compound prepared in the second synthesis. Since **7** was reported to be converted into modhephene,[4] a formal total synthesis of modhephene was completed.

The isomeric ratio of **6** reflects the stereoselectivity during the radical cyclization reaction. The selectivity was very close to the ratio reported by Sha[6] in his radical cyclization reaction. Presumably, the allylic side of the radical centre places more steric demand than methylene side of the radical centre to result in the observed stereoselectivity. This led us to envision that increased steric demand on the allylic side would impose the better selectivity during the radical cyclization. In the second modhephene synthesis, the vinyl radical was generated from the tributyltin radical addition to the triple bond.[14] The allyl radical generated from the first radical cyclization reaction might provide a large steric bias during the second radical cyclization and could produce the better stereoselectivity than the previous synthesis. The synthesis started from the same starting material as in the synthesis of **7**. The butenyl chain was attached first and the butynyl chain was introduced second. When the alkyne was introduced first, the second alkylation produced complex mixture without any desired product.[15] After the decarboxylation, *N*-aziridinyl imine **11** was prepared. Tributylin hydride mediated radical cyclization reaction underwent smoothly to produce, after the destanylation with wet silica, a mixture of the propellanes **12** and **12′** with the ratio better than 9:1 (determined by NMR integration of alkenic protons). This result supports our steric argument for the stereoselectivity, since the additional carbon and tributyltin group provided more steric bias for the cyclization of **11** than **5**. Compound **12** lacked only two methyl groups of modhephene. However, attempts to introduce two methyl groups of modhephene onto **12** were not successful. Selenium dioxide oxidation of the alkene of **12** proceeded smoothly to give **13**. All the efforts to methylate the enolate of **13** produced only the *O*-methylated product. Thus compound **12** was converted into **14** through the known sequence[4] after the ozonolysis of the alkene of **12**. The structure of **14** was confirmed by the comparison of the spectroscopic data of **14** with the literature values.[2d,3a] Since **14** has already been converted into modhephene by several groups, this completed another formal total synthesis of modhephene.

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