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Synthetic Studies towards Compounds Related to Sterpurene and Protoilludene

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As part of synthetic strategies towards the sesquiterpenes 6-protoilludene and sterpurene the intramolecular aldol condensation of 1-(2-oxopropyl)-2-acetyl-4,4-dimethylcyclopentane was studied in detail. Mixtures of 5,8,8-trimethylbicyclo[4.3.0]-4-nonen-3-one and 4,8,8-trimethylbicyclo[4.3.0]-3-nonen-2-one were formed. The reaction was carried out under different acidic and basic conditions, giving the two compounds in ratios varying from 1:1 to 12:1. The best conditons were found to be methanesulfonic acid in methanol. The preparation of *trans*-5,8,8-trimethylbicyclo[4.3.0]-4-nonen-3-one by our route in about 70% overall yield constitutes formally a new synthesis of sterpurene.

Over the past two decades several sesquiterpenes with the unique 4/6/5 ring system have been isolated from natural sources and characterised.[1] Sterpurene (**1b**) and Δ^6-protoilludene (**2b**) are representative of two subclasses of this family of sesquiterpenes, i.e., the sterpuranes and protoilludanes (Scheme 1). Both classes of compounds show interesting biological activities, but equally interesting is their possible role as intermediates in the biosyntheses of other sesquiterpenes.[2] Finally, the unique skeletons represent a synthetic challenge, and a few syntheses of **1b** and **2b** have already appeared.[2a,3,4] With these compounds as targets the retrosynthetic analysis presented in Scheme 1 leads to the isomeric bicyclo[4.3.0]nonenones **3b** and **4b** and the precursor **5b**. Hence, the essential step in the syntheses becomes the aldol condensation of the latter, which can produce either of two structural isomers **3b** and **4b** depending on which enolate is formed. The present paper presents a study of this reaction aiming at conditions that would bring about a useful degree of selectivity.

We chose to do some preliminary experiments on the demethylated analogue **5a** which is readily available from photochemical cycloaddition of 2,4-pentanedione to cyclopentene according to de Mayo and Takeshita,[5a] followed by ring opening of the initially formed cyclobutanol derivative. They also described an aldol condensation of **5a** using sodium hydroxide in methanol, which gave the isomeric ketones **3a** and **4a** in a 2:3 ratio, but did not comment on any stereoisomerism. No attempt to optimize the reaction conditions was reported. Furthermore, Takeshita *et al.*[6] reported on an acid-catalyzed aldol condensation of methyl 2-(2-oxopropyl-4,4-dimethylcyclopentyl)-2-oxoacetate that furnished a mixture of the corresponding *cis*- and *trans*-fused bicyclic ketones, but no ratio between the stereoisomers was provided. In the present work the condensation of **5a** was carried out under either acidic or basic conditions. All reactions produced mixtures of the ketones **3a** and **4a**, in most cases with the former as the most abundant component. Use of conditions similar to those reported by de Mayo and Takeshita afforded the two ketones in a 1:1 ratio. The highest degree of selectivity was achieved using methanesulfonic acid in methanol at 5 °C, conditions that yielded **3a** and **4a** in a 14:1 ratio, as mixtures of stereoisomers. For each ketone one stereoisomer predominated. Flash chromatography furnished the major stereoisomers of **3a** and **4a**, respectively. Both compounds were assigned the *trans* configuration based on analogy with the NMR data on **3b** reported by Little and coworkers.[3b] In most cases several other products were formed as well, but usually in amounts too small for isolation. However, one of the minor components was separated and identified as 2-acetyl-3-methyl-1,3-cycloheptadiene (**6**) on the basis of spectroscopic evidence. This by-product seems unprecedented and it cannot result from a concerted thermal ring-

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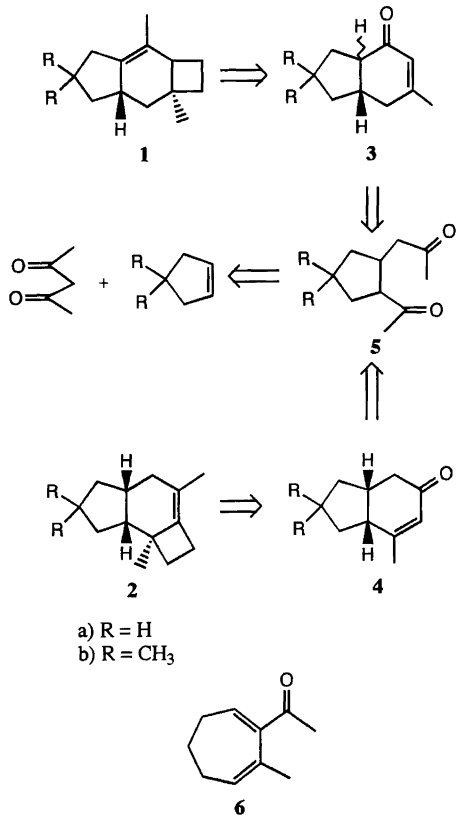
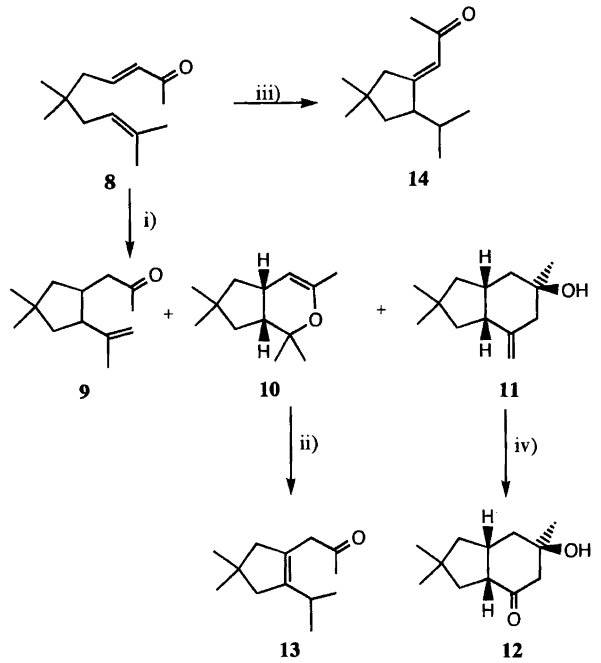


Scheme 1.

opening of an intermediate cyclobutene, a conrotatory process, and we suggest that it results from ring-opening of the protonated cyclobutanol intermediate. The selectivity of the aldol condensation was not as good under basic conditions; the best result was obtained with sodium hydroxide in methanol at room temperature with either water or HMPA as co-solvents. In either case the product consisted of a 4:1 ratio of the same ketones.

The above results encouraged us to attempt reactions with the diketone **5b**. This compound had previously been prepared from 4,4-dimethylcyclopentene by the de Mayo reaction;[5] however, the need for an excess of 4,4-dimethylcyclopentene, only available by multi-step syntheses,[7] seemed at first a less convenient approach to this molecule. An alternative route to **5b** began by transforming the readily available aldehyde **7**[8] into the ketone **8**. The *E*-configuration of **8** was proved by the ^{1}H NMR spectrum. An intramolecular ene-reaction should convert **8** into the ketone **9**, which by ozonolysis should furnish the diketone **5b**. Heating of **8** resulted indeed in the formation of the desired ketone **9** but unfortunately accompanied by the bicyclic dihydropyran **10** and the bicyclic alcohol **11** in 35, 46 and 8% yields, respectively. The compounds were separated by flash chromatography. The ketone **9** was formed as a 7:3 mixture of *trans* and *cis* isomers, respectively, whereas compounds **10** and **11** were obtained as single stereoisomers. The structural assignements were all based on spectroscopic data. The reactions are depicted in Scheme 2.



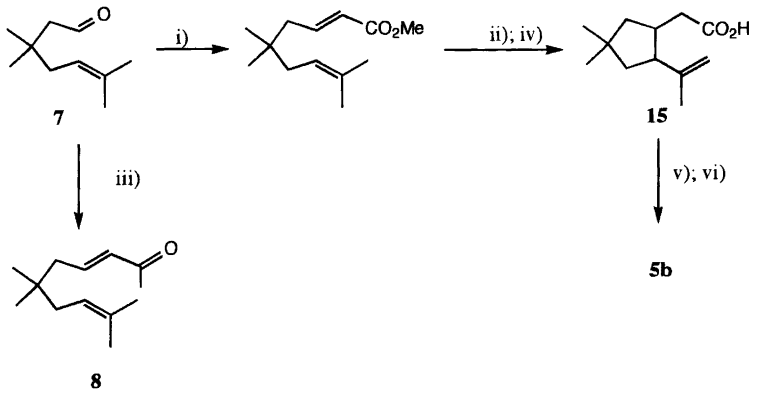
Scheme 2. i), △, 89%; ii) H^+, 62%; iii) Lewis acid, 66%; iv) O_3, 98%.

In the IR spectrum of **10** absorptions at 1670 and 1130 cm^{-1} are due to the vinyl ether moiety, and the NMR spectra support the bicyclic dihydropyran structure. Compound **10** is most probably formed by a concerted hetero Diels–Alder reaction of **8**, demanding a *cis* configuration of the product, which is substantiated by spectroscopic data. The two geminally substituted methyl groups of the *cis* isomer will occupy chemically different environments, whereas for the *trans* isomer only an insignificant difference is expected; hence, two separate signals at 0.91 and 0.97 ppm in the ^{1}H NMR spectrum as well as signals at 25.54 and 27.54 ppm in the ^{13}C NMR spectrum due to the methyl groups suggest that **10** has a *cis* configuration. The ^{13}C NMR spectra of a number of *cis*- and *trans*-fused [4.*n*.0] bicyclic compounds have been reported in the literature,[9] and by comparison with these data the chemical shift values of **10** are quite consistent with a *cis*-configuration. Spectral evidence of the third component indicated a bicyclic alcohol with a methylene double bond as in structure **11**, but the stereochemistry was not established. When a stereoisomeric mixture of the ketone **9** was subjected to the same thermal conditions as above only the *cis* isomer underwent an ene-reaction producing the alcohol **11** together with unreacted *trans* isomer. Hence, the ring junction in **11** must be *cis*. This was shown to be true by X-ray diffraction[10] of the ketone **12**, obtained by ozonolysis of **11**, which also established the configuration of the hydroxy group as depicted in Scheme 2. According to the mechanism of a concerted ene-reaction it is expected that only *cis*-**9** will react, and it is quite reasonable that the hydroxyl group should be formed stereoselectively as observed. Hence, the alcohol **11** results

from an unavoidable secondary reaction that contributes to a reduced yield of the desired ketone **9**. Attempts to isomerize the dihydropyran derivative **10** to the ketone **9** gave instead a single compound in 62% yield, identified as the isomeric ketone **13**. The ^{1}H NMR spectrum exhibited characteristic absorptions due to the isopropyl group, and the exocyclic methylene group appeared as a singlet at 3.06 ppm. The ^{13}C NMR spectrum displayed signals at 144.34, and 124.56 ppm due to the two quaternary olefinic carbons.

Although the hetero Diels–Alder reaction has an inverse electron demand it is clearly competitive in rate with that of the ene-reaction. Both reactions are known to be catalyzed by Lewis acids, but we hoped for some selectivity in favour of the ketone **9**. However, when the reaction of **8** was conducted in the presence of $EtAlCl_2$ at 0 °C the α,β-unsaturated ketone **14** was obtained as the major product in 66% yield accompanied by small amounts of other compounds (Scheme 2). The structure of **14** was established from spectroscopic evidence. In particular, a singlet at 6.13 ppm in the ^{1}H NMR spectrum indicated the presence of one olefinic proton, and in the ^{13}C NMR spectrum three peaks at 198.00, 170.27, and 120.98 ppm were assigned to the carbonyl, quaternary and tertiary olefinic carbons, respectively. According to both GLC and NMR data only one stereoisomer was formed, but it was not possible to establish which one from the spectroscopic data alone. However, Snider *et al.*[11] have proposed a mechanism to account for the formation of α,β-unsaturated carbonyl compounds, such as **14**, from $EtAlCl_2$-catalyzed ene reactions. According to this mechanism both stereoisomers of the alkene can be formed, but for steric reasons the *E* configuration should be preferred. Other Lewis acids such as $AlCl_3$, $MgCl_2$, $SnCl_4$ and $TiCl_4$ were also employed as catalysts, resulting in more complex product mixtures containing the ketone **14** as one of the components, but without any detectable amount of **9**.

In view of these problems another approach to **5b** was attempted (Scheme 3), starting from the acid **15** that was easily prepared from the aldehyde **7** according to the protocol of Thompson and Heathcock.[12] Reaction of **15** with methyllithium furnished **9** as a mixture of stereoisomers according to GLC and NMR analyses, and subsequent ozonolysis produced the diketone **5b** as a 7:3 mixture of *cis* and *trans* isomers, respectively. The ratio is the same as that reported for the starting material **15**.[12] The subsequent aldol condensation resulted in mixtures of **3b** and **4b** in ratios quite similar to those obtained from the reactions of **5a**. A variety of reaction conditions were employed and the results are recorded in Table 1. It is noteworthy that the best conditions with respect to regioselectivity were achieved with methanesulfonic acid (entry 11). However, acidity alone is not sufficient, since use of hydrochloric acid in methanol led to no regioselectivity at all (entry 7). On the other hand, basic conditions gave at best reactions with only fair regioselectivity, and with some base systems no regioselectivity was observed (entries 1, 5). Apparently neither base strength nor the steric bulk of the base influence the regioselectivity significantly. The use of anhydrous magnesium chloride in triethylamine gave actually the best result (entry 15). The complexing ability of the magnesium ion must be important since the use of triethylamine alone resulted in a very slow reaction: after several days the conversion was only a few percent and **3b** was formed only slightly in favour of **4b**. Other Lewis acids, as $AlCl_3$ and $FeCl_3$, combined with triethylamine did not perform as well with regard to selectivity (entries 13, 14). In a recent publication Nagao *et al.*[13] have found that for a Dieckmann-type condensation changing the base from NaH or LDA to a Lewis acid–triethylamine reversed the regiochemistry of the reaction. This was not the case for our aldol-type condensation using the Lewis acid–triethylamine combination as base; the diketone **3b** was always formed in favour of **4b**. In all cases variations of the acid or base concentration, reaction temperature and reaction time caused no improvement with regard to selectivity. Furthermore, with an enolizable carbonyl group as in the ketones **3b** and **5b** isomerization was unavoidable under the reaction conditions, leading to product mixtures with the thermodynamically favoured *trans* isomers predominating. The structurally isomeric ketones **3b** and **4b** were easily



Scheme 3. i) $Ph_3P{=}CHCO_2Me$; ii) △; iii) $Ph_3P{=}CHAc$, 83%; iv) OH^-; v) MeLi, 88%; vi) O_3, 69%.

Table 1. Aldol condensations of the diketone **5b**.

Entry	Acid/base[a]	Mol equiv. acid/base	Solvent	T/°C	t/h	Product ratio **3b**:**4b**[b]
1	NaOH	0.2	MeOH	25	2	1:1
2	NaOH	5	MeOH	25	1	3:2
3	KO^{t}Bu	0.2	^{t}BuOH	25	5	5:2
4	NaOMe	0.2	MeOH	25	1	2:1
5	LDA	0.5	$(^i Pr)_2NH$	−78→25	2.5	1:1
6	LDCHA	0.2	$(C_6H_{11})_2NH$	25	2	3:2
7	HCl	1	MeOH	25	1	1:1
8	TFA	0.2	MeOH	25	6	2:1
9	PTSA	0.2	MeOH	5	12	8:1
10	PTSA	0.2	MeOH	25	12	6:1
11	CH_3SO_3H	0.2	MeOH	5	10	12:1[c]
12	H_2NSO_3H	0.2	MeOH	25	12	2:1
13	$AlCl_3$–Et_3N	1	Et_3N	25	2	1:1
14	$FeCl_3$–Et_3N	1	Et_3N	25	2	2:1
15	$MgCl_2$–Et_3N	1	Et_3N	25	2	6:1

[a] LDA = lithium diisopropylamide, LDCHA = lithium dicyclohexylamide, TFA = trifluoroacetic acid, PTSA = *p*-toluenesulfonic acid. [b] According to GLC. [c] These conditions were used for the preparation of **3b** (see Experimental).

separated by column chromatography as mixtures of stereoisomers, but further separation of these was difficult. However, pure samples of the stereoisomers of **3b** were obtained by separate experiments; the *trans* isomer was obtained by base-induced equilibration of the *cis*/*trans* mixture, while the *cis* isomer was obtained by acid-catalyzed elimination of water from the *cis*-fused hydroxy ketone **12**. On the other hand we were unable to obtain pure stereoisomers of **4b**.

The ketone *trans*-**3b** has previously been transformed into racemic sterpurene (**1b**).[3b] Hence, the preparation of **3b** by our route in about 70% overall yield constitutes formally a new synthesis of **1b**, which in simplicity is comparable to several of those published. On the other hand, the low yield of **4b** by the present route discouraged us from further synthetic manipulations of this ketone with Δ^6-protoilludene (**2b**) as the target.

Experimental

General. The NMR spectra were recorded on Varian Gemini 200 and JEOL JNM-GX270 instruments using $CDCl_3$ as the solvent and TMS as an internal standard. ^1H spectra are recorded at 200 and 270 MHz, and ^{13}C spectra were recorded at 50 and 67.5 MHz, respectively. IR spectra were recorded on either a Perkin-Elmer infrared spectrometer or a Magna-550 IR spectrometer. MS spectra were recorded on a JEOL DX-303 GC–MS. Analytical GLC was performed on a 25 m SP2100 capillary column on a Varian GC 3300 instrument. When required, reactions were carried out under an atmosphere of nitrogen or argon.

1-(2-Oxopropyl)-2-acetylcyclopentane (**5a**),[5] 3,3,6-trimethylhept-5-enal (**7**)[8] and *cis*- and *trans*-4,4-dimethyl-2-(1-methylethenyl)cyclopentylacetic acid (**15**)[12] were prepared according to literature procedures.

4-Methylbicyclo[4.3.0]-3-nonen-2-one (**3a**), *5-methylbicyclo[4.3.0]-4-nonen-3-one* (**4a**) *and 2-acetyl-3-methyl-1,3-cycloheptadiene* (**6**). To a solution of **5a** (2.00 g, 12 mmol) in MeOH (90 ml), kept at 5 °C, methanesulfonic acid (300 mg, 3.1 mmol) was added dropwise. The reaction mixture was stirred for 16 h, and quenched by the addition of 10% $NaHCO_3$. Extraction with petroleum ether, washing of the collected organic phases with water, drying ($MgSO_4$) and evaporation of the solvent yielded a mixture of *trans*-**3a**, *cis*-**3a**, *trans*-**4a** and **6** in a ratio of 67:13:6:8 together with 6% unidentified material (GLC). The isomers were separated by repeated flash chromatography (silica gel, 12% EtOAc in hexane), yielding 530 mg of *trans*-**3a** (30%) and analytically pure samples of the other compounds.

trans-*4-Methylbicyclo[4.3.0]-3-nonen-2-one* (**3a**): ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (m, 2 H), 1.60 (m, 3 H), 1.82 (s, 3 H), 1.95 (m, 1 H), 2.10 (br s, 1 H), 2.25 (m, 1 H), 2.35 (br s, 2 H), 5.70 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.8 (CH_2), 24.2 (CH_3), 28.5 (CH_2), 30.6 (CH_2), 32.5 (CH_2), 39.2 (CH), 49.2 (CH), 124.9 (CH), 159.6 (C), 201.0 (C). IR (CCl_4): 3025 (w), 2960 (s), 2930 (s), 2880 (m), 1669 (s), 1640 (w), 1440 (m), 1425 (w), 1370 (m), 750 (s) cm^{-1}.

cis-*4-Methylbicyclo[4.3.0]-3-nonen-2-one* (**3a**): ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (m, 2 H), 1.65 (m, 3 H), 1.88 (s, 3 H), 2.10 (m, 3 H), 2.40 (dd, 2 H), 5.75 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.9 (CH_2), 23.0 (CH_2), 24.0 (CH_3), 31.2 (CH_2), 38.2 (CH_2), 44.2 (CH), 53.7 (CH), 126.8 (CH), 161.4 (C), 201.3 (C). IR (CCl_4): 3025 (w), 2960 (s) 2930 (s), 2880 (m), 1670 (s), 1615 (w), 1445 (m), 1430 (m), 1420 (w), 1370 (m) cm^{-1}.

trans-*5-Methylbicyclo[4.3.0]-4-nonen-3-one* (**4a**): ^1H NMR (200 MHz, $CDCl_3$): δ 1.20 (s, 1 H), 1.40 (m, 1 H), 1.65 (m, 2 H), 1.75 (m, 2 H), 1.87 (s, 3 H), 1.9–2.3 (m, 2 H), 2.50 (m, 2 H), 5.75 (s, 1 H). ^{13}C NMR (50 MHz,

$CDCl_3$): δ 23.7 (CH_3), 24.3 (CH_2), 30.5 (CH_2), 31.5 (CH_2), 38.9 (CH), 40.1 (CH_2), 45.1 (CH), 125.9 (CH), 163.9 (C), 200.1 (C). IR (CCl_4): 3025 (w), 2960 (s), 2930 (s), 2880 (m), 1673 (s), 1635 (w), 1440 (m), 1420 (w), 1380 (m), 750 (s) cm^{-1}.

2-Acetyl-3-methyl-1,3-cycloheptadiene (**6**): MS: *m/z* 150 (M^+), 122 (100). ^1H NMR (200 MHz, $CDCl_3$): δ 1.75 (m, 2 H), 2.15 (s, 3 H), 2.25 (s, 3 H), 2.45 (m, 4 H), 6.04 (s, 1 H), 6.25 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.7 (CH_3), 23.0 (CH_3), 32.0 ($2\times CH_2$), 33.6 (CH_2), 122.5 (CH), 136.2 (CH), 145.3 (C), 148.2 (C), 199.3 (C). IR (CCl_4): 3040 (w), 2940 (s), 2840 (m), 1710 (m), 1675 (s), 1430 (m), 1350 (m), 1170 (s) cm^{-1}.

(E)-6,6,9-Trimethyl-3,8-decadien-2-one (**8**). A suspension of triphenylphosphoranylidene–acetone (38.2 g, 0.12 mol) and the aldehyde **7** (18.37 g, 0.12 mol) in dry benzene (250 ml) was heated under reflux until complete consumption of the aldehyde (52 h). Most of the benzene was evaporated off and the semi-solid residue was extracted several times with petroleum ether (b.p. 40–60 °C). Evaporation of solvents followed by flash chromatography (silica gel, 9 : 1 petroleum ether–EtOAc) gave 19.1 g (83%) of the ketone **8**. ^1H NMR (200 MHz, $CDCl_3$): δ 0.89 (s, 6 H) 1.58 (s, 3 H), 1.72 (s, 3 H), 1.90 (d, *J* 7.8 Hz, 2 H), 2.10 (dd, *J* 1.4, 7.8 Hz, 2 H), 2.29 (s, 3 H), 5.16 (t, *J* 7.8 Hz, 1 H), 6.05 (dt, *J* 1.4, 15.8 Hz, 1 H), 6.85 (dt, *J* 7.8, 15.8 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.42 (CH_3), 26.55 (CH_3), 27.36 (CH_3), 27.46 (2 CH_3), 35.66 (C), 40.79 (CH_2), 45.24 (CH_2), 120.89 (=CH), 133.68 (=CH), 133.89 (=C), 146.52 (=CH), 198.96 (C=O). IR (film): 2920 (s), 1670 (s), 1620 (s), 1440 (m), 350 (s), 1250 (s), 1175 (m), 880 (s) cm^{-1}.

Thermal reaction of **8**. The ketone **8** (5.79 g, 0.03 mol) was placed in a Pyrex glass tube and degassed by performing three freeze–pump–thaw cycles. Argon was admitted and the tube was sealed. The ampoule was heated at 200–210 °C (bath temperature) for 10 h. GLC and TLC analysis of the reaction mixture showed complete consumption of the starting material and formation of three major components . Column chromatography (silica gel, 95:5 petroleum ether–EtOAc) gave 2.03 g (35%) of the ketone **9**, as 3:7 *cis/trans* mixture, 2.66 g (46%) of **10** and 0.46 g (8%) of **11**. The stereoisomeric mixture of **9** (2.65 g, 3.65 mmol) was subjected to the above thermal conditions for 24 h. Chromatography afforded 0.45 g (17%) of the hydroxy compound **11** and 1.89 g of unreacted *trans*-**9**.

trans-*1-(2-Oxopropyl)-4,4-dimethyl-2-isopropenyl cyclopentane* (**9**). MS: 194 (M^+, 10), 179 (21), 151 (22), 136 (28), 121 (63), 95 (41), 55 (23), 43 (100%). ^1H NMR (300 MHz, $CDCl_3$): δ 0.93–1.02 (m, 1 H), 0.95 (s, 3 H), 0.97 (s, 3 H), 1.32 (m, 1 H), 1.47–1.62 (m, 2 H), 1.59 (s, 3 H), 1.79 (m, 1 H), 2.02–2.24 (m, 2 H), 2.03 (s, 3 H), 2.50 (dd, *J* 3.0, 15.9 Hz, 1 H), 4.65 (s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.83 (CH_3), 30.24 (CH_3), 31.20 (CH_3), 31.36 (CH_3), 36.75 (C), 38.24 (CH), 46.23 (CH_2), 47.68 (CH_2), 48.44 (CH_2), 53.92 (CH), 111.00 (=CH_2), 146.14 (=C), 208.82 (C=O). IR (film): 3045 (w), 2920 (s), 2845 (s), 1710 (s), 1635 (m), 1440 (s). 1355 (s), 1150 (s), 885 (s) cm^{-1}.

cis-*3,5,5,8,8-Pentamethyl-4-oxabicyclo[4.3.0]non-2-ene* (**10**). HRMS: *m/z* 194.1699 (M^+), calc. for $C_{13}H_{22}O$: 194.1671. ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (s, 3 H), 0.97 (s, 3 H), 1.12 (s, 6 H), 1.22–1.34 (m, 3 H), 1.59–1.66 (m, 1 H), 1.60 (s, 3 H), 1.89 (m, 1 H), 2.50 (t, *J* 7.5 Hz, 1 H), 4.14 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.59 (CH_3), 25.54 (CH_3), 27.54 (CH_3), 31.90 (CH_3), 32.36 (CH_3), 34. 89 (CH), 37.43 (C), 41.14 (CH_2), 46.44 (CH), 47.74 (CH_2), 74.79 (C–O), 100.35 (=CH), 146.33 (=C–O). IR (film): 2920 (s), 2850 (s), 1670 (m), 1440 (m), 1370 (s), 1360 (s), 1305 (s), 1180 (m), 1130 (s), 1015 (m) cm^{-1}.

cis-*5-Methylene-3,8,8-trimethylbicyclo[4.3.0]nonan-3-ol* (**11**). ^1H NMR (300 MHz, $CDCl_3$): δ 0.99 (s, 3 H), 1.07 (s, 3 H), 1.18 (s, 3 H), 1.23–1.43 (m, 2 H), 1.47–1.61 (m, 2 H), 1.65–1.72 (m, 2 H), 2.02 (dd, *J* 2.7, 10.2 Hz, 1 H), 2.13–2.27 (m, 2 H), 2.30 (d, *J* 13.8 Hz, 1 H), 2.73 (m, 1 H), 4.73 (t, *J* 2.7 Hz, 1 H), 4.87 (t, *J* 2.7 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.27 (CH_3), 32.69 (CH_3), 32.91 (CH_3), 38.59 (C), 39.14 (CH), 42.35 (CH_2), 44.52 (CH_2), 44.92 (CH_2), 47.10 (CH), 47.49 (CH_2), 71.74 (C–O), 112.51 (=CH_2), 147.50 (=C). IR (film): 3400 (s), 3040 (w), 2920 (s), 2840 (s), 1630 (m), 1450 (s), 1350 (s), 1250 (s), 875 (s) cm^{-1}.

cis-*4-Hydroxy-4,8,8-trimethylbicyclol4.3.0]nonan-2-one* (**12**). Compound **11** (1.2 g, 6.185 mmol) in methanol (35 ml) was ozonized at −78 °C for 1.5 h. Excess dimethyl sulfide (2 ml) was added dropwise and the reaction mixture allowed gradually to attain room temperature overnight. Work-up in the usual way followed by flash chromatography (silica gel, 4 : 1 petroleum ether–EtOAc) gave 1.19 g (98%) of the hydroxy ketone **12**, m.p. 82–84 °C (from hexane). ^1H NMR (200 MHz, $CDCl_3$): δ 0.97 (s, 3 H), 1.10 (s, 3 H), 1.31 (s, 3 H), 1.17–1.90 (an envelope of multiplets, 6 H), 2.16 (s, 2 H), 2.40 (s, 1 H). 2.80 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 30.39 (CH_3), 31.32 (CH_3), 31.40 (CH_3), 38.04 (C), 39.32 (CH), 42.60 (CH_2), 43.65 (CH_2), 48.16 (CH_2), 48.91 (CH), 51.95 (CH_2), 73.87 (C–O), 202.00 (C–O). IR (KBr): 3377 (s), 2962 (s), 2940 (s), 2854 (m), 1702 (s), 1466 (m), 1380 (m), 1301 (m), 936 (m) cm^{-1}.

1-(2-Oxopropyl)-4,4-dimethyl-2-isopropylcyclopentene (**13**). A solution of the bicyclic ether **10** (6.6 g, 0.034 mol) and 0.4 g *p*-toluenesulfonic acid in dry benzene (100 ml) was heated under reflux for 3 h. Solid K_2CO_3 was added to the cold reaction mixture. Filtration, solvent evaporation and column chromatography (silica gel, 95 : 5 petroleum ether–EtOAc) gave 4.1 g (62%) of the ketone **13**. ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (d, *J* 6.6 Hz, 6 H), 1.02 (s, 6 H), 2.06–2.11 (m, 4 H), 2.07 (s, 3 H), 2.64 (m, 1 H), 3.06 (s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): 22.44 ($2\times CH_3$), 28.45 (CH), 30.41 (CH_3), 30.89 ($2CH_3$), 36.23 (C), 45.70 (CH_2), 47.14 (CH_2), 52.03 (CH_2),

124.56 (=C), 144.34 (=C), 207.12 (C=O). IR (film): 2920 (s), 2820 (s), 1705 (s), 1605 (s), 1450 (s), 1350 (s), 1150 (s), 1030 (m) cm^{-1}.

2-Isopropyl-1-(2-oxopropylidene)-4,4-dimethylcyclopentane (**14**). A solution of **8** (2.0 g, 10.3 mmol) in dry dichloromethane (30 ml) was cooled to 0 °C and ethylaluminium dichloride (6.87 ml, 10.3 mmol) was added dropwise over a period of 25 min. Stirring at 0 °C was continued for 50 min, when the reaction was quenched by dropwise addition of sat. aqueous NaH_2PO_4. A small volume of 10% HCl was added to dissolve the alumina. The product was extracted with ether, washed with brine and dried ($MgSO_4$). Evaporation followed by flash chromatography (silica gel, 95:5 petroleum ether–EtOAc) gave 1.31 g (66%) of **14**. ^1H NMR (200 MHz, $CDCl_3$): δ 0.72 (d, *J* 6.6 Hz, 3 H), 0.85 (s, 3 H), 0.93 (d, *J* 6.6 Hz, 3 H), 1.11 (s, 3 H), 1.22–1.43 (m, 2 H), 1.97–2.26 (m, 2 H), 2.17 (s, 3 H), 2.75 (m, 1 H), 3.00 (dt, *J* 18.6, 1.8 Hz, 1 H), 6.13 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): 17.70 (CH_3), 22.88 (CH_3), 28.83 (CH_3), 30.41 (CH_3), 31.34 (CH_3), 32.82 (CH), 38.75 (C), 40.02 (CH), 50.40 (CH_2), 51.87 (CH_2), 120.98 (=CH), 70.27 (=C), 198.00 (C=O). IR (film): 2925 (s), 2850 (s), 1675 (s), 1455 (m), 1355 (s), 1195 (s), 960 (m), 840 (m) cm^{-1}.

1-(2-Oxopropyl)-4,4-dimethyl-2-isopropenylcyclopentane (**9**). A solution of methyllithium in ether (1.6 M, 10.25 ml, 16.40 mmol) was added dropwise to a cold (0 °C) solution of the acid **15** (1.61 g, 8.20 mmol) in dry ether (100 ml). Stirring was continued for 20 min and saturated NH_4Cl was added. The product was extracted with ether, washed successively with 10% $NaHCO_3$ and brine, and dried ($MgSO_4$). Evaporation followed by flash chromatography (silica gel, petroleum ether–EtOAc 95:5) gave 1.32 g (88%) of the ketone **9** as a 7:3 *cis/trans* mixture.[11]

1-(2-Oxopropyl)-2-acetyl-4,4-dimethylcyclopentane (**5b**). Ozone was introduced into a solution of **9** (2.44 g, 12.5 mmol) in methanol (75 ml) at −78 °C until a blue color persisted. Dimethyl sulfide was added and work-up in the usual way followed by flash chromatography (silica gel, 5:1 hexane–EtOAc) gave the diketone **5b** (1.69 g, 69%) as a 7:3 *cis/trans* mixture. ^1H NMR (200 MHz, $CDCl_3$): δ 0.94 (s, 3 H), 0.95 (s, 3 H), 0.96 (s, 3 H), 0.99–1.08 (m, 1 H), 1.05 (s, 3 H), 1.25 (m, 1 H), 1.42 (m, 1 H), 1.60 (m, 3 H), 1.75 (m, 2 H), 2.03 (s, 3 H), 2.05 (s, 3 H *cis*, 3 H *trans*), 2.08 (s, 3 H), 2.28–2.46 (m, 2 H), 2.31–2.48 (m, 1 H), 2.54–2.63 (m, 1 H), 2.64–2.83 (m, 2 H *cis*, 1 H *trans*), 3.34 (m, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.8, 29.3, 29.7, 29.8, 30.2, 30.3, 30.7, 32.2, 36.5, 36.7, 38.3, 38.6, 44.6, 44.7, 46.0, 47.4, 48.0, 49.3, 52.7, 58.1, 208.2, 209.3, 210.3, 213.1. IR (film): 2920 (s), 2840 (s), 2820 (s), 1690 (m), 1350 (s), 1325 (m) cm^{-1}.

4,8,8-Trimethylbicyclo[4.3.0]-3-nonen-2-one (**3b**) *and 5,8,8-trimethylbicyclo[4.3.0]-4-nonen-3-one* (**4b**). To a solution of the diketone **5b** (985 mg, 5 mmol) in MeOH (40 ml), kept at 5 °C, methanesulfonic acid (240 mg, 2.5 mmol) in MeOH (5 ml) was added dropwise. The reaction mixture was stirred for 10 h, and 10% $NaHCO_3$ (25 ml) was added, followed by the addition of water. Extraction with hexane, drying ($MgSO_4$) and evaporation of the solvent yielded a 12:1 mixture of the isomeric ketones **3b** and **4b**. The isomers were separated by flash chromatography (silica gel, 5% EtOAc in hexane, then 10% in hexane, then 20% EtOAc in hexane followed by EtOAc), yielding 652 mg of **3b** (73%), as a 3:5 *cis/trans* mixture and 35 mg (4%) of **4b** as a mixture of stereoisomers.

trans-**3b**. A solution of the stereoisomeric mixture of **3b** (179 mg, 1 mmol), NaOH (400 mg, 10 mmol) in 20 ml MeOH was stirred until the *cis* isomer could no longer be detected (GLC). The reaction mixture was neutralized with 10% HCl. Extraction with hexane, drying ($MgSO_4$) and evaporation of the solvent yielded 165 mg (92%) of *trans*-**3b**: MS: 178 (95), 163 (77), 122 (55), 109 (33), 82 (100). ^1H NMR (270 MHz, $CDCl_3$): δ 1.05 (s, 3 H), 1.06 (s, 3 H), 1.25–1.35 (m, 1 H), 1.47–1.57 (m, 1 H), 1.66–1.80 (m, 2 H), 1.95 (s, 3 H), 2.05–2.20 (m, 2 H), 2.25–2.39 (m, 1 H), 2.41 (d, *J* 14 Hz, 1 H), 5.83 (s, 1 H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 24.9 (C-12), 32.6, 32.65 (C-10, C-11), 37.7 (C-8), 39.0, 40.4, (C-7, C-9), 44.2 (C-6), 48.2 (C-5), 54.3 (C-1), 127.5 (C-4), 162.3 (C-3), 202.3 (C-2).

cis-**3b**. A solution of the hydroxy ketone **12** (1.25 g, 6.37 mmol) in dry benzene (25 ml) containing a few drops of trifluoroacetic acid was heated under reflux until complete consumption of starting material. Evaporation of solvent followed by flash chromatography (silica gel, petroleum ether–EtOAc 4:1) gave 1.04 g (92%) of *cis*-**3b**. MS: *m/z* 178 (M^+). ^1H NMR (300 MHz, $CDCl_3$): δ 0.97 (s, 6 H), 1.27 (m, 1 H), 1.49 (m, 1 H), 1.62 (m, 1 H), 1.85 (s, 3 H), 1.86–1.95 (m, 1 H), 2.10 (dd, *J* 4.8, 12.9 Hz, 1 H), 2.40 (dd, *J* 4.8, 12.9 Hz, 1 H), 2.55 (m, 2 H), 5.83 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.48 (CH_3), 31.11 (CH_3), 31.15 (CH_3), 33.08 (CH_2), 37.52 (CH), 39.50 (C), 43.18 (CH_2), 46.56 (CH_2), 48.35 (CH), 125.40 (=CH), 159.52 (=C), 201.24 (C=O). IR (film): 2953 (s), 2931 (s), 2867 (s) 1663 (s), 1438 (w), 1384 (w) cm^{-1}.

4b: MS: 176 (100), 163 (95), 146 (50), 133 (60), 91 (35), 77 (20). ^1H NMR (270 MHz, $CDCl_3$): δ 1.02 (s, 3 H), 1.03 (s, 3 H), 1.25 (m, 1 H), 1.49 (m, 1 H), 1.65 (m, 1 H), 1.78–1.84 (m, 1 H), 1.85 (s, 3 H,), 2.20–2.39 (m, 2 H), 2.58–2.70 (m, 2 H) and 5.75 (s, 1 H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 23.1 (C-12), 30.4 (C-11), 30.6 (C-10), 37.3 (C-1), 38.4 (C-8), 40.3 (C-7), 43.8 (C-6), 45.5 (C-9), 46.6 (C-2), 125.2 (C-5), 163.3 (C-4), 199.5 (C-3). IR (film): 2963 (s), 2875 (s), 1672 (s), 1630 (m), 1462 (m), 1440(m), 1381 (m), 1255 (m) cm^{-1}.

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