

Photoinduced Molecular Transformations. Part 155.¹ General Synthesis of Macrocyclic Ketones based on a Ring Expansion involving a Selective β -Scission of Alkoxy Radicals, its Application to a New Synthesis of (\pm)-Isocaryophyllene and (\pm)-Caryophyllene, and a Conformational Analysis of the Two Sesquiterpenes and the Radical Intermediate in the Synthesis by MM3 Calculations

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The method used for a general synthesis of macrocyclic ketones based on a ring expansion involving a selective β -scission of alkoxy radicals devised by Suginome and Yamada was extended and modified. Thus, cycloalkanones was transformed into the corresponding α -(ω -iodoalkyl)-cycloalkanones by alkylation of the corresponding lithium enolates with either 1,3-diiodopropane or 1,4-diiodobutane. Treatment of these α -iodoalkyl cyclic ketones with samarium iodide gave bicyclic tertiary alcohols. The generation of the alkoxy radicals from the bicyclic alcohols by irradiation of the corresponding hypoiodites generated with mercury(II) oxide-iodine-pyridine in benzene resulted in a selective β -scission of their ring-junction bond to give high yields of macrocyclic ketones carrying an iodine which can be removed with tributyltin hydride. The method was then applied to new syntheses of (\pm)-isocaryophyllene and (\pm)-caryophyllene. Thus, ω -iodopropylation of ethyl 7,7-dimethyl-2-oxobicyclo[4.2.0]octane-3-carboxylate, followed by cyclization of the resulting α -(ω -iodoalkyl)cycloalkanone with samarium diiodide, gave *cis-transoid-cis*-ethyl 1-hydroxy-4,4-dimethyltricyclo[6.3.0.0^{2,5}]undecane-8-carboxylate (69%). The ethoxycarbonyl group of this tricyclic alcohol was transformed into a methyl group by the standard method. Irradiation of a solution of the hypoiodite, prepared by the method mentioned above, with Pyrex-filtered light gave the corresponding *cis*-bicyclo[7.2.0]undecenone (15%), its exomethylene isomer (<11%), and rearranged lactones (21%), all arising from cleavage of the ring-fusion bond of the generated alkoxy radical. Basic isomerization of the *cis*-bicycloundecenone to its *trans*-isomer, followed by Wittig methylenation, gave (\pm)-isocaryophyllene. Sensitized photoisomerization of (\pm)-isocaryophyllene in hexane in the presence of methyl benzoate gave (\pm)-caryophyllene.

The populations of conformers of caryophyllene, isocaryophyllene, and several related compounds, including a radical intermediate in the synthesis, were calculated by the empirical force-field method. The relative populations of conformers comprising the radical intermediate generated by β -scission of the ring-junction bond of the alkoxy radicals derived from *cis-transoid-cis*-4,4,8-trimethyltricyclo[6.3.0.0^{2,5}]undecan-1-ol mentioned above were correlated with the three products.

In our previous papers, we have reported that a variety of molecules, including natural products, can be synthesized by methods involving the selective β -scission of alkoxy radicals generated by photolysis of the corresponding hypoiodites as the key step.^{2,3}

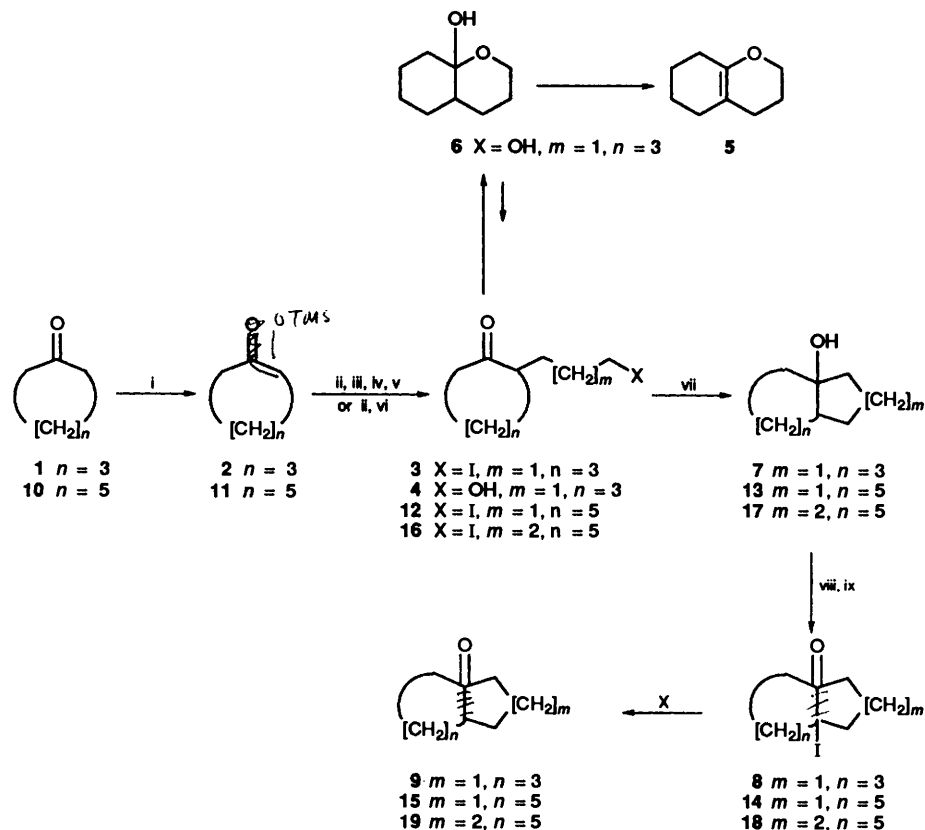
Among these synthetic applications of the β -scission reaction of alkoxy radicals, we showed that medium-sized and macrocyclic ketones, such as muscone,⁴ can generally be synthesized by a three-carbon ring expansion involving a regioselective β -scission of the ring-junction bond of the alkoxy radicals generated from catacondensed bicyclic alcohols.

This paper deals with (a) an extension and modification of a method previously devised by Suginome and Yamada for a three-carbon ring expansion involving selective β -scission of the alkoxy radicals; (b) an application of the method to a new total synthesis of racemic forms of the sesquiterpenes (\pm)-caryophyllene and (\pm)-isocaryophyllene, isolated from many essential oils, especially clove oil, and synthesized by Corey and colleagues;⁵ (c) calculations of the relative free energies and conformer populations of isocaryophyllene, caryophyllene, their regio- and stereo-isomers, the related fused nine-membered cyclic ketones, and a nine-membered radical intermediate in

the synthesis of isocaryophyllene and caryophyllene by an empirical force-field method.

Modified General Synthesis of Macrocyclic Ketones based on a Ring Expansion involving a Selective β -Scission of Alkoxy Radicals.—An investigation concerning an extension and modification of our original method⁴ was undertaken for the synthesis of macrocyclic ketones, consisting of a three-carbon annelation of cyclic ketones and a regioselective cleavage of the ring-junction bond of the alkoxy radicals generated from the resulting bicyclic alcohols. The modified general method for the synthesis of macrocyclic ketones, exemplified by a ring expansion of 6- and 8-membered monocyclic ketones, is outlined in Scheme 1.

Using our original method⁴ we prepared 2-(ω -iodoalkyl)cycloalkanones, such as 2-(3-iodopropyl)cyclohexanone **3**, from an appropriate trimethylsilyl enol ether *via* 2-(ω -hydroxyalkyl)cycloalkanones by a five-step procedure. This multi-step procedure, however, cannot be applied to the preparation of certain 2-(ω -iodoalkyl)cycloalkanones, such as 2-(3-hydroxypropyl)cyclohexanone **4**; the equilibrium between hydroxy ketone form **4** and lactol form **6** lies on the side of the latter, which is readily dehydrated to give a condensed dihydropyran **5**.⁶



Scheme 1 Reagents and conditions: i, Me_3SiCl , Et_3N , DMF; ii, MeLi , DME; iii, $[\text{CH}_2]_3\text{OCH}(\text{OEt})\text{Me}$, THF, HMPA; iv, PPTS, aq. THF; v, TsCl , Py; vi, $[\text{CH}_2]_3\text{I}$ or $[\text{CH}_2]_4\text{I}$, THF, HMPA; vii, SmI_2 , THF, HMPA; viii, HgO , I_2 , Py; ix, $h\nu > 300 \text{ nm}$; x, Bu_3SnH , AIBN, $h\nu$

This multi-step procedure for the preparation of 2-(ω -iodoalkyl)cycloalkanones was therefore modified in the present work. Thus, treatment of cyclohexanone **1** by the standard method⁷ gave the corresponding trimethylsilyl enol ether **2**^a in 77% yield. The enol ether **2** was then transformed into the corresponding lithium enolate by treatment with methyl-lithium.^{7b,8} Reaction of the lithium enolate with 1,3-diiiodopropane in 1,2-dimethoxyethane (DME) gave α -(ω -iodopropyl)-cyclohexanone **3**⁹ in 40% yield. Treatment of this α -iodoalkyl cyclic ketone **3** with samarium iodide^{4,10} in tetrahydrofuran-hexamethylphosphoric triamide (THF-HMPA)¹¹ afforded a bicyclic tertiary alcohol **7**^{9,10} in 68% yield. Treatment of bicyclic alcohol **7** with red mercury(II) oxide-iodine^{12,13} in benzene containing a few drops of pyridine, followed by irradiation with a 100 W high-pressure Hg arc at room temperature, gave an iodo ketone **8** in 76% yield. Irradiation of the iodo ketone **8** with tributyltin hydride in benzene in the presence of azoisobutyronitrile (AIBN) by the standard method gave cyclononanone **9** in excellent yield.

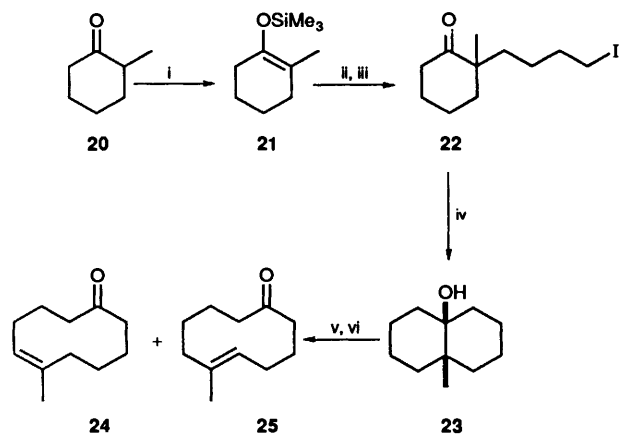
A similar series of reactions was carried out with cyclo-octanone **10**, resulting in a successful ring expansion (Scheme 1); an enolate anion generated from trimethylsilyl enol ether **11** of cyclooctanone was treated with either 1,3-diiiodopropane or 1,4-diiiodobutane to give the corresponding α -(ω -iodoalkyl)cyclo-octanones **12** and **16** in 39 and 31% yield, respectively. These iodides were then transformed into the corresponding bicyclic tertiary alcohols **13** (59%) and **17** (83%). The ring-expansion procedure (as described above) gave the corresponding cyclo-alkyl iodides, **14** (52%) and **18** (65%). Reduction of iodides **14** and **18** with tributyltin hydride-AIBN in benzene gave, respectively, cycloundecanone **15** and cyclododecanone **19** in excellent yield.

These model experiments indicated that the scission of the ring-junction bond is so selective that no product derived from

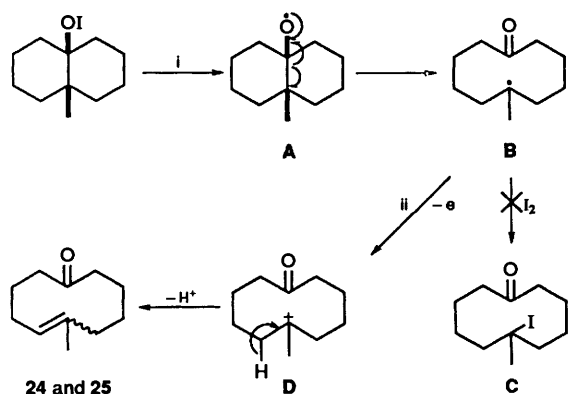
the non-ring-junction bond is formed, and that the method can be applied not only to a three-carbon ring expansion,¹⁴ but also to a four-carbon ring expansion.

We then investigated the effect of an alkyl substituent on the ring-expansion process, as outlined in Scheme 2. Thus, trimethylsilyl enol ether **21**^{7,15} of 2-methylcyclohexanone **20** as a model substrate was transformed into the corresponding α,α -disubstituted cyclohexanone **22**, which was in turn transformed into *cis*-bicyclic alcohol **23** according to Molander's procedure.¹⁰ Treatment of this bicyclic alcohol **23** with mercury(II) oxide-iodine in benzene, followed by photolysis under the conditions mentioned above, gave a mixture of (*Z*)- and (*E*)-6-methylcyclodec-5-enone, **24** and **25**, in 70% yield. The ¹H NMR spectrum of this mixture indicated that the ratio of *Z*- to *E*-isomer was 1:4. No cyclodecyl iodide was formed in this ring expansion, as has been reported in similar reactions of steroidal substrates carried out in the absence of pyridine.^{16,17}

The reactive species and the intermediates involved in hypohalite photochemistry were adequately described elsewhere.^{3,13} The pathway leading to two isomers of 6-methylcyclodec-5-enone (**24/25**) in this alkoxy radical-induced ring expansion is outlined in Scheme 3; alkoxy radical **A** generated from the corresponding hypiodite rearranges to a carbon-centred tertiary radical **B** which is susceptible to a metal-catalysed one-electron oxidation to give the corresponding carbocation **D**. Removal of a proton from the cation **D** gave the observed mixture of geometrical isomers, **24** and **25**, of cycloalkenes. An alternative route from the *tert*-radical **B** to the olefins **24** and **25** would be an E2 elimination of iodide **C** with pyridine as a base. This latter path is, however, very unlikely since: (a) exclusive formation of the olefins also takes place in the absence of pyridine in the photolysis of hypiodites having similar structural features; and (b) simple formation of tertiary carbocation from tertiary carbon-centred radical in the



Scheme 2 Reagents and conditions: i, Me_3SiCl , Et_3N , DMF; ii, MeLi, DME; iii, $\text{I}[\text{CH}_2]_4\text{I}$, THF, HMPA; iv, SmI_2 , THF; v, HgO , I_2 , Py; vi, $h\nu > 300 \text{ nm}$

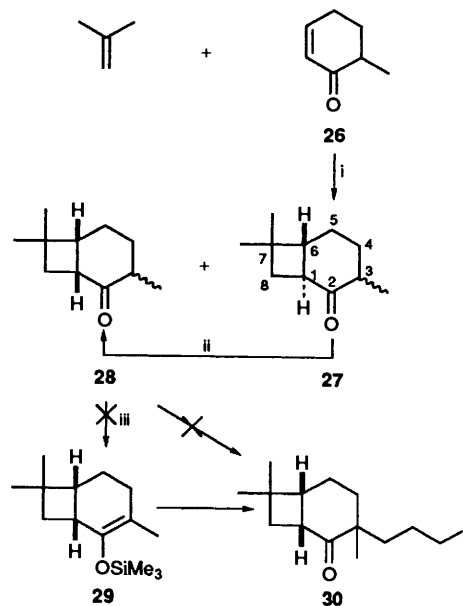


Scheme 3 Reagents and conditions: i, $h\nu$; ii, Hg^{2+}

photolysis of the hypiodites of certain substrates in the presence of an excess of mercury(II) oxide and iodine was confirmed by the formation of characteristic by-products such as formates and lactones^{2,3,18} (see below).

The aforementioned model study concerning the general synthesis of macrocyclic ketones using simple monocyclic ketones indicated that this method is useful for organic synthesis. We thus applied it to a new total synthesis of racemic forms of (\pm)-caryophyllene and (\pm)-isocaryophyllene. These fused nine-membered cyclic molecules were excellent targets in our examination of the scope of our strategy for ring expansion by β -scission of alkoxy radicals.

New Synthesis of (\pm)-Caryophyllene and (\pm)-Isocaryophyllene based on a Three-carbon Ring Expansion involving a Selective β -Scission of Alkoxy Radicals as the Key Step.—In our first approach we attempted the syntheses of (\pm)-caryophyllene and (\pm)-isocaryophyllene via 3-(3-iodopropyl)-3,7,7-trimethylbicyclo[4.2.0]octan-2-one **30**, which corresponds to α -(ω -iodoalkyl)cycloalkanones such as the intermediates **3** and **12** (Scheme 1), as outlined in Scheme 4. Thus, irradiation of 6-methylcyclohex-2-enone **26**, prepared via 4-steps from 2-methylcyclohexanone **20** according to a published procedure,¹⁹ with an excess of isobutene in pentane resulted in regioselective addition to give a mixture of *cis* and *trans* photoadducts, **27** and **28**, in 34% yield. Both the *cis*- and *trans*-fused isomers, **27** and **28**, were shown to be a mixture of two stereoisomers with respect to their methyl group attached to C-3; treatment of the mixture of isomers **27** and **28** with a base gave the more stable isomer **28** to which the *cis* ring-junction is assigned on the basis of an analogy with the result of the photoaddition between cyclohex-2-enone and isobutene.⁵ The ¹H NMR spectrum of



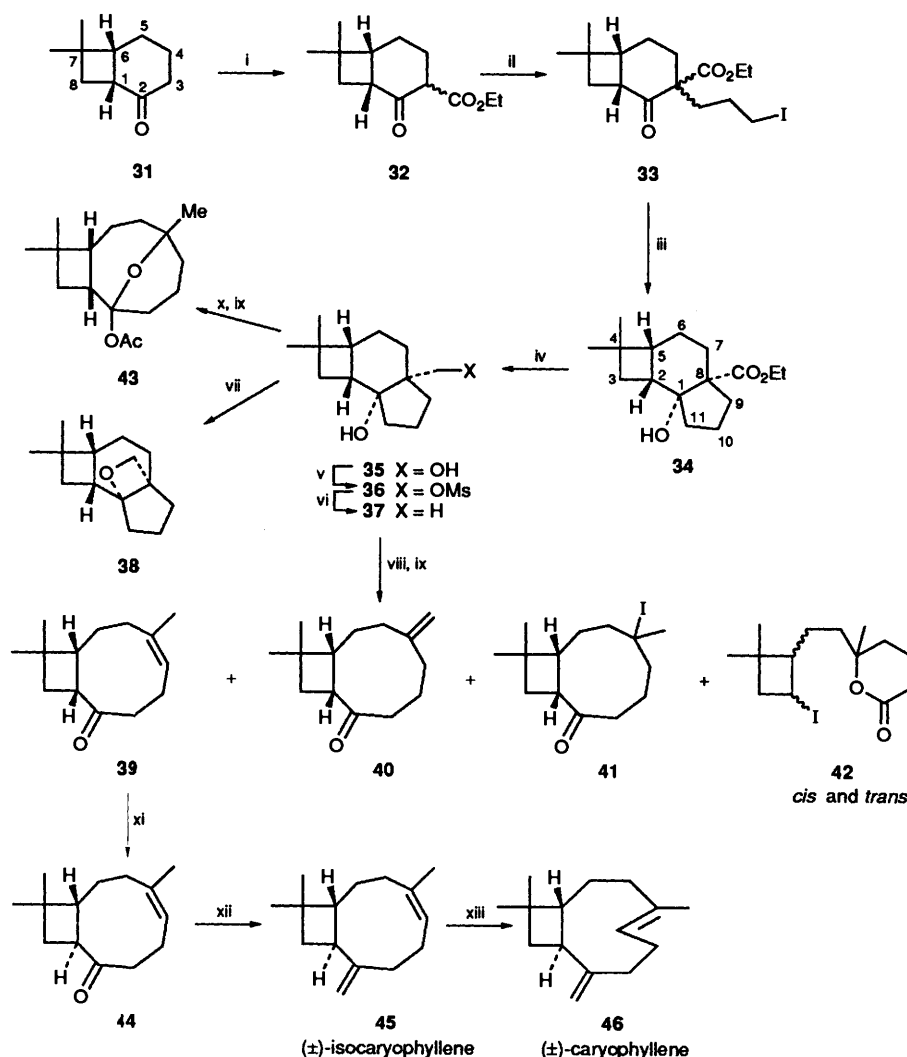
Scheme 4 Reagents and conditions: i, $h\nu$, pentane; ii, aq. KOH, MeOH; iii, Me_3SiCl , Et_3N , DMF

cis-isomer **28** indicated it to be a 1:1 mixture of stereoisomers with respect to C-3 since two doublets (1:1) assignable to their 3-Me were present in the spectrum. Attempted preparation of silyl enol ether **29** by the standard method, however, gave only a complex mixture. Attempted ω -iodoalkylation of bicyclic ketone **28** with 1,3-diiodopropane in the presence of various bases also failed to give the ω -iodoalkyl bicyclic ketone **30**. We therefore abandoned this approach.

An alternative, successful approach to the sesquiterpenes **45** and **46** via the 3-(3-iodopropyl)bicyclo[4.2.0]octan-2-one **33** and 1-hydroxytricyclo[6.3.0.0^{2,5}]undecane **35** is outlined in Scheme 5. Thus, ethoxycarbonylation of the *cis*-bicyclo[4.2.0]octan-2-one **31**, prepared according to the method of Corey,⁵ in 1,4-dioxane with diethyl carbonate containing sodium hydride for 2 h at 80 °C gave a stereoisomeric mixture of ethyl 7,7-dimethyl-2-oxobicyclo[4.2.0]octane-3-carboxylate **32** in 65% yield. ω -Iodopropylation of keto ester **32** in dimethylformamide (DMF) with 1,3-diiodopropane in the presence of NaH for 3 h at room temperature gave a mixture of stereoisomers of ethyl 3-(3-iodopropyl)-7,7-dimethyl-2-oxobicyclo[4.2.0]octane-3-carboxylate **33** in 45% yield.

Cyclization of the 3-(iodopropyl)bicyclo[4.2.0]octan-2-one **33** with samarium diiodide^{4,10} (freshly prepared from powdered samarium and 1,2-diiodoethane) in THF at -20 °C for a few minutes and then at room temperature for 16 h gave ethyl *cis-transoid-cis*-1-hydroxy-4,4-dimethyltricyclo[6.3.0.0^{2,5}]undecane-8-carboxylate **34** as a single tricyclic alcohol in 69% yield. The stereochemical assignment of tricyclic alcohol **34** is based on both the reaction stereochemistry and an NOE measurement of tricyclic alcohol **35** derived from it (*vide infra*). Reduction of the ethoxycarbonyl group of tricyclic alcohol **34** in THF with lithium aluminium hydride at 0 °C for 2 h gave *cis-transoid-cis*-8-hydroxymethyl-4,4-dimethyltricyclo[6.3.0.0^{2,5}]undecan-1-ol **35** in 86% yield. Mesylation of diol **35** in pyridine with methanesulfonyl chloride at 0 °C gave its monomesyl ester **36**, while mesylation at 50 °C resulted in an intramolecular displacement of the initially formed mesyl ester **36** to give an oxetane derivative **38**. Formation of oxetane **38** eventually established the *cis* disposition between the 2-hydroxy and 8-hydroxymethyl groups attached to the tricyclicundecane skeleton **35**.

Reaction of monomesyl compound **36** with lithium triethylboranuide ('Super Hydride') in boiling THF then gave *cis*-4,4,8-



Scheme 5 Reagents and conditions: i, NaH, (EtO)₂CO, 1,4-dioxane; ii, NaH, DMF, 1,3-diiodopropane; iii, SmI₂, THF; iv, LiAlH₄, THF; v, MsCl, Py, 0 °C; vi, LiEt₃BH, THF; vii, MsCl, Py, 50 °C; viii, HgO, I₂, Py; ix, hv; x, Pb(OAc)₄, I₂ or PhI(OAc)₂, I₂; xi, Bu^tOK, Bu^tOH; xii, Ph₃PMe Br⁻, BuLi, Et₂O; xiii, PhCO₂Me, hexane, hv

trimethyltricyclo[6.3.0.0^{2,5}]undecan-1-ol **37** (76% from **35**). Irradiation of the signal due to 2-H in the ¹H NMR spectrum resulted in no enhancement of any of the three signals due to the methyl groups. This result was consistent with the assigned *cis-transoid-cis* stereochemistry.

The formation of the hypiodite of tricyclic alcohol **37** in benzene containing pyridine with yellow mercury(II) oxide and iodine, followed by irradiation of the resulting solution with Pyrex-filtered light generated by a 100 W high-pressure Hg arc lamp for 8 h under nitrogen, gave a fused nine-membered unsaturated cyclic ketone **39** (15%), a mixture of its exomethylene isomer **40** and an iodide **41** (11%), and a 2.5:1 mixture of *cis* and *trans* lactones **42** (21%). The ¹H NMR spectrum of unsaturated cyclic ketone **39** exhibited a signal at δ 5.23 assignable to the olefinic 5-H. The *Z* geometry of the double bond was determined by NOE measurements; irradiation of the signal at δ 5.23 resulted in an enhancement of the signal at δ 1.62 (3 H, 6-Me) and *vice versa*.

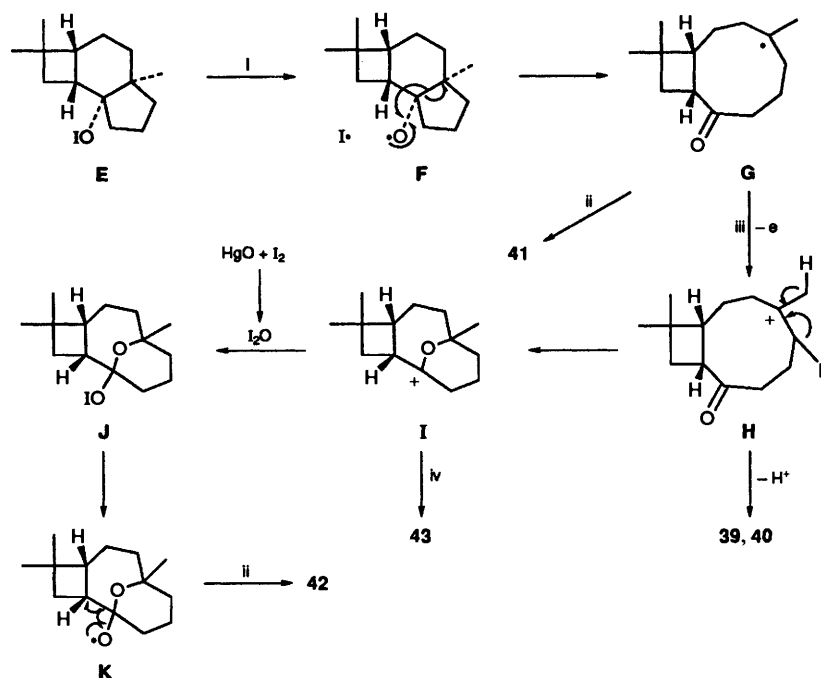
The structures of the mixture of products **40** and **41** were assigned on the basis of the spectral results and from consideration of the pathway for their formation; the IR spectrum exhibited a band assignable to the unstrained carbonyl groups. The mass spectrum of the mixture exhibited two peaks, at *m/z* 206 and 334, which correspond to the molecular-ion peaks of products **40** and **41**. The ¹H NMR spectrum showed the presence of signals assignable to the

exomethylene protons of product **40** and the absence of any signal due to protons attached to the carbon carrying the iodine.

The structure of lactones **42** was also assigned on the basis of an analysis of their spectra and from consideration of the pathway for their formation;^{1,2,3,18} mass spectrometry showed the compounds to have the molecular formula C₁₄H₂₃IO₂. The product exhibited a band assignable to a lactone-type carbonyl in the IR spectrum. The ¹H NMR spectrum showed two signals (2.5:1) at δ 4.71 (dt) and 4.01 (q) assignable to the protons attached to the cyclobutane carbons carrying the iodine²⁰ of the two stereoisomeric lactones **42**. Details of the analysis are described in the Experimental section.

We also tried this ring expansion under several different conditions and reagents; the ring expansion using red mercury(II) oxide instead of the yellow form gave a lower yield of the nine-membered cyclic ketone **39** (7%) together with its exomethylene isomer **40** (6%) and lactones **42** (15%), while a ring expansion in the absence of pyridine, using either yellow or red mercury(II) oxide, gave only lactones **42** in 38 and 35% yield, respectively. An attempted ring expansion with lead tetraacetate resulted in the formation of an intractable mixture.

Ring expansion by a hypiodite reaction with lead tetraacetate-iodine reagent^{3,21} gave no nine-membered ketone **39** but a product for which we tentatively assign an epoxide structure **43** on the basis of an analysis of the spectra and the mechanism of formation. It showed the molecular-ion peak at



Scheme 6 Reagents and conditions: i, $h\nu$; ii, I_2 ; iii, Hg^{2+} ; iv, AcOH

m/z 266 in the mass spectrum. The IR spectrum exhibited a band assignable to OAc but no band attributable to a nine-membered cyclic ketone. The ring expansion with (diacetoxyiodo)benzene-iodine reagent²² in benzene also gave the product **43** as the only isolable product.

Treatment of the *cis*-fused nine-membered cyclic ketone **39** with a base, to give its *trans*-fused isomer **44**, as reported by Corey and colleagues,⁵ and subsequent treatment of the resultant cyclic ketone **44** with methyltriphenylphosphonium bromide and butyllithium, gave (\pm)-isocaryophyllene **45**, the ¹H NMR spectrum of which was in agreement with the reported one.²³ Moreover it showed a GLC retention time the same as that of (–)-isocaryophyllene obtained by thermal isomerization of (–)-caryophyllene in the presence of selenium.²⁴

The final step, the transformation of (\pm)-isocaryophyllene **45** into (\pm)-caryophyllene **46**, was achieved by a sensitized photoisomerization; irradiation of a solution of (\pm)-isocaryophyllene in hexane in the presence of methyl benzoate²⁵ as a singlet sensitizer with a 100 W high-pressure Hg arc gave a mixture of *Z*-**45** and *E*-isomer **46**. Separation of the mixture by preparative TLC (PLC) on silica gel containing silver nitrate, with (5:1) hexane–ethyl acetate as the solvent, gave (\pm)-caryophyllene in 24% (conversion) yield; the spectral and GLC properties were identical with those of natural caryophyllene.

The photochemical isomerization of caryophyllene into the more stable (*vide infra*) isocaryophyllene has already been reported.^{26,27} As far as we are aware, however, this reverse photochemical isomerization has never been reported, and the present phototransformation represents the first achievement of this.

Scheme 6 outlines the paths leading to products **39**, **40**, **41** and **42**. As expected, the highly selective cleavage of the ring-fusion bond of alkoxy radical **F** generated from hypoiodite **E** takes place to give a nine-membered cyclic radical **G**. Part of the cation **H** generated from a one-electron oxidation of radical **G**, however, is trapped by the carbonyl oxygen to give a bridged cation **I**. The cation **I** then reacts with excess of I_2O , which is the reactive species produced by a reaction of HgO and I_2 , to give a second hypoiodite **J**. Although I_2O is an unisolable species, its formation from HgO and I_2 is certain since isolable Br_2O is produced by an analogous reaction of HgO and

Br_2 .²⁸ Photoreaction of the hypoiodite **J** finally gives lactones **42** via hemiketal radical **K**. We have reported numerous examples^{1,2,18} of reactions analogous to this formation of the lactone. The epoxide **43**, a major product in the attempted ring expansion when $\text{PhI}(\text{OAc})_2$ or $\text{Pb}(\text{OAc})_4\text{-I}_2$ reagent is used to generate the hypoiodites, should be produced by a reaction of cation **I** with acetic acid present in the solution. One of the conformers which comprised the nine-membered radical **G** or cation **H** is assumed to be such that it allows a transannular combination between the carbocation and carbonyl oxygen of intermediate **H**.

A conformational analysis of intermediate **G** by molecular mechanics calculations (as described below) supported this assumption.

Relative Free Energies and Conformer Populations of Fused Nine-membered Cyclic Ketones 39 and 40, and Their Isomers Calculated by Means of an Empirical Force-field Method (MM3/Conflex).^{29,30}—As described in the previous part, photolysis of a solution of the hypoiodite of the 1-hydroxytricyclo[undecane **37** gave the *cis*-bicyclo[7.2.0]undecenone **39**, its exomethylene isomer **40**, iodide **41**, and rearranged lactones **42**, all arising from the common intermediate **G** generated by cleavage of the ring-junction bond of the alkoxy radical **F** (Scheme 6). No regioisomeric nine-membered cyclic ketone **47** was formed in this β -scission reaction. These results aroused our interest as to whether product **39** is more stable than its isomer **47**, which was not formed. The experiment described above also showed that *cis*-fused product **39** is isomerized to the corresponding *trans*-fused isomer **44** by treatment with a base.⁵ We thus investigated the relative stabilities of fused tricyclo[7.2.0]undecenones **39**, **40**, **44**, and their isomers **47** and **48** by means of empirical force-field calculations. Table I summarizes the results of our calculations (MM3/Conflex) of the relative energies as well as all of the conformer populations of these fused nine-membered cyclic ketones. Table I indicates that there is one principal conformer, **39a**, (85.2%) for product **39**, while there are two major conformers, **40a** (87.3%) and **40b** (10.7%), for product **40**.

Comparisons of the averages of the relative free energies of all the conformers of products **39** and **40** and the regioisomer **47**

Table 1 Relative free energies and conformer populations of fused nine-membered cyclic ketones, **39** and **40**, and their isomers **44–48** calculated by MM3/Conflex

Compound or structure	Conformer	Rel. free energy (kcal mol ⁻¹) ^a	Population (%)	
39	a	3.041	85.24	
	b	4.652	5.63	
	c	4.720	5.02	
	d	5.162	2.38	
	e	5.659	1.03	
	f	6.234	0.39	
	g	6.463	0.27	
	h	7.977	0.02	
		Av.	3.313	Total 99.98
	40	a	8.423	87.26
		b	9.670	10.66
		c	10.991	1.15
		d	11.354	0.62
e		11.874	0.26	
f		13.007	0.04	
g		13.645	0.01	
		Av.	8.612	Total 100.00
44	a	0.844	82.32	
	b	1.986	12.00	
	c	2.538	4.73	
	d	3.491	0.95	
	Av.	1.085	Total 100.00	
47	a	0.000	61.38	
	b	0.279	38.34	
	c	3.434	0.19	
	d	3.999	0.07	
	e	5.411	0.01	
	f	5.420	0.01	
	Av.	0.117	Total 100.00	
48	a	0.946	92.07	
	b	2.756	4.35	
	c	3.082	2.51	
	d	3.697	0.89	
	e	4.957	0.11	
	f	5.609	0.04	
	g	5.935	0.02	
	h	6.238	0.01	
	Av.	1.109	Total 100.00	

^a 1 cal = 4.184 J.**Table 2** Relative free energies and conformer population of the intermediate **G** in the β -scission of alkoxy radical **F** calculated by MM3/Conflex

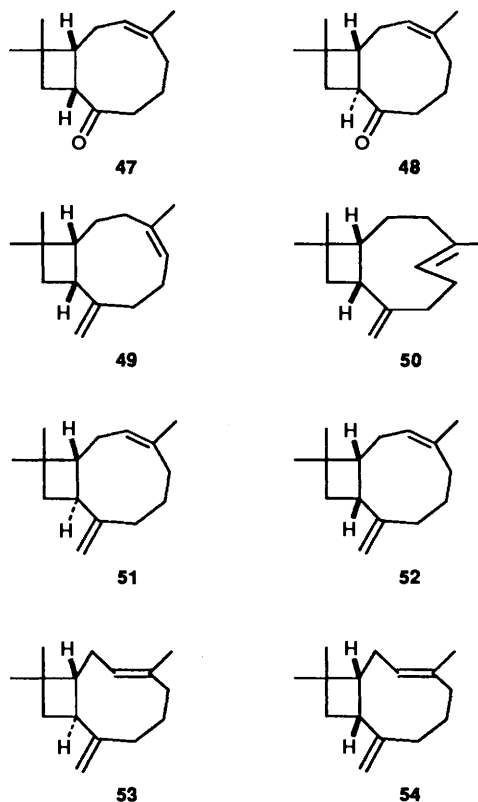
Compound or structure	Conformer	Rel. free energy (kcal mol ⁻¹) ^a	Population (%)
Intermediate G	a	10.664	54.02
	b	10.806	42.52
	c	12.727	1.67
	d	12.927	1.19
	e	13.677	0.34
	f	14.135	0.16
	g	14.322	0.11
	Av.	10.802	Total 100.01

^a 1 cal = 4.184 J.

(which is not formed in the reaction) indicate that products **39** and **40** are 3.20 and 8.50 kcal mol⁻¹* less stable than the regioisomer **47**, respectively. This result may imply that the removal of a proton from the cationic intermediate **H** (Scheme 6) to give products **39** and **40** is a kinetically controlled reaction.

The calculations also indicated that *cis*-fused product **39**

arising from the ring expansion was less stable than the *trans*-fused isomer **44** obtainable by its treatment with base. The result of the calculations was thus in agreement with that from the reaction described above; the average of the relative free energies of the conformers of product **39** was shown to be 2.23 kcal mol⁻¹ less stable than that of the isomer **44** obtained by the base treatment.



Correlation between the Conformer Population of a Nine-membered Radical Intermediate G arising from a β -Scission of the Alkoxy Radical F generated from cis-transoid-cis-4,4,8-Trimethyltricyclo[6.3.0.0^{2,5}]undecan-1-ol 37 calculated by an Empirical Force-field Method.—As described earlier in this paper, the highly selective cleavage of the ring-junction bond of alkoxy radical **F**, which is a key step in the present synthesis, takes place to afford a nine-membered radical **G** (Scheme 6). The radical intermediate **G** affords four products: **39**, **40**, **41** and **42**. The formation of these products was assumed to depend upon the populations of the conformers of the nine-membered cation **H**. While the MM3 program has not yet been implemented with the parameters for cations, it has been parametrized for alkyl radicals, which are known to behave like sp²-hybridized carbon.³¹ Structural information obtained for radical **G** may thus apply to cation **H** as well, although it would be desirable to calculate carbocation **H** rather than radical **G**. We therefore calculated the conformer populations of radical **G** by a force-field method (MM3/Conflex). The calculations indicated that radical **G** involves two principal conformers, **G_a** and **G_b**, in 54.0 and 42.5% (Table 2). ORTEP stereodrawings of these two major conformers are shown in Fig. 1. Calculations indicated that the distance between C(6) and carbonyl oxygen in the most stable conformer **G_a** was 3.057 Å, while the corresponding distance in conformer **G_b** was 3.820 Å. Thus, a transannular reaction between carbonyl oxygen and the C(6) radical or cation may readily take place in conformer **G_a** to give by-product **42** while the preferred reaction path of the

* 1 cal = 4.184 J.

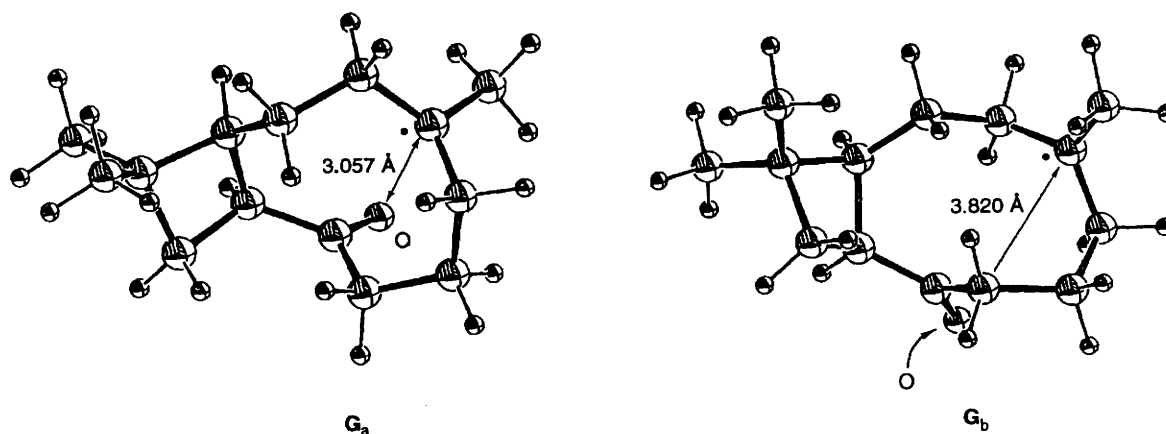


Fig. 1 ORTEP drawings of two major conformers G_a and G_b of an enantiomer of 9-membered radical intermediate G calculated by MM3/Conflex

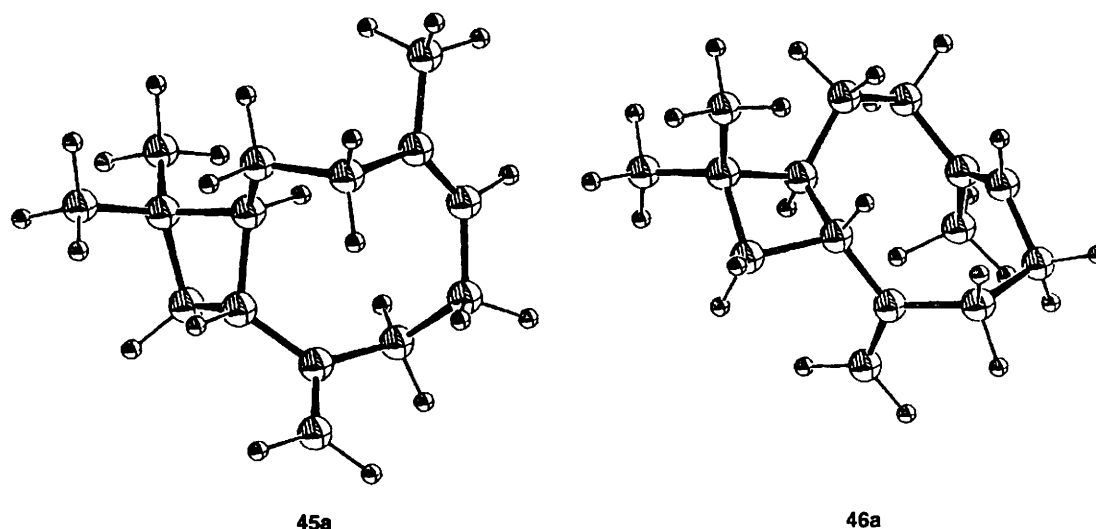


Fig. 2 ORTEP drawings of the most stable conformers $45a$ and $46a$ of isocaryophyllene 45 and caryophyllene 46 calculated by MM3/Conflex

conformer G_b would be the kinetic removal of a proton to give the observed nine-membered ketones, 39 and 40 . We nevertheless refrain from discussing the mechanism of the formation of crucial product 39 in great detail in view of the potential role of cationic charge in the deprotonation reaction.

Relative Free Energies and Conformer Populations of the Two Sesquiterpenes, 45 and 46, and the Related Isomers calculated by an Empirical Force-field Method.—Calculation of the relative free energy of the populated conformers in (\pm)-isocaryophyllene 45 and (\pm)-caryophyllene 46 indicated that there are three major conformers for each of the two sesquiterpenes, as shown in Table 3. Fig. 2 shows ORTEP stereodrawings of the most stable conformers of the enantiomers of isocaryophyllene and caryophyllene. Comparison of the averages of the free energies of all the populated conformers of the two sesquiterpenes 45 and 46 indicates that (\pm)-isocaryophyllene is $3.24 \text{ kcal mol}^{-1}$ more stable than (\pm)-caryophyllene.

We also calculated the relative free energies and conformer populations of the six stereo- and regio-isomers 49 – 54 of sesquiterpenes 45 and 46 . The results shown in Table 3 are summarized below: (a) isocaryophyllene 45 and caryophyllene 46 are 0.96 and $3.93 \text{ kcal mol}^{-1}$ more stable than their *cis*-fused isomers, 49 and 50 , respectively; (b) isocaryophyllene 45 is $3.47 \text{ kcal mol}^{-1}$ less stable than its regioisomer 51 , while caryophyllene 46 has nearly the same stability as its regioisomer 53 ; (c) comparisons of the relative free energies of two pairs of isomers of isocaryophyllene and caryophyllene, (i) regioisomer

51 of isocaryophyllene 45 and its *cis*-fused isomer 52 , (ii) regioisomer 53 of caryophyllene 46 and its *cis*-fused isomer 54 , showed that the *cis*-fused isomers 52 and 54 were 1.68 and $0.72 \text{ kcal mol}^{-1}$ less stable than their *trans*-fused isomer, respectively.

Experimental

M.p.s were determined with a Yanagimoto micro m.p. apparatus and are uncorrected. IR spectra were determined for Nujol mulls with a JASCO IR 810 infrared spectrophotometer (unless stated otherwise). ^1H NMR spectra were determined in CDCl_3 (SiMe_4 as internal reference) with a Hitachi R90 FT-NMR spectrometer operating at 90 MHz , or with a JEOL JNM-JX 270 high-resolution spectrometer operating at 270 MHz , or with JEOL JNM-EX 400 FT high-resolution spectrometer operating at 400 MHz . J -Values are in Hz. High- and low-resolution mass spectra were recorded with a JEOL JMS-DX 300 spectrometer (70 eV) at the Faculty of Pharmaceutical Sciences of this University. GLC was carried out with a Hitachi 263-50 Gas Chromatograph using a Tokyo Kasei 'quadrex' Bonded Fused Capillary Column, Methyl Silicone, OV-1, 25 m . PLC was carried out on Merck silica gel 60 PF_{254} (Art 7747). Column chromatography was carried out with Merck silica gel 60 (Art 7734). All photoreactions, except the photoaddition of the enone 26 , were carried out with a 100 W high-pressure Hg arc lamp (EIKOSH, PIH-100). The photoaddition of the enone 26 was carried out with a 500 W high-pressure Hg arc lamp (EIKOSHA, PIH-5005-HPL-3).

Table 3 Relative free energies and conformer population of isocaryophyllene, 45, caryophyllene 46, and their six stereo- and regioisomers 49–54

Compound or structure	Conformer	Rel. free energy kcal mol ⁻¹ ^a	Population (%)
45	a	3.131	39.51
	b	3.444	23.31
	c	3.696	15.24
	d	4.043	8.49
	e	4.183	6.70
	f	4.404	4.62
	g	4.933	1.89
	h	6.139	0.25
	Av.	3.536	Total 100.01
46	a	6.607	43.29
	b	6.750	40.19
	c	7.280	16.44
	d	10.817	0.04
	e	11.359	0.02
	f	12.018	0.01
	Av.	6.775	Total 99.99
49	a	4.332	71.76
	b	4.891	27.96
	c	8.000	0.15
	d	8.386	0.08
	e	8.837	0.04
	f	9.201	0.02
	Av.	4.498	Total 100.01
50	a	10.617	94.73
	b	12.333	5.25
	c	15.590	0.02
	Av.	10.707	Total 100.00
51	a	0.000	97.74
	b	2.658	1.11
	c	2.887	0.75
	d	3.450	0.29
	e	4.489	0.05
	f	4.504	0.05
	Av.	0.064	Total 99.99
52	a	1.636	95.73
	b	3.901	2.10
	c	4.073	1.57
	d	4.684	0.56
	e	6.819	0.02
	f	7.238	0.01
	Av.	1.740	Total 99.99
53	a	7.025	81.82
	b	8.165	11.97
	c	8.604	5.71
	d	10.595	0.20
	e	10.714	0.16
	f	10.965	0.11
	g	11.694	0.03
	Av.	7.268	Total 100.00
54	a	7.967	99.14
	b	10.883	0.73
	c	11.993	0.11
	d	13.429	0.01
	e	13.493	0.01
	Av.	7.992	Total 100.00

^a 1 cal = 4.184 J.

Trimethylsilyl Enol Ether 2⁷ of Cyclohexanone 1.—To a solution of cyclohexanone 1 (5.0 g, 51 mmol) in DMF (25 cm³) were added triethylamine (20.8 cm³, 150 mmol) and trimethylsilyl chloride (8.9 cm³, 70 mmol) under nitrogen. The solution was heated under reflux for 12 h and then cooled to room temperature. The solution was then filtered to remove crystals, which were washed with diethyl ether. The filtrate and washings were combined and the combined solution was washed with 5% aq. sodium hydrogen carbonate. The solution was then made slightly acidic by addition of 5% hydrochloric acid and was washed successively with 5% aq. sodium hydrogen carbonate

solution and brine, and dried over anhydrous sodium sulfate. Removal of the solvent gave a crude silyl enol ether. Distillation of the enol ether under reduced pressure gave pure material 2 (6.7 g, 77%), b.p. 60–62 °C/15 mmHg (lit.,⁷ 74–75 °C/20 mmHg); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 1669 (C=C); $\delta(90 \text{ MHz})$ 0.17 (9 H, s, SiMe₃), 1.1–2.1 (8 H, m) and 4.86 (1 H, br s, =CH).

2-(3-Iodopropyl)cyclohexanone 3.—To a solution of enol ether 2 (200 mg, 1.17 mmol) in DME (2 cm³) at –20 °C was added methyllithium (1.4 mol dm⁻³ diethyl ether solution; 10 cm³). The solution was stirred for 1 h at 0 °C and the solvent was removed under reduced pressure. To the residue were added THF (2 cm³) and HMPA (0.5 cm³). To this solution was added dropwise 1,3-diiodopropane (346 mg, 1.17 mmol). The solution was stirred for 5 h at room temperature and diluted with diethyl ether. The solution was then washed successively with water and brine, and dried over anhydrous sodium sulfate. Removal of the solvent gave an oily product (417 mg), which was subjected to PLC [(6:1) hexane–ethyl acetate] to give 2-(3-iodopropyl)cyclohexanone 3 (124 mg, 40%) as an oil, $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 1709; $\delta(270 \text{ MHz})$ 1.2–2.2 (10 H, m), 2.2–2.45 (3 H, m) and 3.14–3.22 (2 H, m, CH₂I); m/z 267 [(M + 1)⁺, 2] and 139 [(M – I)⁺, 100%] (Found: M⁺, 266.0154. C₉H₁₅IO requires M, 266.0168).

Bicyclo[4.3.0]nonan-1-ol 7.—A solution of 1,2-diiodoethane (211 mg, 0.75 mmol) in THF (10 cm³) was added dropwise to samarium metal (225 mg, 1.50 mmol). The solution was stirred for 1 h at room temperature. To this blue-coloured solution were added HMPA (0.3 cm³) and then dropwise a solution of 2-(3-iodopropyl)cyclohexanone 3 (100 mg, 0.37 mmol) in THF (0.5 cm³). The solution was stirred for 5 h and diluted with diethyl ether. To the solution was added 5% hydrochloric acid until all the crystals disappeared. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The organic layer and the ether extracts were combined. The combined solution was neutralized (universal indicator) with 5% sodium hydrogen carbonate and washed successively with 5% aq. sodium thiosulfate, water, and brine, and then dried over anhydrous sodium sulfate. Removal of the solvent gave a crude oily product (50 mg), which was subjected to PLC [(6:1) hexane–ethyl acetate] to give bicyclo[4.3.0]nonan-1-ol 7 (36 mg, 68%), m.p. 54–56 °C (from MeOH); $\nu_{\max}(\text{CHCl}_3)/\text{cm}^{-1}$ 3290 (OH); $\delta(90 \text{ MHz})$ 1.1–2.2 (15 H, m); m/z 140 (M⁺, 29), 123 (8), 111 (83) and 98 (100%).

Ring Expansion by Photolysis of Bicyclo[4.3.0]nonan-1-ol Hypoiodite in Benzene in the Presence of Red Mercury(II) Oxide–Iodine.—To a solution of bicyclononanol 7 (20 mg, 0.14 mmol) in benzene (5 cm³)–pyridine (0.03 cm³) was added red mercury(II) oxide (61 mg, 0.28 mmol) under nitrogen. The solution was irradiated for 1.5 h with a 100 W high-pressure Hg arc. All the starting material was consumed by this time. The solution was filtered, and the filtrate was washed successively with 5% aq. sodium thiosulfate, water, and brine, and was then dried over anhydrous sodium sulfate. Removal of the solvent gave an oily product (36 mg), which was subjected to PLC [(3:1) hexane–ethyl acetate] to give 5-iodocyclononane 8 (29 mg, 76%), $\nu_{\max}/\text{cm}^{-1}$ 1700 (C=O); $\delta(270 \text{ MHz})$ 1.4–2.1 (8 H, m), 2.2–2.7 (6 H, m) and 4.37 (1 H, quint, J 6.14, CHI); m/z 267 [(M + 1)⁺, 2], 139 [(M + I)⁺, 32], 121 (88) and 41 (100%) (Found: M⁺, 266.0139. C₉H₁₅IO requires M, 266.0168).

Cyclononane 9.—To a solution of iodocycloalkane 8 (50 mg, 0.19 mmol), obtained as mentioned above, in benzene (3 cm³) in a Pyrex vessel were added tributyltin hydride (0.1 cm³, 0.34 mmol) and AIBN (3 mg) under nitrogen. The solution was irradiated with a 100 W Hg arc for 30 min. The solvent was then evaporated to give a residue, which was

dissolved in diethyl ether. To the stirred solution was added 10% aq. KF for 2 h. The organic layer was washed successively with water and brine, and dried over anhydrous sodium sulfate. Removal of the solvent gave the cycloalkane **9** (30 mg), which was purified by PLC [(3:1) hexane–ethyl acetate] to give cyclononane **9** (23 mg, 87%), which was identical with a commercial material.

Trimethylsilyl Enol Ether 11 of Cyclooctanone 10.—To a solution of cyclooctanone **10** (5.0 g, 40 mmol) in DMF (40 cm³) were added triethylamine (22 cm³, 159 mmol) and trimethylsilyl chloride (10 cm³, 79 mmol) under nitrogen. The solution was heated under reflux for 48 h, and was worked up as described for the preparation of enol ether **2** to give crude product **11**. This was purified by distillation under reduced pressure to give enol ether **11**, b.p. 54–56 °C/2 mmHg; $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 1663 (C=C); δ (270 MHz) 0.18 (9 H, s, SiMe₃), 1.4–1.7 (8 H, m), 1.9–2.3 (4 H, m) and 4.74 (1 H, t, *J* 8.4, =CH).

2-(3-Iodopropyl)cyclooctanone 12.—To a solution of enol ether **11** (2.0 g, 10.1 mmol) in DME (10 cm³) at –20 °C was added methyllithium (1.4 mol dm⁻³ diethyl ether solution; 8.66 cm³). The solution was stirred for 1 h and the solvent was evaporated off under reduced pressure. To the residue were added THF (20 cm³) and HMPA (4 cm³). To this solution was added a solution of 1,3-diiodopropane (3.0 g, 10.1 mmol) in THF (2 cm³) dropwise. The solution was stirred for 2 h at room temperature and was then diluted with diethyl ether. The solution was then worked up by the usual method. The crude oily product (3.28 g) was subjected to column chromatography [silica gel (80 g); (9:1) hexane–ethyl acetate] to give pure 2-substituted cyclooctanone **12** (1.158 g, 39%) as an oil, $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 1700 (C=O); δ (270 MHz) 1.3–2.1 (14 H, m), 2.25–2.7 (3 H, m) and 3.08–3.22 (2 H, m, CH₂I); *m/z* 295 [(M + 1)⁺, 6] and 167 [(M – I)⁺, 100%] (Found: M⁺, 294.0454. C₁₁H₁₉IO requires M, 294.0481).

2-(4-Iodobutyl)cyclooctanone 16.—To a solution of enol ether **11** (2.0 g, 10.1 mmol) in DME (10 cm³) at –20 °C was added methyllithium (1.4 mol dm⁻³ diethyl ether solution; 7.94 cm³). The solution was stirred for 1 h at 0 °C and the solvent was removed. To the residue were added THF (20 cm³) and HMPA (4 cm³) and then, dropwise, 1,4-diiodobutane (2.82 g, 9.1 mmol). The solution was stirred for 5 h at room temperature and was then diluted with diethyl ether. The solution was worked up in the usual manner to give a crude oily product (3.84 g). It was subjected to column chromatography [silica gel (80 g); (9:1) hexane–ethyl acetate] to give the oily 2-substituted cyclooctanone **16** (965 mg, 31%), $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 1700 (C=O); δ (270 MHz) 1.1–2.1 (16 H, m), 2.3–2.7 (3 H, m) and 3.16 (2 H, dt, *J* 1.7 and 6.9, CH₂I); *m/z* 308 (M⁺, 4), 181 [(M – I)⁺, 22], 126 (91), 98 (84) and 55 (100%) (Found: M⁺, 308.0610. C₁₂H₂₁IO requires M, 308.0637).

Bicyclo[6.3.0]undecan-1-ol 13.—A solution of 1,2-diiodoethane (384 mg, 1.36 mmol) in THF (20 cm³) was added dropwise to samarium metal (4.08 mg, 2.71 mmol). The solution was stirred for 1 h at room temperature. To this blue-coloured solution were added HMPA (0.1 cm³) and 2-(3-iodopropyl)cyclooctanone **12** (200 mg, 0.68 mmol) dropwise. The solution was stirred for 5 h, treated with diethyl ether (15 cm³) and saturated aq. potassium carbonate (10 cm³), and stirred. The aqueous layer was then extracted with diethyl ether and the combined organic layers were worked up by the usual method to give an oily product. The product was subjected to PLC [(5:1) hexane–ethyl acetate] to give pure bicyclo[6.3.0]undecan-1-ol **13** (67 mg, 59%), $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3392 (OH); δ (270 MHz) 1.25–1.95 (17 H, m), 2.16 (1 H, t, *J* 6.3) and 2.29 (1 H, t, *J*

6.3); *m/z* 168 (M⁺, 25), 150 (3), 139 (15), 125 (76) and 111 (100%) (Found: M⁺, 168.1530. C₁₁H₂₀O requires M, 168.1514).

Bicyclo[6.4.0]dodecan-1-ol 17.—A solution of 1,2-diiodoethane (180 mg, 0.64 mmol) in THF (10 cm³) was added dropwise to samarium metal (192 mg, 1.28 mmol). The solution was stirred for 1 h at room temperature. To this blue-coloured solution were added HMPA (0.1 cm³) and, dropwise, the 2-substituted cyclooctanone **16** (100 mg, 0.32 mmol). The solution was stirred for 12 h and was then diluted with diethyl ether. To the solution was added 5% hydrochloric acid until all the solid dissolved. The organic layer was worked up as described for the preparation of bicyclononanol **7**. The oily product (113 mg) was subjected to PLC [(5:1) hexane–ethyl acetate] to give bicyclo[6.4.0]dodecan-1-ol **17** (49 mg, 83%), $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3468 (OH); δ 1.0–1.9 (21 H, m); *m/z* 182 (M⁺, 36), 139 (25), 125 (17) and 111 (100%) (Found: M⁺, 182.1693. C₁₂H₂₂O requires M, 182.1671).

Ring Expansion by the Photolysis of the Hypiodite of Bicyclo[6.3.0]undecan-1-ol 13 in Benzene in the Presence of Red Mercury(II) Oxide–Iodine.—To a solution of bicycloundecanol **13** (45 mg, 0.27 mmol) in benzene (5 cm³)–pyridine (0.03 cm³) were added red mercury(II) oxide (117 mg, 0.54 mmol) and iodine (137 mg, 0.54 mmol) under nitrogen. The solution was irradiated for 2 h with a 100 W high-pressure Hg arc. All the starting alcohol disappeared by this time. The solution was filtered and the filtrate was worked up as described for the ring expansion of bicyclo[4.3.0]nonan-1-ol **7** to give a crude product, which was subjected to PLC [(5:1) hexane–ethyl acetate] to give an oily 5-iodocycloundecanone **14** (41 mg, 52%), $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 1703 (C=O); δ 1.2–2.2 (14 H, m), 2.4–2.7 (4 H, m) and 4.26 (1 H, quint, *J* 6.6, CHI); *m/z* 295 [(M + 1)⁺, 1], 167 [(M – I)⁺, 94], 149 (59) and 67 (100%) (Found: M⁺, 295.0564. C₁₁H₂₀IO requires M, 295.0559).

Ring Expansion by the Photolysis of the Hypiodite of Bicyclo[6.4.0]dodecan-1-ol 17 in Benzene in the Presence of Red Mercury(II) Oxide–Iodine.—The ring expansion of bicyclododecanol **17** (48 mg, 0.26 mmol) in benzene (5 cm³) in the presence of pyridine (0.03 cm³), red mercury(II) oxide (113 mg, 0.52 mmol) and iodine (132 mg, 0.52 mmol) was carried out as described for that of bicycloundecanol **13**. Product **18** (53 mg, 65%) was an oil, $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 1702 (C=O); δ (270 MHz) 1.2–2.1 (16 H, m), 2.3–2.7 (4 H, m) and 4.27 (1 H, dt, *J* 14.2 and 5.3); *m/z* 309 [(M + 1)⁺, 1], 181 [(M – I)⁺, 95], 163 (23) and 55 (100%) (Found: M⁺, 308.0607. C₁₂H₂₁IO requires M, 308.0637).

Cycloundecanone 15.—A solution of 5-iodocycloundecanone **14** (36 mg, 0.12 mmol) in benzene (3 cm³) in the presence of tributyltin hydride (0.07 cm³, 0.24 mmol) and AIBN (3 mg) under nitrogen was irradiated for 30 min and the solution was worked up as described for the reduction of 5-iodocyclononane **8**, to give a crude ketone (35 mg). This oil was purified by PLC [(3:1) hexane–ethyl acetate] to give cycloundecanone **15** (18 mg, 88%), which was identical with an authentic specimen.

Cyclododecanone 19.—A solution of 5-iodocyclododecanone **18** (50 mg, 0.16 mmol) in benzene (3 cm³) in the presence of tributyltin hydride (0.1 cm³, 0.34 mmol) and AIBN (3 mg) under nitrogen was irradiated for 30 min as described above. The solution was worked up as described for the preparation of cycloundecanone **15**, to give cyclododecanone **19** (21 mg, 71%), which was identical with an authentic sample.

Trimethylsilyl Enol Ether 21^{7,15} of 2-Methylcyclohexanone 20.—This trimethylsilyl enol ether was prepared by heating 2-

methylcyclohexanone **20** (5.0 g, 45 mmol) in DMF (25 cm³) with triethylamine (9 cm³, 71 mmol) and trimethylsilyl chloride (9 cm³, 71 mmol) under reflux for 13 h. The solution was worked up as described for the preparation of trimethylsilyl enol ether **2** of cyclohexanone. The crude product was purified by vacuum distillation (7.41 g, 90%), b.p. 70–72 °C/15 mmHg (lit.,¹² 82–84 °C/16 mmHg); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 1661 (C=C); δ 0.16 (9 H, s, SiMe₃), 1.02 (3 H, d, *J* 6.6) and 1.2–2.4 (8 H, m). This ¹H NMR spectrum also exhibited a triplet (*J* 3.3) ascribable to a contaminating few percent of the regioisomer. This enol ether **21** was, however, used for the next step immediately.

2-(4-Iodobutyl)-2-methylcyclohexanone 22.—To a solution of the enol ether **21** (1.00 g, 5.43 mmol) in DME (10 cm³) at –20 °C was added methyl lithium (1.4 mol dm⁻³ diethyl ether solution; 3.9 cm³). The solution was stirred for 1 h at 0 °C and the solvent was then removed to give a residue, which was dissolved in THF (10 cm³) and HMPA (5 cm³). To this solution was added dropwise 1,4-diiodobutane (1.68 g, 5.43 mmol) at 0 °C. The solution was then stirred for 12 h at room temperature, and diluted with diethyl ether. The solution was worked up as described for the preparation of α -substituted cyclohexanone **3** to give a crude product (1.52 g), which was then subjected to PLC [(7:1) hexane–ethyl acetate] to give 2,2-disubstituted cyclohexanone **22** (400 mg, 25%) as an oil, $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 1705 (C=O); δ (90 MHz) 1.07 (3 H, s, Me), 1.2–2.0 (12 H, m), 2.2–2.5 (2 H, m) and 3.18 (2 H, t, *J* 6.8, CH₂I).

6-Methylbicyclo[4.4.0]dodecan-1-ol 23.—A solution of 1,2-diiodoethane (772 mg, 2.74 mmol) in THF (5 cm³) was added dropwise to samarium metal (536 mg, 3.57 mmol). The solution was stirred for 2 h at room temperature. To this blue-coloured solution was added dropwise 2-(4-iodobutyl)-2-methylcyclohexanone **22** (350 mg, 1.19 mmol). The solution was stirred for 20 h and then diluted with diethyl ether before being worked up as described for the preparation of bicyclononanol **7** to give crude bicyclic alkanol **23** (248 mg). The crude product was subjected to PLC [(5:1) hexane–ethyl acetate] to give 6-methylbicyclododecan-1-ol **23** (54 mg, 27%), $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 2924 (OH); δ (90 MHz) 0.97 (3 H, s, Me) and 1.0–2.0 (16 H, m); *m/z* 168 (M⁺, 7) and 112 (100%).

Ring Expansion by the Photolysis of 6-Methylbicyclo[4.4.0]dodecan-1-ol Hypoiodite in Benzene in the Presence of Red Mercury(II) Oxide–Iodine.—To a solution of methylbicyclododecanol **23** (50 mg, 0.30 mmol) in benzene (6 cm³) were added pyridine (0.1 cm³), red mercury(II) oxide (194 mg, 0.90 mmol) and iodine (229 mg, 0.90 mmol) under nitrogen. The solution was irradiated for 2 h, diluted with diethyl ether, and worked up as described for the ring expansion of bicyclononanol **7** to give a crude product (58 mg), which was subjected to PLC [(5:1) hexane–ethyl acetate] to give a 1:4 mixture of (*Z*)- and (*E*)-6-methylcyclodec-5-enones **24** and **25** (34 mg, 70%) as an oil, δ (270 MHz) 1.72 (3 H, s, =CMe, *E*), and 4.92 and 5.02 (1 H, br m, =CH *E*); and 1.66 (3 H, s, =CMe) and 5.14 (1 H, t, *J* 8.9, =CH).

6-Methylcyclohex-2-enone 26.¹⁶—This α,β -unsaturated monocyclic ketone was prepared from 2-methylcyclohexanone according to a published procedure *via* three-steps; a kinetic silyl enolate anion^{7,15} generated from 2-methylcyclohexanone was brominated to give 6-bromo-2-methylcyclohexanone which was dehydrobrominated with lithium carbonate¹⁶ to afford the cyclohexenone **26**.

[2 + 2] **Photoaddition of 6-Methylcyclohex-2-enone 26 with Isobutene**.—A solution of isobutene (~3 g) in pentane (40 cm³) was flushed with nitrogen. To this solution was added 6-methyl-

cyclohex-2-enone **26** (300 mg, 2.73 mmol). The solution was irradiated for 8 h under nitrogen. Removal of the solvent and excess of isobutene gave an oily product (625 mg), which was subjected to PLC to give two oily fractions. The more mobile fraction (79 mg) was a mixture of olefinic ketones. The less mobile fraction (184 mg, 34%) was a mixture of the cycloadducts **27** and **28**. Treatment of this mixture with 4% methanolic potassium hydroxide gave a mixture of *cisoid*- and *transoid*-methyl isomers of the *cis*-fused adducts **28**, $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 1716 (C=O); δ (400 MHz) 0.958 and 1.097 (each 3 H, each s, 7,7-*gem*-dimethyl of isomer A), 0.976 and 1.171 (each 3 H, each s, 7,7-*gem*-dimethyl of isomer B), 1.079 (3 H, d, *J* 7.3, 3-Me of isomer A), 1.087 (3 H, d, *J* 7.3, 3-Me of isomer B), 1.3–2.2 (m), 2.30–2.42 (3 H, m), 2.60–2.68 (1 H, m), 2.89 (1 H, dt, *J* 5.9 and 9.8), and 2.99 (1 H, q, *J* 9.3). The ratio of isomer A to B was 1:1; *m/z* 166 (M⁺, 19), 151 [(M – Me)⁺, 6.1] and 111 (100%). Trimethylsilyl enolation of this photoadduct by the standard method gave only an intractable mixture.

cis-7,7-Dimethylbicyclo[4.2.0]octan-2-one 31.—A solution of isobutene (100 cm³) and cyclohex-2-enone (15.0 g) in pentane (100 cm³) at 20 °C under nitrogen was irradiated for 24 h with 100 W high-pressure Hg arc. After removal of the solvent and excess of isobutene by evaporation, the residue was distilled under vacuum to remove excess of cyclohexenone (10.2 g), to leave an oily product, which was subjected to column chromatography [silica gel (100 g); (20:1) hexane–ethyl acetate] to give a 4:1 mixture of *cis*- and *trans*-bicyclooctanes, $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 1704 (C=O); δ_{H} (270 MHz) 1.07 and 1.16 (each 3 H, each s, *gem*-dimethyl of *trans*-isomer) and 0.98 and 1.16 (each 3 H, each s, *gem*-dimethyl of *cis*-isomer).

The mixture of *cis*-**31** and its *trans*-isomer (4.62 g) obtained as mentioned above was dissolved in methanolic 4% potassium hydroxide. The solution was stirred for 14 h at room temperature and neutralized (universal indicator) by addition of 5% hydrochloric acid. After removal of the solvent, the residue was extracted with diethyl ether. The extract was washed successively with water and brine, and dried over anhydrous Na₂SO₄. Removal of the solvent gave an oil, which was distilled under vacuum to give pure *cis*-isomer **31** (4.53 g, 98%), b.p. 47–49 °C/0.3 mmHg (lit.,⁵ 56–58.5 °C/1.1 mmHg); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 1704 (C=O); δ_{H} (270 MHz) 0.98 and 1.16 (each 3 H, each s, *gem*-dimethyl), 1.6–2.1 (6 H, m), 2.32–2.38 (2 H, m), 2.43 (1 H, q, *J* 7.9) and 3.01 (1 H, dt, *J* 8.6 and 8.9); *m/z* 152 (M⁺, 25), 137 (7), 124 (4), 109 (8) and 97 (100%).

Ethyl 7,7-Dimethyl-2-oxobicyclo[4.2.0]octane-3-carboxylate 32.—To a suspension of sodium hydride (60%; 1.58 g) and diethyl carbonate (4.67 g) in 1,4-dioxane at 80 °C under nitrogen was added the bicyclooctan-2-one **31** (3.00 g) during the course of 1 h. The solution was stirred for 2 h at 80 °C and was then cooled to 0 °C. Aq. acetic acid was added until the solution became weakly acidic (universal indicator), and the solvent was then removed. Water was added to the residue and the mixture was extracted with diethyl ether. The extract was washed successively with 5% aq. sodium hydrogen carbonate, water, and brine, and dried over anhydrous Na₂SO₄. Removal of the solvent gave an oily product (4.1 g), which was distilled under reduced pressure to afford *keto ester* **32** (2.87 g, 65%), b.p. 75–79 °C/0.2 mmHg; $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 1743 (CO₂Et) and 1713 (C=O); *m/z* 224 (M⁺, 16), 179 (8), 168 (100), 139 (22) and 122 (81%) (Found: M⁺, 224.1408. C₁₃H₂₀O₃ requires M, 224.1412).

Ethyl 3-(3-Iodopropyl)-7,7-dimethyl-2-oxobicyclo[4.2.0]octane-3-carboxylate 33.—To a suspended solution of sodium hydride (60%; 0.53 g, 13.2 mmol) in DMF (30 cm³) was added dropwise a solution of *keto ester* **32** (2.68 g, 12.0 mmol) in DMF

(10 cm³) during the course of 30 min, under nitrogen. The solution was stirred for 1 h, and then 1,3-diiodopropane (3.90 g, 13.2 mmol) was added dropwise; the solution was stirred for 2 h at room temperature, and then neutralized with aq. acetic acid. The solution was then diluted with water, and extracted with diethyl ether. The extract was washed successively with water and brine, and dried over anhydrous Na₂SO₄. Removal of the solvent gave an oily product (5.42 g), which was subjected to column chromatography [silica gel (100 g); (10:1) hexane-ethyl acetate] to give *iodide 33* (2.11 g, 45%), $\nu_{\max}/\text{cm}^{-1}$ 1733 (CO₂Et) and 1704 (C=O); δ_{H} (270 MHz) 0.98 and 1.16 (each 3 H, each s, *gem*-dimethyl), 1.28 and 1.29 (3 H, each t, *J* 7.3), 1.5–2.7 (11 H, m), 2.95–3.10 (1 H, m), 3.15 (2 H, t, *J* 5.6) and 4.21 and 4.22 (2 H, each q, *J* 7.3); *m/z* 392 (M⁺, 16), 337 (20), 319 (21), 291 (16), 265 (61), 209 (47) and 68 (100) (Found: M⁺, 392.0851. C₁₆H₂₅IO₃ requires M, 392.0849).

Ethyl cis-transoid-cis-1-Hydroxy-4,4-dimethyltricyclo[6.3.0.0^{2,5}]undecane-8-carboxylate 34.—1,2-Diiodoethane (839 mg, 2.98 mmol) as a solution in THF (5 cm³) was added dropwise to samarium metal (40 mesh; 596 mg, 3.96 mmol) under argon at room temperature. The solution was stirred for 3 h at room temperature. To this blue-coloured solution was added dropwise a solution of the bicyclooctan-2-one **33** (518 mg, 1.32 mmol) in THF (1 cm³) at –20 °C. The solution was stirred for 16 h at room temperature, and then saturated aq. sodium carbonate was added. The solution was then stirred and extracted with diethyl ether. The extract was washed successively with water and brine, and dried over anhydrous Na₂SO₄. Removal of the solvent gave an oily product (352 mg), which was purified by PLC [(6:1) hexane-ethyl acetate] to give oily *tricyclic alcohol 34* (241 mg, 69%), $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3493 (OH) and 1704 (CO₂Et); δ_{H} (270 MHz) 0.89 and 1.17 (each 3 H, each s, *gem*-dimethyl), 1.30 (3 H, t, *J* 7.3, CH₂Me), 1.3–2.1 (12 H, m), 2.2–2.35 (1 H, m), 2.63 (1 H, dt, *J* 11.2 and 8.3) and 4.22 (2 H, q, *J* 7.3, CH₂Me); *m/z* 266 (M⁺, 4), 248 [(M – H₂O)⁺, 8], 210 (16), 193 (47), 167 (62) and 119 (100%) (Found: M⁺, 266.1902. C₁₆H₂₆O₃ requires M, 266.1882).

cis-transoid-cis-8-Hydroxymethyl-4,4-dimethyltricyclo[6.3.0.0^{2,5}]undecan-1-ol 35.—To lithium aluminium hydride (121 mg, 3.2 mmol) in THF (10 cm³) under nitrogen at 0 °C was added dropwise a solution of tricyclic ester **34** (850 mg, 3.2 mmol) in THF (3 cm³). The solution was stirred at 0 °C for 2 h, and diluted with diethyl ether. The solution was then treated with saturated aq. sodium thiosulfate and stirred. The organic layer was then washed successively with water and brine, and dried over anhydrous sodium sulfate. Removal of the solvent gave a crude diol (874 mg), which was subjected to PLC [(3:1) hexane-ethyl acetate] to give pure *diol 35* (615 mg, 86%), $\nu_{\max}/\text{cm}^{-1}$ 3310 (OH); δ_{H} (270 MHz) 0.98 and 1.17 (each 3 H, each s, *gem*-dimethyl), 1.5–2.0 (13 H, m), 2.63 (1 H, dd, *J* 10.1 and 8.9) and 3.62 and 3.67 (2 H, ABq, *J* 10.9, CH₂OH); *m/z* 224 (M⁺, 1), 206 [(M – H₂O)⁺, 8], 191 (10), 175 (10), 168 (27), 163 (15), 150 (63) and 137 (100%) (Found: M⁺, 224.1756. C₁₄H₂₄O₂ requires M, 224.1776).

(cis-transoid-cis-1-Hydroxy-4,4-dimethyltricyclo[6.3.0.0^{2,5}]undecan-8-yl)methyl Methanesulfonate 36.—To a solution of diol **35** (312 mg, 1.39 mmol) in pyridine (3 cm³) at 0 °C was added dropwise methanesulfonyl chloride (0.13 cm³, 1.67 mmol). After the solution had been stirred for 2 h, water was added. The solution was then extracted with diethyl ether. The organic layer was washed successively with 5% hydrochloric acid, 5% aq. sodium carbonate, water, and brine, and dried over anhydrous sodium sulfate. Removal of the solvent gave crude mesylester **36** (444 mg), δ_{H} (90 MHz) 0.99 and 1.18 (each 3 H, each s, *gem*-dimethyl), 1.5–2.6 (14 H, m), 3.02 (3 H, s, SO₂Me)

and 4.26 and 4.52 (2 H, ABq, *J* 10.8, CH₂OMs). This mesylester was immediately subjected to the next step.

An oxetane derivative **38** was obtained when the mesylation described above was carried out at 50 °C; for compound **38**, δ 1.03 and 1.18 (each 3 H, each s, *gem*-dimethyl), 1.2–2.3 (14 H, m), 4.20 (1 H, d, *J* 5.9) and 4.37 (1 H, dd, *J* 5.9 and 1.3); *m/z* 206 (M⁺, 11), 191 (23), 163 (26), 151 (63), 150 (70) and 41 (100%).

cis-transoid-cis-4,4,8-Trimethyltricyclo[6.3.0.0^{2,5}]undecan-1-ol 37.—To a solution of mesylester **36** (444 mg) in THF (5 cm³) under nitrogen at 0 °C was added dropwise lithium triethylboranuide (1 mol dm⁻³ THF solution; 8.82 cm³). The solution was heated under reflux for 3 h and then diluted with diethyl ether. To the solution were added successively water, 2 mol dm⁻³ aq. sodium hydroxide (2 cm³) and aq. hydrogen peroxide (33%; 3 cm³) in small portions. The organic layer was then separated. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed successively with water and brine, and dried over anhydrous sodium sulfate. Removal of the solvent gave an oily product (455 mg), which was subjected to PLC [(5:1) hexane-ethyl acetate] to give *tricyclic alcohol 37* (220 mg, 76% from diol **35**), $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3480 (OH); δ_{H} (270 MHz) 0.97, 1.14 and 1.18 (each 3 H, each s, 3 × Me), 1.25–2.0 (13 H, m) and 2.60 (1 H, dt, *J* 10.9 and 8.3); *m/z* 208 (M⁺, 0.4), 140 [(M – H₂O)⁺, 8], 152 (7.6), 137 (36) and 109 (100%) (Found: M⁺, 208.1833. C₁₄H₂₄O requires M, 208.1827).

Ring Expansion of Tricyclic tert-Alcohol 37 by the Photolysis of its Hypoiodite.—(a) *In the presence of yellow mercury(II) oxide-iodine*.—(a) *In the presence of yellow mercury(II) oxide-iodine*. To a stirred solution of tricyclic alcohol **37** (100 mg, 0.48 mmol) in benzene (10 cm³) were added yellow mercury(II) oxide (311 mg, 1.44 mmol), iodine (366 mg, 1.44 mmol) and pyridine (0.1 cm³). The stirred solution was then irradiated under nitrogen for 8 h with Pyrex-filtered light generated by a 100 W high-pressure Hg arc lamp. The solution was then filtered, and the filtrate was washed successively with 5% aq. sodium thiosulfate, water and brine, and dried over anhydrous sodium sulfate. Removal of the solvent gave a product mixture (87 mg), which was subjected to PLC [(5:1) hexane-ethyl acetate] to give three fractions, A (15 mg, 15%), B (11 mg, 11%), and C (21 mg, 21%) in order of their mobility on TLC.

Fraction A was the nine-membered product **39**, $\nu_{\max}/\text{cm}^{-1}$ 1704 (C=O); δ_{H} (270 MHz) 0.97 and 1.15 (each 3 H, each s, *gem*-dimethyl), 1.62 (3 H, s, C=CMe), 1.4–2.55 (11 H, m), 3.33 (1 H, dt, *J* 10.2 and 8.3) and 5.23 (1 H, dd, *J* 10.4 and 5.9); *m/z* 206 (M⁺, 42), 191 (14), 150 (53), 135 (84) and 122 (100%) (Found: M⁺, 206.1650. C₁₄H₂₂O requires M, 206.1671).

Fraction B was a mixture of products **40** and **41**, $\nu_{\max}/\text{cm}^{-1}$ 1704 (C=O); δ_{H} (270 MHz) 0.98 and 1.22 (each 3 H, each s, *gem*-dimethyl), 3.12–3.24 (1 H, m) and 4.90 and 4.94 (each 1 H, each s, C=CH₂); *m/z* 334 (M⁺, 0.1), 206 (M⁺, 23), 188 (41), 150 (58) and 132 (100%) (Found for **40**, M⁺, 206.1659. C₁₄H₂₂O requires M, 206.1671).

Fraction C was a mixture of lactones **42a** and **42b**, $\nu_{\max}/\text{cm}^{-1}$ 1719 (lactones C=O); δ_{H} (270 MHz) 1.06, 1.23 and 1.42 (each 3 H, each s, 3 × Me of major isomer) and 4.71 (1 H, dt, *J* 7.8 and 4.9, CHI of major isomer); and 0.99, 1.18 and 1.37 (each 3 H, each s, 3 × Me of minor isomer) and 4.01 (1 H, q, *J* 8.9, CHI of minor isomer); *m/z* 223 [(M – I)⁺, 11], 167 (15) and 95 (100%). The ratio of **42a**:**42b** was 2.5:1 (Found: M⁺, 350.074 36. C₁₄H₂₃IO₂ requires M, 350.074 39).

(b) *In the presence of lead tetraacetate-iodine*. To a stirred solution of tricyclic alcohol **37** (26 mg, 0.13 mmol) in benzene (5 cm³) were added lead tetraacetate (186 mg, 0.38 mmol) and iodine (96 mg, 0.38 mmol). The stirred solution was then irradiated for 2 h with Pyrex-filtered light under nitrogen. The

solution was then filtered and the filtrate was washed successively with 5% aq. sodium thiosulfate, water and brine, and dried over anhydrous sodium sulfate. Removal of the solvent gave an oily product mixture, which was subjected to PLC [(5:1) hexane-ethyl acetate] to give product **43** (17 mg, 52%), $\nu_{\max}/\text{cm}^{-1}$ 1734 (OAc); δ_{H} 0.94, 1.15 and 1.29 (each 3 H, each s, $3 \times \text{Me}$), 1.99 (3 H, s, Ac) and 3.0–3.4 (1 H, m); m/z 266 (M^+ , 1), 207 [($\text{M} - \text{OAc}$) $^+$, 15], 151 (27) and 43 (100%).

(c) *In the presence of (diacetoxyiodo)benzene-iodine.* Photolysis of tricyclic alcohol **37** in the presence of (diacetoxyiodo)benzene-iodine for 2 h gave product **43** in 60% yield.

Synthesis of (\pm)-Isocaryophyllene 45.—To a solution of nine-membered ketone **39** (25 mg, 0.12 mmol), obtained as mentioned above, in *tert*-butyl alcohol (1 cm^3) at 40 °C under nitrogen was added potassium *tert*-butoxide (15 mg, 0.13 mmol). The solution was stirred for 48 h. After removal of the solvent, water was added to the residue. The solution was then extracted with diethyl ether. The extract was washed successively with water and brine, and dried over anhydrous sodium sulfate. Removal of the solvent gave crude *trans*-bicyclic ketone **44** [$\nu_{\max}/\text{cm}^{-1}$ 1704; δ_{H} (90 MHz) 1.03 and 1.19 (each 3 H, each s, *gem*-dimethyl), 1.55 (3 H, s, C=CMe) and 5.15–5.30 (1 H, br m)].

To a solution of butyllithium (1.6 mol dm^{-3} hexane solution; 0.06 cm^3) in diethyl ether (2 cm^3) under nitrogen at room temperature was added methyl triphenylphosphonium bromide (35 mg, 0.097 mmol) in small portions. The solution was stirred for 2 h. To the solution was added a solution of *trans*-bicyclic ketone **44** (20 mg, 0.097 mmol) in diethyl ether (1 cm^3) at room temperature. The solution was stirred for 16 h. After the addition of water, the solution was extracted with diethyl ether. The organic layer was washed successively with water and brine, and dried over anhydrous sodium sulfate. Removal of the solvent gave a crude oily product, which was subjected to PLC (hexane) to give (\pm)-isocaryophyllene **45** (6 mg, 30%), δ_{H} (270 MHz) 0.98 and 1.00 (each 3 H, each s, *gem*-dimethyl), 1.67 (3 H, s, C=CMe), 1.4–2.3 (m), 2.53 (1 H, q, *J* 9.2), 4.76 (1 H, d, *J* 2.0), 4.84 (1 H, d, *J* 2.0) and 5.23 (1 H, dd, *J* 7.9 and 7.3) [lit.,²³ 0.98 and 1.00 (each s), 1.66 (br s), 4.65–4.83 (2 H, m) and 5.20 (br m)].

(\pm)-Caryophyllene **46.**—A solution of (\pm)-isocaryophyllene **45** (100 mg, 0.49 mmol) in hexane (10 cm^3) containing methyl benzoate (7 mg, 0.05 mmol) in a quartz tube was irradiated with a 100 W Hg arc for 65 h at room temperature. The solvent was then removed to give a residue, which was subjected to PLC on silica gel coated with silver nitrate [(5:1) hexane-ethyl acetate] to give (\pm)-caryophyllene **46** (10 mg, 10%) as an oil, δ_{H} (270 MHz) 0.97 and 1.00 (each 3 H, each s, *gem*-dimethyl) 1.61 (3 H, s, C=CMe), 1.4–2.6 (m), 4.82–4.94 (each 1 H, each s, C=CH₂) and 5.31 (1 H, br dd, *J* 9.9 and 4.3). IR, ¹H NMR and mass spectra of this product were identical with those of authentic caryophyllene. (\pm)-Isocaryophyllene **45** (32 mg) was recovered unchanged.

Calculations by the MM3 (92) Program.—MM3 (92) Program²⁹ package was obtained from Technical Utilization Corporation, 235 Glen Village Court, Powell, OH 43065 USA, under licence agreements, and run on an HP 9000/750 workstation operating under the HP-UX system. Conformational isomers arising from differing ring structures were automatically generated by the Confex program³⁰ which uses MM3 as the geometry optimizer. Conformer distributions were obtained in the free-energy term by including vibrational analysis and temperature effects. The present results should be distinguished from the previous enthalpic results obtained by conventional molecular mechanics. For example, previously reported conformer distributions of caryophyllene based on

$\Delta H_{\text{f}}^{\text{calc}}/\text{MM2}^{32}$ may have to be revised in the light of the present results.

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