Photochemical Oxa-di-π-methane Rearrangement Approach to [3.3.3]Propellanes. Total Synthesis of Sesquiterpene Hydrocarbon (±)-Modhephene

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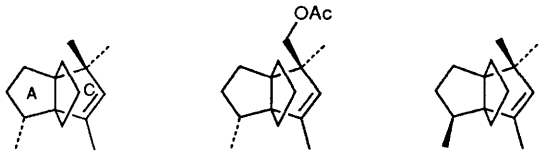
A photochemical approach to the construction of the [3.3.3]propellane and tricyclo[5.3.1.$0^{4,11}$]undecane ring systems through a common strategy employing oxa-di-π-methane rearrangement as the key step is delineated. Starting from the readily available bicyclo[4.3.0]nona-1(6),2-diene **6**, the tricyclo[5.2.2.$0^{1,5}$]undecenones **5** and **12** were prepared through a Diels–Alder strategy employing α-chloroacrylonitrile as the ketene equivalent. Sensitised irradiation of enone **5** furnished the tetracyclo[4.3.2.$0^{2,6}$.$0^{2,9}$]undecanone **4**, which on regioselective, reductive C–C bond cleavage provided access to [3.3.3]propellanone **14**. The tricyclic ketone **12** through a similar protocol furnished the tricyclo[5.3.1.$0^{4,11}$]undecanone **16**. The tetracyclic ketone **4** has been further elaborated in a straightforward manner to afford the sesquiterpene hydrocarbon (±)-modhephene.

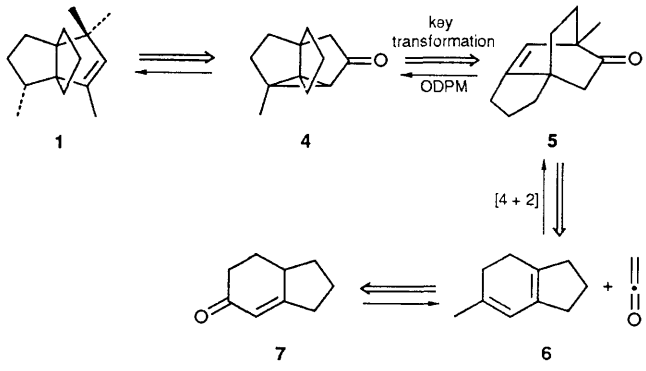
In 1978, Zalkow *et al.*[1] reported the isolation of a novel sesquiterpene hydrocarbon, modhephene **1**, bearing a [3.3.3]-propellane skeleton, from the hexane extracts of the rayless goldenrod plant (*Isocoma wrightii*), known for its toxicity to cattle and sheep. The structure **1** was established through a single-crystal X-ray analysis performed on the *cis*-diol derived from modhephene.[1] Subsequently Bohlmann's group in 1979 isolated acetoxymodhephene **2**, an oxygenated derivative of compound **1** from *Liabum eggersii*.[2] To date, compounds **1** and **2** remain unique among terpenes, being the only known examples of the occurrence of the [3.3.3]propellane framework in Nature.



1 **2** **3**

Understandably, modhephene **1** has attracted the attention of many contemporary synthetic chemists. Besides the construction of the [3.3.3]propellane framework, the synthetic challenge of modhephene **1** resides in the creation of a network of methyl groups on the carbocyclic framework. This requires methyl 'loading' on ring 'C' and stereoselective installation of a 'naked' tertiary methyl group on ring 'A'. Since 1980, close to a dozen successful syntheses of modhephene **1** have emanated from the research laboratories of Dreiding,[3a] Smith,[3b] Paquette,[3c] Oppolzer,[3d] Wender,[3e] Cook,[3f] Tobe,[3g] Mundy,[3h] Mash,[3i] Fitzer,[3j] Suri [3k] and us.[3l] Herein, we describe the details of our synthesis of modhephene **1** and its methyl epimer **3**, in which a photochemical oxa-di-π-methane (ODPM) rearrangement was a pivotal step.[4]

In our quest for new synthetic routes to modhephene **1**, we devised a novel transformation based on the retrosynthetic strategy[5] shown in Scheme 1. In this approach, the tetracyclic ketone **4** with a [3.3.3]propellane framework was considered equivalent to the tricyclic framework **5** through a key ODPM transformation.[6] Indeed, such equivalence between two diverse looking carbocyclic skeleta has much wider ramifications.[7] Thus, the construction of the tricyclic skeletal core of modhephene **1** is reduced to the comparatively simpler problem of assembling the appropriately substituted tricyclo[5.2.2.$0^{1,5}$]-



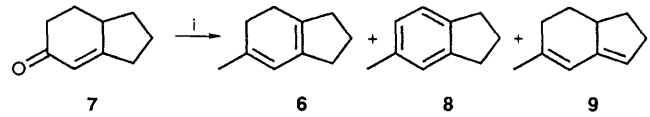
1 **4** **5** **7** **6**

Scheme 1

undecane framework **5**. The tricyclic ring system **5** in turn could be generated through a Diels–Alder cycloaddition-based strategy employing bicyclic diene **6** and a dienophile, which is a ketene equivalent, as depicted in the retrosynthetic analysis in Scheme 1. The diene **6** appeared to be readily accessible from the bicyclic enone **7**, available from cyclopentanone in two steps *via* Stork's enamine annulation methodology.[8]

Addition of methylmagnesium iodide to enone **7** and usual work-up furnished directly an unstable mixture (86%) of hydrocarbons **6**, **8** and **9** in which the required homoannular diene **6** predominated, Scheme 2. UV, GLC and ^{1}H NMR analyses of the hydrocarbon mixture indicated that the diene **6** was present in *ca.* 60% yield. Since compounds **8** and **9** were expected to be inactive towards dienophiles, a separation at this stage was not attempted and the mixture was used as such for the Diels–Alder cycloaddition. α-Chloroacrylonitrile and nitroethylene, known to be efficient ketene equivalents,[9] were chosen as suitable addends for diene **6**.

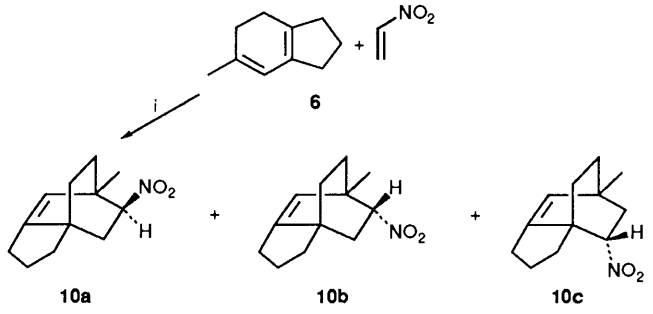
Diels–Alder reaction between the diene **6** and freshly prepared nitroethylene[10] gave a mixture of three (4 + 2)-adducts **10a**, **10b** and **10c** in the proportions 5:1:1 (30% yield), consisting of regio- and stereo-isomers, Scheme 3. All three isomers could be separated and characterised (IR, ^{1}H NMR,



7 **6** **8** **9**

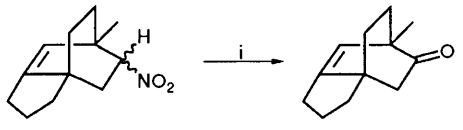
Scheme 2 *Reagent:* i, MeMgI, Et_2O

and ^{13}C NMR spectra). The stereochemical assignments for compounds **10a–c** are tentative and are mostly extracted from their spectral data. However, for our further transformation, this point was not regarded as critical and we attempted the Nef reaction on a mixture of **10a** and **10b** to generate the carbonyl group, and secure the pre-target molecule **5**. The classical Nef conditions[11] (EtOH–NaOH and HCl) completely failed to bring about the desired $-CH-NO_2 \longrightarrow -C=O$ transformation. Recourse was taken, therefore, of the recently described alternative procedures of McMurry[12] and Mazur[13] which use aq. $TiCl_3$ and basic SiO_2, respectively, Scheme 4. Both these procedures did furnish the required ketone **5** but in poor and unacceptable yields (~10–15%). It was, therefore, decided to change over to a different ketene-equivalent.



Scheme 3 *Conditions:* i, Et_2O, −10 °C

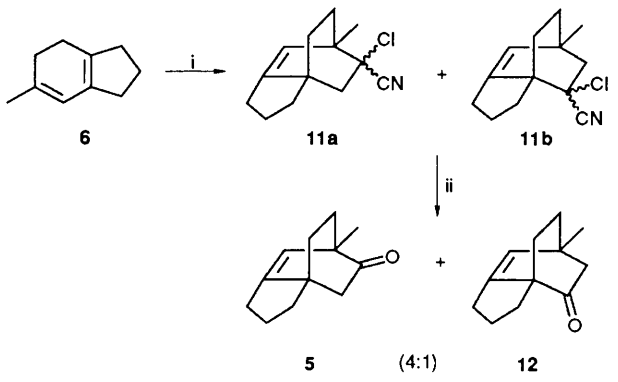
Diels–Alder reaction between the diene **6** and α-chloroacrylonitrile proceeded smoothly and a mixture of adducts **11a** and **11b** was obtained in 40% yield. These adducts were not separated and their gross structures were characterised on the basis of spectral data (IR, ^1H NMR). Formation of the carbonyl functionality in adducts **11a** and **11b** proved to be smooth. Application of Evans' methodology[14] to adducts **11a** and **11b** provided a mixture of β,γ-unsaturated ketones **5** and **12** (58%



Scheme 4 *Reagents and conditions:* i, NaOMe, MeOH, aq. $TiCl_3$, NH_4OAc or NaOMe–SiO_2; 150 °C; 10 h; 10% yield

yield) in the ratio 4:1, respectively, Scheme 5. The substantial regioselectivity observed in the cycloaddition reaction between the α-chloroacrylonitrile and the diene **6** is in conformity with predictions based on substituent effects and also on HOMO (diene)–LUMO (dienophile) interactions.[15]

At this stage, it was essential to identify completely the regioisomeric structures of tricyclic ketones **5** and **12**. This was accomplished through incisive analyses of their ^1H NMR and ^{13}C NMR spectral data. Grossly, the ^1H and ^{13}C spectra of ketones **5** and **12** appear quite similar; however, there are subtle chemical-shift differences emanating from the methyl and the carbonyl group effects, and which enable definitive structural assignments to be made. The two main effects that are operative in the ^{13}C NMR spectra of the bicyclo[2.2.2]octenones are the deshielding of the α-olefinic carbon and the shielding of the β-olefinic carbon due to bridgehead methyl substitution,[16a] and the shielding of the β-olefinic carbon and the deshielding of the γ-olefinic carbon due to the carbonyl group.[16b] In Fig. 1, ^{13}C NMR assignments for **5** and **12** have been shown along with those of appropriate model compounds from the literature. The alternative assignment of the structures **5** and **12** to the spectral data will not be consistent with the observed chemical shifts.



Scheme 5 *Reagents and conditions:* i, α-chloroacrylonitrile, toluene; 80 °C; 16 h; 43% yield; ii, $Na_2S \cdot 10H_2O$, EtOH; 60 °C; 6 h; 58% yield

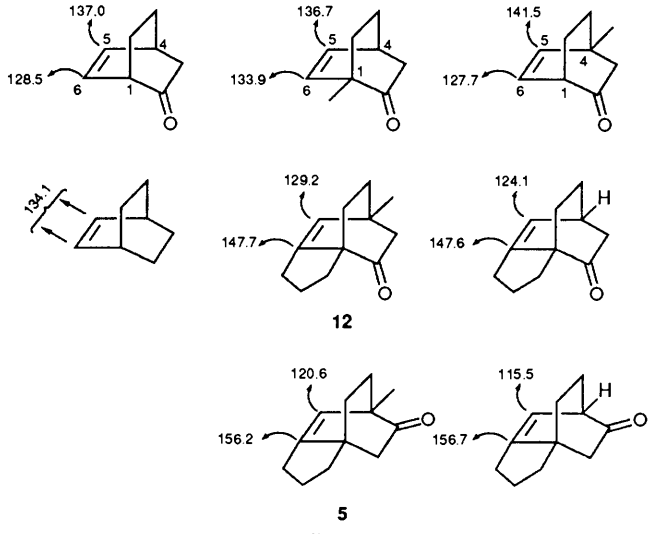
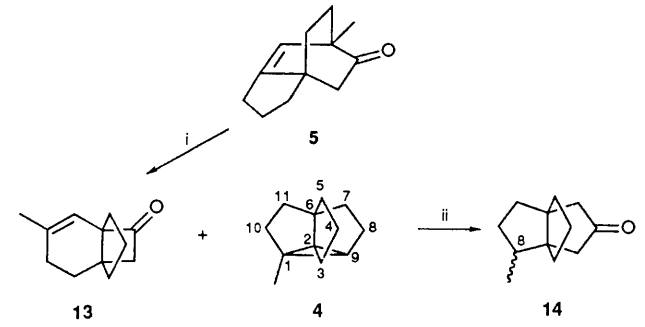


Fig. 1

Having synthesized the pre-target molecule **5**, Scheme 1, in two steps, we turned our attention to the crucial ODPM rearrangement. Irradiation of compound **5** in acetone with a Hanovia medium-pressure mercury vapour lamp in a quartz vessel furnished a mixture of two ketones **4** and **13** (15:1) in 50% yield, Scheme 6. The structure of the major tetracyclic product **4** was indicated by the presence of three quaternary carbon resonances, at δ_C 62.3 (s), 57.5 (s), 42.9 (s), and the absence of olefinic carbons in its ^{13}C NMR spectrum. The ^1H NMR spectrum of product **4** showed a quaternary methyl group at δ 1.20 (3 H, s) and was completely transparent in the olefinic region. The minor product **13** exhibited a carbonyl absorption at 1780 cm^{-1} in its IR spectrum (cyclobutanone moiety). The presence of an olefinic proton at δ 5.40 (s) and a vinylic methyl group at δ 1.65 (3 H, s) were in agreement with the assigned structure. The tetracyclic ketone **4** and the tricyclic ketone **13** arise from the β,γ-unsaturated ketone **5** through 1,2- and 1,3-acyl shifts, respectively. The formation of compound **13** through 1,3-acyl migration can be attributed to the competitive unsensitised photochemistry of the β,γ-unsaturated ketone **5**.

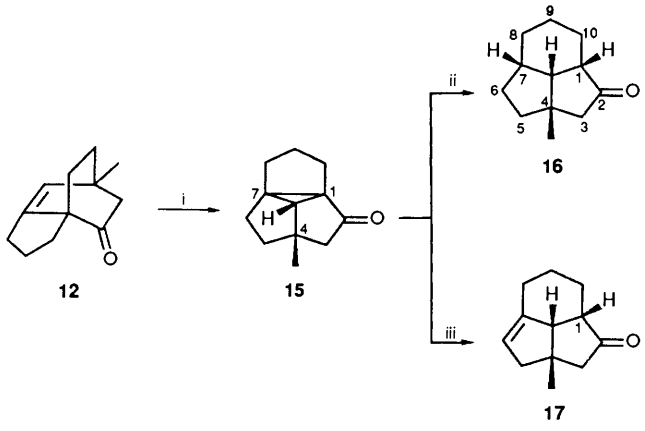
Regioselective, reductive cleavage of the C(1)–C(9) bond in ketone **4** was achieved through Li–liq. NH_3 reduction which furnished an epimeric mixture of alcohols. Oxidation with pyridinium chlorochromate (PCC) provided the requisite [3.3.3]-propellanone **14** as a mixture (1:1) of C(8) epimers. The structure of compound **14** was readily identified by the shift in the carbonyl frequency to 1740 cm^{-1} (*cf.* 1720 cm^{-1} for ketone **4**) and the presence of methyl signals at δ 0.98 (3 H, d, *J* 7 Hz) and 0.95 (3 H, d, *J* 7 Hz) in its ^1H NMR spectrum.

Having accomplished the proposed synthesis of the [3.3.3]-propellane framework, we also investigated the photochemistry



Scheme 6 *Reagents and conditions:* i, *hv*, acetone; 45 min; 50% yield; ii, Li–liq. NH_3, THF, NH_4Cl; PCC–CH_2Cl_2, 4 Å molecular sieves; 60% yield

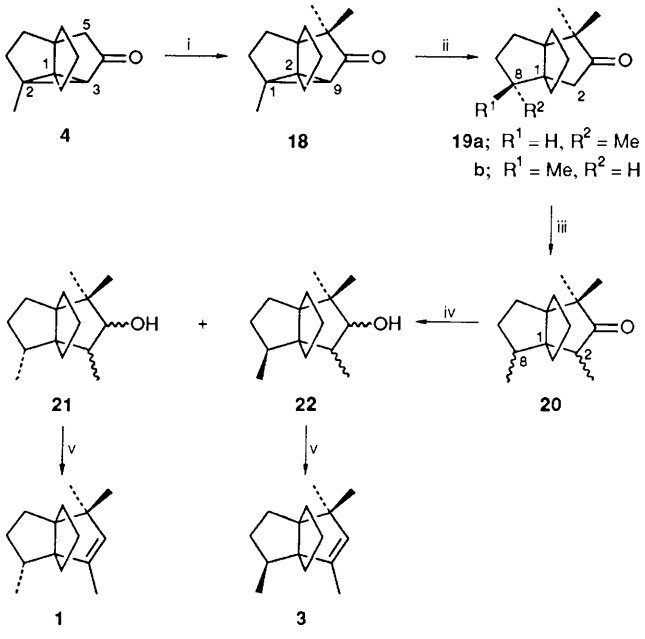
of the minor tricyclic isomer **12**. This was expected to result in a different but important tricyclic ring system. Irradiation of compound **12** in acetone with a 450 W Hanovia mercury lamp in a quartz vessel led to the formation of the strained cyclopropyl ketone **15** as the only isolable product in 65% yield, Scheme 7. The spectral characteristics of compound **15** as revealed through its ^1H and ^{13}C NMR spectra were fully in accord with its structure. Regioselective cleavage of the C(1)–C(7) bond in compound **15** was achieved employing reductive as well as acid-catalysed bond cleavage. Reductive cleavage using Li–liq. NH_3 followed by oxidation of the resulting alcohols with PCC afforded the tricyclic framework **16**. A carbonyl frequency at 1735 cm^{-1} in the IR spectrum and a quaternary methyl group as a singlet at δ 1.22 in the ^1H NMR



Scheme 7 *Reagents and conditions:* i, *hv*, acetone; 30 min; 65% yield; ii, Li–liq. NH_3, THF; PCC, CH_2Cl_2, 4 Å molecular sieves; 60% yield; iii, BF_3–diethyl ether, CH_2Cl_2; 12 h; 56% yield

spectrum established the structure of compound **16**. Exposure of compound **15** to BF_3–diethyl ether in dichloromethane transformed this cyclopropyl ketone to an olefinic ketone **17**. A carbonyl absorption at 1740 cm^{-1} in the IR spectrum, an olefinic proton at δ 5.20 (1 H, s) and a quaternary methyl group at δ 1.30 (3 H, s) in the ^1H NMR spectrum, and resonances at δ_C 219.51, 144.0 and 120.76 due to the three sp^2 carbons in the ^{13}C NMR spectrum were fully in agreement with the assigned structure. Thus, a synthesis of the tricyclic ring systems **16** and **17** present in the novel sesquiterpenes, *e.g.*, 8 α-hydroxypresilphiperfolene,[17] was achieved by employing ODPM rearrangement as the key step.

Returning to our main synthetic objective **1**, we decided to operate on the tetracyclic compound **4** which offered two distinct advantages. First, the crucial C(8) methyl group present in the natural product **1** is correctly positioned in compound **4**. Secondly, the installation of a *gem*-dimethyl group at C(4) and a methyl group at C(2) can be achieved regioselectively through the C(3)-carbonyl functionality. Consequently, the C_{12}-tetracyclic ketone **4** was dialkylated with MeI in the presence of potassium t-butoxide to yield the requisite *gem*-dimethylated product **18** in 65% yield. The presence of three methyl singlets at δ 1.20, 1.00 and 0.84 in its ^1H NMR spectrum, and a 14-line ^{13}C NMR spectrum, fully supported the structure of compound **18**. At this stage, an attempt was also made to install directly the fourth methyl group at the C(9) carbon of compound **18** by employment of bases like Bu^{t}Li, but this proved to be unsuccessful. We therefore proceeded to cleave the C(1)–C(9) bond in a regioselective manner to obtain the [3.3.3]propellanone derivative. Li–liq. NH_3 reduction of compound **18** furnished a mixture of alcohols, which upon oxidation with PCC produced [3.3.3]propellanones **19a** and **19b** as an epimeric mixture (~1:1) at C(2) in 75% yield, Scheme 8. The gross structure of the C_{14}-ketones **19a** and **19b** was indicated by the presence of a cyclopentanone absorption at 1740 cm^{-1} and the



Scheme 8 *Reagents and conditions:* i, Bu^{t}O$^-$K$^+$–MeI, THF; 65% yield; ii, Li–liq. NH_3, THF, NH_4Cl; PCC–4 Å molecular sieves, CH_2Cl_2; 75% yield; iii, $(Me_3Si)_2NH$–Bu^{n}Li–MeI, THF; 0 °C; 60% yield; iv, LAH–Et_2O; 68% yield; v, $POCl_3$–pyridine–CH_2Cl_2, DBU, 38% yield

resonances at δ 2.6–2.0 (4 H, two sets of AB q) corresponding to –C–CH_2–C(O)–(α-methylene ketone) in the ^1H NMR spectrum. All efforts to separate the methyl epimers, at this stage, proved unsuccessful.

We therefore decided to proceed further with the epimeric mixture **19a** and **19b** with the intent of separation at the final stage. To complete the C_{15}-skeleton of modhephene **1**, a methyl group at C(2) in compounds **19a,b** had to be introduced. Kinetically controlled methylation of this mixture with lithium hexamethyldisilazide (LHMDS) as the base proceeded smoothly to give tetramethylpropellanone **20** as a mixture of C(2) and C(8) epimers in 60% yield. The epimeric mixture **20** was once again not amenable to separation by means available to us and we decided to carry on working with the mixture. However, we had a fortuitous break. Reduction of the ketone mixture **20** with $LiAlH_4$ (LAH) in diethyl ether solvent provided an epimeric mixture of alcohols **21** and **22** which were reasonably well resolved on TLC and which could be separated. The two alcohols **21** and **22** were now individually subjected to dehydration with $POCl_3$ in pyridine containing traces of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The alcohol **21** furnished the natural product (±)-modhephene **1**, identified

through comparison of its IR and ^{1}H NMR spectra with the authentic spectra provided by Professor Paquette. Dehydration of alcohol **22** afforded the isomeric hydrocarbon (±)-epimodhephene **3** and once again its identity was established through spectral comparison. The goal of the total synthesis of the sesquiterpene hydrocarbon modhephene **1** was thus successfully achieved.

Experimental

UV (MeOH), IR and ^{1}H (100 MHz) and ^{13}C NMR (25.0 MHz) spectra were recorded on Schimadzu 200S and Perkin-Elmer 297 spectrophotometers, and JEOL MH-100 and JEOL FX-100 spectrometers, respectively. ^{1}H and ^{13}C NMR chemical shifts are given from $SiMe_4$ as the internal standard, with $CDCl_3$ as the solvent. In the ^{13}C NMR spectra, off-resonance multiplicities, when recorded, are given in parentheses.

Liquid samples were bulb-to-bulb distilled and b.p.s refer to bath temperatures. Analytical TLC was performed on (10 × 5 cm) glass plates coated (250 nm) with Acme silica gel G (containing 13% calcium sulphate as binder). Visualisation of the spots was achieved by exposure to iodine vapour. Acme silica gel (100–200 mesh) was used for column chromatography. Moisture-sensitive reactions were carried out using standard syringe-septum techniques. Dry diethyl ether and tetrahydrofuran (THF) were prepared by distillation over sodium and were stored over pressed sodium wire. Dichloromethane was distilled over P_2O_5. Light petroleum refers to the fraction boiling over the range 60–80 °C. All solvent extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated on a Buchi-EL rotary evaporator.

3-*Methylbicyclo*[4.3.0]*nona*-1(6),2-*diene* **6**.—In a flame-dried, 100 cm^3, three-necked RB flask equipped with a reflux condenser, pressure-equalising addition funnel and a N_2-inlet was placed a mixture of magnesium turnings (1 g, 43 mmol, 1.2 mol equiv.) in dry diethyl ether (20 cm^3). The flask was cooled to ice temperature and a solution of iodomethane (6 cm^3; 2.5 mol equiv.) in dry diethyl ether (10 cm^3) was added dropwise over a period of 10 min. After the complete disappearance of the magnesium, a solution of bicyclic enone **7**[8] (5 g, 36 mmol) in dry diethyl ether (20 cm^3) was added dropwise over a period of 10 min with continuous stirring of the mixture. After 1.5 h the reaction mixture was carefully quenched with saturated NH_4Cl. The aq. layer was extracted with diethyl ether (2 × 40 cm^3) and the combined organic phase was washed successively with water and brine, and dried. Removal of the solvent gave a mixture of hydrocarbons **6**, **8** and **9** (4.73 g, 86%), b.p. 100 °C/0.2 Torr;* λ_{max}/nm 242 and 282; ν_{max}(neat)/cm^{-1} 3050, 1450 and 880; δ_H 7.2 (3 H, m), 6.0 (1 H, m, CH=C), 5.6 (1 H, m, HC=C), 5.3 (1 H, m, CH=C), 2.4–1.2 (19 H, m) and 1.75 (6 H, s, 2 × CH=C*Me*). The GLC and ^{1}H NMR analysis indicated that compounds **6**, **8** and **9** were present in 3:1:1 proportions, respectively, in the hydrocarbon mixture. This mixture was not separated further but was used as such in the next step.

7-*Methyl*-8-*nitrotricyclo*[5.2.2.0^{1,5}]*undec*-5-*ene* **10a,b** *and* 7-*Methyl*-9-*nitrotricyclo*[5.2.2.0^{1,5}]*undec*-5-*ene* **10c**.—To a solution of the mixture of hydrocarbons **6**, **8** and **9** (1.2 g, 8 mmol) in dry diethyl ether (10 cm^3), cooled to −10 °C, was slowly added a solution of freshly prepared nitroethylene[10] (0.9 g, 1.5 mol equiv.) in dry diethyl ether (10 cm^3) over a period of 30 min under N_2. The reactants were stirred for 14 h at room temperature. Removal of solvent gave an oily material, which was charged on a silica gel (15 g) column. Elution of the column with light petroleum removed the non-polar impurities. Further elution of the column with 10% benzene–light petroleum furnished three adducts, **10a** (75 mg), **10b** (350 mg) and **10c** (75 mg).

Spectral data of adduct **10a**: ν_{max}(neat)/cm^{-1} 3020, 1550, 1460 and 1380; δ_H 5.8 (1 H, s, CH=C), 4.8 (1 H, t, *J* 8 Hz, $CHNO_2$), 2.4–1.25 (12 H, m) and 1.20 (3 H, s, CMe).

Spectral data of adduct **10b**; ν_{max}(neat)/cm^{-1} 3020, 1550, 1440 and 1360; δ_H 5.4 (1 H, s, CH=C), 4.60 (1 H, dd, *J* 4 Hz, $CHNO_2$), 2.5–1.20 (12 H, m) and 1.20 (3 H, s, CMe); δ_C 152.8 (s), 120.17 (d), 91.17 (d), 43.79 (s), 40.15 (s), 39.45 (t), 35.69 (t), 34.18 (t), 30.94 (t), 30.29 (t), 25.95 (t) and 21.77 (q).

Spectral data of adduct **10c**: ν_{max}(neat)/cm^{-1} 3020, 1550, 1460 and 1360; δ_H 5.5 (1 H, t, *J* 2 Hz CH=C), 4.30 (1 H, dd, *J* 4 Hz, $CHNO_2$), 2.4–1.1 (12 H, m) and 1.1 (3 H, s, CMe); δ_C 155.23, 123.29, 92.1, 44.1, 40.3, 37.69, 35.98, 31.7, 30.29, 29.17, 26.19 and 22.07.

7-*Methyltricyclo*[5.2.2.0^{1,5}]*undec*-5-*en*-8-*one* **5**.—To a solution of freshly prepared sodium methoxide (100 mg, 3 mol equiv.) in dry methanol (2 cm^3) was added a solution of compound **10b** (100 mg, 0.8 mmol) in dry methanol (2 cm^3) under N_2 atmosphere. After the reaction mixture had been stirred for 30 min, 30% aq. $TiCl_3$ (5 cm^3) and NH_4OAc (40 mg) mixture[12] was added and the reaction mixture was stirred for an additional 1 h. The reaction mixture was then quenched with water and extracted with diethyl ether (2 × 20 cm^3). The extract was washed successively with water and brine, and dried. Evaporation of the solvent and purification of the resulting residue over silica gel (20 g) column chromatography gave the *title ketone* **5** (15 mg, 10%), b.p. 100 °C/0.2 Torr; ν_{max}(neat)/cm^{-1} 3025 and 1720; δ_H 5.44 (1 H, unresolved t, CH=C), 2.42–1.40 (12 H, m) and 1.20 (3 H, s, CMe); δ_C 214.4 (s), 156.2 (s), 120.6 (d), 49.6 (s), 46.9 (s), 45.9 (t), 35.8 (t), 31.9 (t), 31.7 (t), 30.2 (t), 26.1 (t) and 17.8 (q) (Found: C, 81.7; H, 9.2. $C_{12}H_{16}O$ requires C, 81.77; H, 9.15%). There were several other unrequired products eluted from the column but these could not be characterised.

Nef Reaction on Adduct **10b** *with Basic Silica Gel.*[13]—To a solution of compound **10b** (50 mg, 0.4 mmol) in dry diethyl ether (10 cm^3) was added basic silica gel (24 g, 10 mol equiv.).[13] Solvent was evaporated off and the dry residue was heated to 150–170 °C for 18 h, then thoroughly washed with dichloromethane, and the resulting extract was concentrated. Purification of the residue over a silica gel (5 g) column by means of 50% benzene–light petroleum furnished the ketone **5** (10 mg, 15%).

8-*Chloro*-7-*methyltricyclo*[5.2.2.0^{1,5}]*undec*-5-*ene*-8-*carbonitrile* **11a** *and* 9-*Chloro*-7-*methyltricyclo*[5.2.2.0^{1,5}]*undec*-5-*ene*-9-*carbonitrile* **11b**.—The mixture of hydrocarbons **6**, **8** and **9** (4 g, 27 mmol) and α-chloroacrylonitrile (5 g, 60 mmol) were heated in dry toluene (30 cm^3) to 80 °C in a 50 cm^3, two-necked RB flask for 14 h under N_2. Toluene was removed under reduced pressure and the crude mixture thus obtained was charged on a silica gel (50 g) column. Elution with light petroleum removed the non-polar impurities. Further elution of the column with 5% ethyl acetate–light petroleum furnished the *Diels–Alder adducts* **11a** and **11b** (2.53 g, 43%) as a mixture of regioisomers, b.p. 130 °C/0.2 Torr; ν_{max}(neat)/cm^{-1} 3020, 2250, 1450 and 780; δ_H 5.65 (1 H, m, CH=C), 5.50 (1 H, br t, HC=C), 2.70–1.20 (24 H, m) and 1.45 (6 H, s, 2 × CMe) (Found: C, 70.4; H, 7.25; N, 6.3. $C_{13}H_{16}ClN$ requires C, 70.42; H, 7.22; N, 6.32%).

7-*Methyltricyclo*[5.2.2.0^{1,5}]*undec*-5-*en*-8-*one* **5** *and* 7-*Methyltricyclo*[5.2.2.0^{1,5}]*undec*-5-*en*-9-*one* **12**.—To a solution of the adducts **11a** and **11b** (7 g, 31 mmol) in dry ethanol (80 cm^3) were added potassium hydroxide (8 g, 124 mmol, 4 mol equiv.) and

* 1 Torr = 133.322 Pa.

aq. sodium sulphide (10 g, 37 mmol, 1.2 mol equiv.)[14] and the resulting mixture was refluxed for 12 h. Ethanol was removed under reduced pressure and the residue was diluted with diethyl ether (200 cm^3). The ethereal extract was washed thoroughly with water (2 × 100 cm^3) and then with brine, and dried. Concentration of the extract furnished a crude mixture, which was charged on a silica gel (80 g) column. Elution of the column with 70% benzene–light petroleum removed the non-polar impurities. Further elution with the same solvent gave the *minor isomer* **12** (640 mg, 11.5%), b.p. 100 °C/0.2 Torr; ν_{max}(neat)/cm^{-1} 3025 and 1720; δ_H 5.80 (1 H, t, *J* 1 Hz, CH=C), 2.5–1.4 (12 H, m) and 1.25 (3 H, s, CMe); δ_C 211.9, 147.7, 129.2, 59.8, 48.0, 38.2, 35.1, 29.8, 29.6, 28.6, 26.1 and 24.1 (Found: C, 81.6; H, 9.0. $C_{12}H_{16}O$ requires C, 81.77; H, 9.15%).

Continued elution of the column with the same solvent yielded the major isomer **5** (2.56 g, 46.5%), identical in all respects with the sample prepared previously.

2-*Methyltetracyclo*[4.3.2.$0^{2,6}$.$0^{2,9}$]*undecan*-8-*one* **4** *and* 3-*Methyltricyclo*[4.3.2.$0^{1,6}$]*undec*-2-*en*-10-*one* **13**.—A solution of the tricyclic β,γ-unsaturated ketone **5** (300 mg, 1.7 mmol) in dry acetone (800 cm^3) was irradiated using a 450 W Hanovia medium-pressure mercury vapour lamp placed in a quartz immersion well for 45 min. Acetone was removed under reduced pressure and the thick oily product obtained was charged on a silica gel (30 g) column for purification. Elution with benzene gave the unchanged starting material **5** (50 mg recovery). Continued elution with the same solvent gave a *minor product* **13** (10 mg), b.p. 110 °C/0.3 Torr; ν_{max}(neat)/cm^{-1} 1780, 1450 and 1100; δ_H 5.4 (1 H, m, C=CH), 3.0–2.4 (2 H, dd, *J* 16 Hz), 2.3–0.9 (10 H, m) and 1.65 (3 H, s, HC=C*Me*) (Found: C, 81.6; H, 9.1. $C_{12}H_{16}O$ requires C, 81.77; H, 9.15%).

Further elution of the column with benzene furnished the *isomeric photorearranged product* **4** (125 mg, 50% based on the starting material consumed), b.p. 110 °C/0.3 Torr; ν_{max}(neat)/cm^{-1} 3020 and 1720; δ_H 2.4–1.3 (13 H, m) and 1.20 (3 H, s, CMe); δ_C 215.4 (s), 62.3 (s), 57.5 (s), 53.4 (t), 50.5 (d), 43.5 (t), 42.9 (s), 38.2 (t), 34.6 (t), 28.6 (t), 24.8 (t) and 19.9 (q) (Found: C, 81.6; H, 9.2%).

8-*Methyl*[3.3.3]*propellan*-3-*one* **14**.—A 50 cm^3, three-necked RB flask equipped with a septum and a guard tube (filled with KOH pellets) was charged with distilled liquid ammonia (10 cm^3). Freshly cut lithium pieces (10 mg, 1.5 mmol) were slowly added to the above solution, followed by a solution of the tetracyclic compound **4** (100 mg, 0.5 mmol) in dry THF (5 cm^3) and the resulting mixture was stirred for one hour. Ammonia was allowed to evaporate off and the excess of lithium metal was quenched with diethyl ether–saturated aq. NH_4Cl (1:1). The aq. layer was extracted with diethyl ether (2 × 10 cm^3) and the extract was washed successively with water and brine, and dried. Removal of solvent furnished a mixture of alcohols, which was subjected to direct oxidation.

To a solution of the above mixture of alcohols (80 mg, 0.4 mmol) in dry dichloromethane (20 cm^3) were added pre-activated 4 Å molecular sieves. PCC (250 mg, 1.2 mmol) was added to the above suspension at ice-bath temperature and the reaction mixture was stirred for one hour at 25 °C, quenched with dry diethyl ether (5 cm^3) and diluted with dichloromethane. The resulting mixture was filtered through a small Florosil column (1 g) to remove the chromium salt impurities. Concentration of the filtrate yielded the [3.3.3]*propellanone* **14** (60 mg, 60%) as a mixture of C(8) epimers, b.p. 110 °C/0.3 Torr; ν_{max}(neat)/cm^{-1} 1740; δ_H 2.48–1.0 (30 H, m), 0.98 (3 H, d, *J* 7 Hz, CMe) and 0.95 (3 H, d, *J* 7 Hz, CMe) (Found: C, 80.8; H, 10.1. $C_{12}H_{18}O$ requires C, 80.85; H, 10.18%).

4-*Methyltetracyclo*[5.3.1.$0^{1,7}$.$0^{4,11}$]*undecan*-2-*one* **15**.—A solution of the β,γ-unsaturated ketone **12** (50 mg, 0.3 mmol) in dry acetone (125 cm^3) was irradiated using a 450 W Hanovia medium-pressure mercury vapour lamp placed in a quartz immersion well for 0.5 h. Acetone was removed under reduced pressure and the resulting oily product was charged on a silica gel (5 g) column. Elution with benzene gave the unchanged starting material **12** (5 mg). Further elution of the column with the same solvent furnished the rearranged *tetracyclic ketone* **15** (32 mg, 65%), b.p. 110 °C/0.3 Torr; ν_{max}(neat)/cm^{-1} 1705; δ_H 2.40–1.24 (13 H, m) and 1.23 (3 H, s, CMe); δ_C 214.5, 55.3, 53.7, 52.8, 47.6, 46.3, 44.7, 31.5, 28.7, 26.1, 25.5 and 21.5 (Found: C, 81.7; H, 9.1. $C_{12}H_{16}O$ requires C, 81.77; H, 9.15%).

4-*Methyltricyclo*[5.3.1.$0^{4,11}$]*undecan*-2-*one* **16**.—Into a flame dried, 50 cm^3, three-necked RB flask equipped with a septum and a guard tube (filled with KOH pellets) was placed freshly distilled liquid ammonia (15 cm^3). Freshly cut lithium pieces (7 mg, 1 mmol) were slowly added, the resulting blue coloured solution was charged with a solution of the ketone **15** (40 mg, 0.22 mmol) in dry THF (5 cm^3) and the solution was stirred for 1 h. Ammonia was allowed to evaporate off, the reaction mixture was quenched with diethyl ether–saturated aq. NH_4Cl (1:1) and the aqueous layer was extracted with diethyl ether. The organic extract was washed successively with water and brine, and dried. Concentration of the solvent gave a mixture of hydroxy epimers (35 mg).

The above mixture of alcohols (35 mg, 0.2 mmol) was dissolved in dry dichloromethane (15 cm^3) and charged with pre-activated 4 Å molecular sieves and PCC (170 mg, 0.8 mmol) at ice temperature, and the resulting suspension was stirred vigorously for 1 h. Dry diethyl ether (10 cm^3) was added to the reaction mixture, followed by dichloromethane (20 cm^3). The crude suspension was passed through a small Florosil column (1 g) to remove the chromium salts. Evaporation of the solvent gave the *tricyclic ketone* **16** (25 mg, 60%), b.p. 110 °C/0.3 Torr; ν_{max}(neat)/cm^{-1} 1735; δ_H 2.4–0.70 (15 H, m) and 1.20 (3 H, s, CMe) (Found: C, 80.8; H, 10.1. $C_{12}H_{18}O$ requires C, 80.85; H, 10.18%).

4-*Methyltricyclo*[5.3.1.$0^{4,11}$]*undec*-6-*en*-2-*one* **17**.—To a solution of the tetracyclic compound **15** (25 mg, 0.14 mmol) in dry dichloromethane (5 cm^3) was added a catalytic amount of BF_3–diethyl ether and the reactants were stirred at room temperature for 14 h. The reaction mixture was quenched with water and extracted with diethyl ether (2 × 10 cm^3). The extract was washed successively with water and brine, and dried. Concentration of the solvent and purification of the resulting oily product over a silica gel (3 g) column with 15% ethyl acetate–light petroleum as eluent gave the *keto olefin* **17**, (15 mg, 56%), b.p. 100 °C/0.2 Torr; ν_{max}(neat)/cm^{-1} 3060 and 1740; δ_H 5.2 (1 H, s,CH=C), 2.80–1.0 (12 H, m) and 1.30 (3 H, s, CMe); δ_C 219.57, 144.0, 120.7, 55.89, 52.67, 48.43, 46.73, 43.78, 28.59, 25.89, 23.95 and 23.48 (Found: C, 81.7; H, 9.1. $C_{12}H_{16}O$ requires C, 81.77; H, 9.15%).

1,7,7-*Trimethyltetracyclo*[4.3.2.$0^{2,6}$.$0^{2,9}$]*undecan*-8-*one* **18**.—In a flame-dried, 50 cm^3, three-necked RB flask fitted with a magnetic pellet and a septum was added a freshly sublimed sample of potassium t-butoxide (1 g, 9 mmol, 5 mol equiv.) in dry THF (5 cm^3) under N_2. A solution of tetracyclic ketone **4** (320 mg, 1.8 mmol) in dry THF (2 cm^3) was injected and the contents were stirred for 20 min at room temperature to produce a deep yellow coloured solution indicating anion formation. Addition of 4–5 drops of iodomethane solution [prepared from MeI (0.3 cm^3) in THF (1 cm^3)] discharged the colour to pale yellow and the colour returned when the solution was stirred for 20 min. Again 4–5 drops of the above iodomethane solution were added and the solution was stirred for an additional 15

min. Finally, the reaction mixture was quenched with excess of MeI and poured into brine. The aq. layer was extracted with diethyl ether (2 × 20 cm^3) and the organic layer was washed successively with water and brine, and dried. Evaporation of solvent yielded the oily *product* **18** (240 mg, 65%), b.p. 110 °C/0.2 Torr; ν_{max}(neat)/cm^{-1} 3020 and 1720; δ_H 2.1–1.3 (11 H, m), 1.2 (3 H, s, CMe), 1.0 (3 H, s, CMe) and 0.84 (3 H, s, CMe); δ_C 219.4 (s), 64.0 (s), 58.5 (s), 52.3 (s), 45.5 (d), 41.4 (s), 40.0 (t), 33.8 (t), 30.7 (t), 29.0 (t), 25.9 (t), 25.1 (q), 19.7 (q) and 17.9 (q) (Found: C, 82.5; H, 10.1. $C_{14}H_{20}O$ requires C, 82.30; H, 9.87%).

4,4,8-*Trimethyltricyclo*[3.3.3.$0^{1,5}$]*undecan*-3-*one* **19a** and **19b**.—Into a flame-dried, 50 cm^3, three-necked RB flask fitted with a magnetic pellet, septum and a guard tube (filled with KOH pellets) was placed distilled liquid ammonia (30 cm^3). Freshly cut lithium pieces (20 mg, 3 mmol) were slowly added, followed by the addition of a solution of ketone **18** (210 mg, 1 mmol) in dry THF (8 cm^3). The reaction mixture was stirred for *ca.* 2 h during which time the ammonia was allowed to evaporate off. Excess of lithium metal was destroyed by the addition of a 1:1 mixture of diethyl ether–saturated aq. NH_4Cl. The aq. layer was extracted with diethyl ether and the extract was washed successively with water and brine, and dried. Removal of solvent gave an oily product (200 mg), which was carried forward to the oxidation step.

The mixture of alcohols (200 mg, 1 mmol) obtained above was dissolved in dry dichloromethane (20 cm^3) and the solution was cooled to ice temperature. Pre-activated 4 Å molecular sieves were suspended in the above solution and the mixture was stirred vigorously for 2 h after the addition of PCC (0.5 g). The reaction mixture was quenched with dry diethyl ether (10 cm^3) and diluted with dichloromethane. The crude material was filtered through a small Florosil column (2 g) to remove the chromium salt impurities. Concentration of the filtrate furnished the *propellanones* **19a** and **19b** (160 mg, 75%) as an epimeric mixture at C-8, b.p. 120 °C/0.2 Torr; ν_{max}(neat)/cm^{-1} 1740; δ_H 2.6–2.0 (two sets of AB q, each 2 H), 2.0–1.20 (22 H, m) and 1.1–0.95 (m, Mes) (Found: C, 81.6; H, 10.7. $C_{14}H_{22}O$ requires C, 81.50; H, 10.73%).

2,4,4,8-*Tetramethyltricyclo*[3.3.3.$0^{1,5}$]*undecan*-3-*one* **20**.—A flame-dried, 25 cm^3, three-necked RB flask equipped with a nitrogen inlet, outlet and a septum was cooled to −78 °C under N_2 and was charged with n-BuLi in hexane (0.8 cm^3, 0.8 mmol, 1.2 mol equiv., in 1 cm^3) followed by the addition of hexamethyldisilazane (0.2 cm^3), and the mixture was stirred for 15 min at −78 °C to give a white precipitate. Dry THF (1 cm^3) was added to dissolve the base and a solution of the mixture **19a** and **19b** (100 mg, 0.5 mmol) in dry THF (1.5 cm^3) was injected. The contents were allowed to warm to 0 °C and the mixture was stirred for 30 min at 0 °C. Iodomethane (0.2 cm^3) was added and the solution was brought to room temperature during 20 min. Finally, the reaction mixture was quenched with brine and extracted with diethyl ether (2 × 20 cm^3). The extract was washed successively with water and brine, and dried. Evaporation of solvent and chromatography over column silica gel (10 g) with 50% benzene–light petroleum as eluent furnished *title compound* **20** (65 mg, 60%) as an inseparable mixture of epimers at C-2 and C-8, b.p. 120 °C/0.2 Torr; ν_{max}(neat)/cm^{-1} 1740; δ_H 2.61–2.30 (two sets of m, each 1 H), 2.0–1.20 (22 H, m) and 1.2–0.95 (m, Mes) (Found: C, 81.7; H, 10.9. $C_{15}H_{24}O$ requires C, 81.76; H, 10.98%).

(±)-*Modhephene* **1** *and* (±)-*Epimodhephene* **3**.—A solution of the propellanone **20** (50 mg, 0.24 mmol) in dry diethyl ether (10 cm^3) was treated with lithium aluminium hydride (20 mg, 2.5 mol equiv.) at ice temperature for 30 min. Excess of hydride was quenched with ethyl acetate followed by saturated aq. sodium sulphate and the mixture was stirred for 10 min. A clear organic layer separated from a white, jelly-like mass. The organic layer was decanted and the aq. layer was extracted with diethyl ether (2 × 10 cm^3). The combined organic layer was washed successively with water and brine, and dried. Evaporation of solvent gave an oily product which showed a clearly separable mixture of alcohols on TLC. Purification of this mixture (50 mg) over a silica gel (4 g) column with 50% benzene–light petroleum as eluent furnished two alcohols, **21** (18 mg), ν_{max}(neat)/cm^{-1} 3300, 2950 and 1050; and **22** (22 mg), ν_{max}(neat)/cm^{-1} 3300, 2950 and 1060, as a mixture of C-2 and C-3 epimers.

To a solution of the alcohol **21** (15 mg, 0.06 mmol) in pyridine (0.5 cm^3) cooled to ice temperature was added freshly distilled phosphorus trichloride oxide (0.1 cm^3) under N_2. The reactants were slowly brought to room temperature during 3 h. A catalytic amount of DBU was added and the mixture was stirred for 1 h, then poured into ice–water and extracted with pentane (2 × 10 cm^3). The extract was washed successively and thoroughly with water and brine, and dried. Removal of solvent gave an oily product, which was charged on a silica gel (1 g) column. Elution with dry pentane furnished (±)-modhephene **1** (5 mg, 38%) as an oily liquid, ν_{max}(neat)/cm^{-1} 2950, 2850, 1460, 1375 and 840; δ_H 4.81 (1 H, m, HC=C), 2.20–1.08 (11 H, series of m), 1.58 (3 H, d, *J* 1.5 Hz, CH=C*Me*), 0.98 (3 H, d, *J* 6 Hz, CH*Me*) and 0.97 (6 H, s, 2 × CMe). The IR and ^1H NMR spectra of compound **1** were identical with those kindly supplied by Professor Paquette.

To a solution of the alcohol **22** (15 mg, 0.06 mmol) in pyridine (0.5 cm^3) cooled to ice temperature was added freshly distilled phosphorus trichloride oxide (0.1 cm^3) under N_2. The reactants were slowly brought to room temperature during 3 h. A catalytic amount of DBU was added and the mixture was stirred for 1 h, poured into ice–water and extracted with pentane (2 × 10 cm^3). The extract was washed successively and thoroughly with water and brine, and dried. Removal of solvent gave an oily product, which was charged on a silica gel (1 g) column. Elution with dry pentane furnished (±)-epimodhephene **3** (5 mg 38%) as an oily liquid, ν_{max}(neat)/cm^{-1} 2950, 2850, 1465 and 1370; δ_H 4.87 (1 H, m, HC=C), 2.09–1.06 (11 H, series of m), 1.60 (3 H, d, *J* 1.6 Hz, CH=CMe), 1.02 (6 H, s, 2 × CMe) and 0.88 (3 H, d, *J* 6 Hz, CH*Me*). The IR and ^1H NMR spectra of compound **3** were identical with those kindly supplied by Professor Paquette.

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