Efficient Formation of a Spirotetrahydrofuran Ring by the *Ionic* Cyclization of Bishomoallyl Tertiary Alcohols *via* their Hypoiodites

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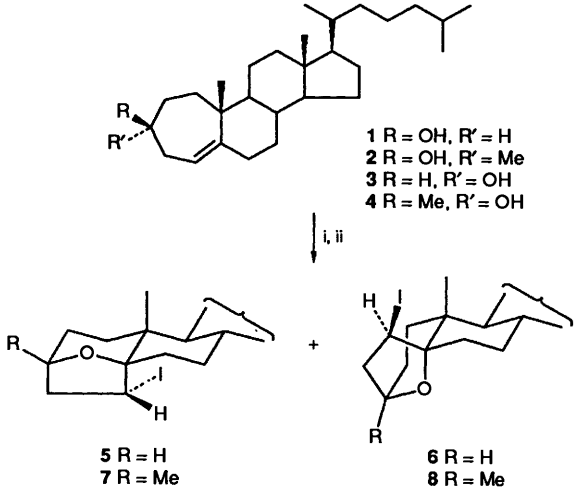
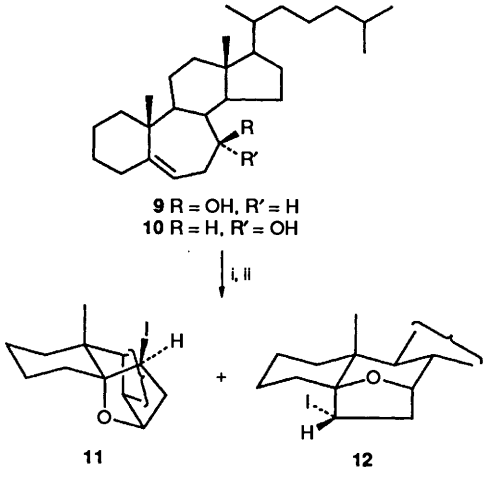
Spirotetrahydrofuran derivatives are produced in high yields by an intramolecular cyclization of several steroidal bishomoallyl tertiary alcohols in benzene containing mercury(II) oxide and iodine at room temperature in the dark. 2-Hydroxy-2-(but-3-enyl)tetrahydrofuran thus cyclizes to give a mixture of the corresponding diastereoisomeric spirotetrahydrofurans in the dark.

An ionic mechanism for the formation of the tetrahydrofuran ring, which involves the formation of the hypoiodite followed by the cyclization of its iodonium ion, is proposed based on studies concerning several model substrates.

In previous papers concerned with the reactions of alkoxyl radicals we reported that the alkoxyl radicals generated from hypoiodites of some steroidal seven-membered cyclic homoallyl alcohols resulted in the formation of tetrahydrofuran rings in preference to products from β-scission of the alkoxyl radicals.[1,2] Thus, photoinduced reactions of the hypoiodites of steroidal cyclic homoallyl alcohols **1**–**4**,[1] such as 4a-homocholest-4a-en-3-ols[1] and 7a-homocholest-5-en-7a-ols **9** and **10**,[2] prepared *in situ* with mercury(II) oxide and iodine in benzene, gave bridged oxasteroids **5**–**8**, **11** and **12** almost exclusively (Schemes 1 and 2).

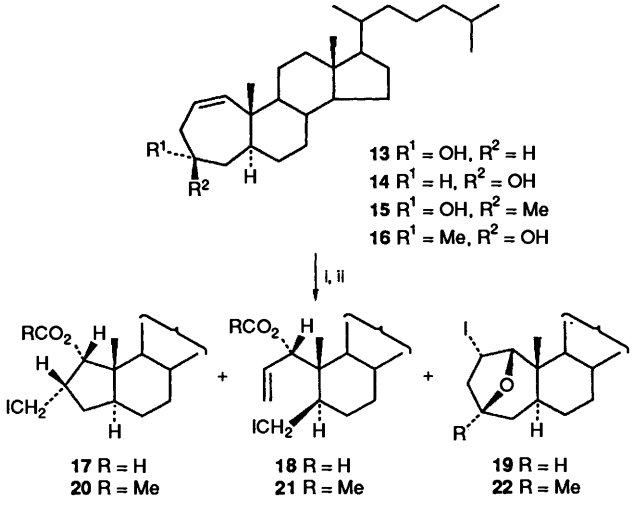


Scheme 1 *Reagents and conditions:* i, $HgO–I_2$, benzene; ii, *hv*



Scheme 2 *Reagents and conditions:* i, $HgO–I_2$, benzene; ii, *hv*

On the other hand, the principal reactions of 4a-homo-5α-cholest-1-en-4-ols **13** and **14** and their 4-methyl derivatives, **15** and **16**, under the same conditions as those mentioned above were found to be β-scissions in preference to the additions;[3] photoinduced reactions of the hypoiodite of 4a-homo-5α-cholest-1-en-4α-ol **13** and its 4-methyl derivative **15** gave a pair of products, **17** and **18** or **20** and **21**, respectively, arising from a β-scission exclusively; reactions of their 4β-isomers, **14** and **16**, however, gave products **17**, **18**, **20** and **21**, arising from a β-scission, along with bridged oxasteroids **19** and **22** arising from intramolecular additions (Scheme 3).[3] The formation of



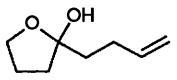
Scheme 3 *Reagents and conditions:* i, $HgO–I_2$, benzene; ii, *hv*

tetrahydrofuran derivatives was also reported to be an exclusive reaction of the hypoiodites of monocyclic unsaturated alcohols, such as cyclohex-3-enols.[4]

At that time we thought that these tetrahydrofuran derivatives arose from an intramolecular addition of alkoxyl radicals.

In connection with these studies regarding the intramolecular addition *vs.* β-scission of the alkoxyl radicals generated from cyclic homoallyl alcohol hypoiodites we were intrigued by a recent paper by Kraus and Thurston,[5] who reported that a *single* diastereoisomer of spirotetrahydrofuran **24** can be obtained upon irradiation of the hypoiodite of an unsaturated alcohol **23** in benzene containing mercury(II) oxide and iodine.

If their claim is correct, it would imply that the intramolecular radical addition in this system is a very fast process, since we had previously found that irradiation of the hypoiodites of similar lactols in the steroid series, such as compound **25** in benzene, resulted in a ready β-scission to give iodo formate **26**;[6]



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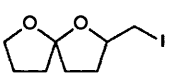

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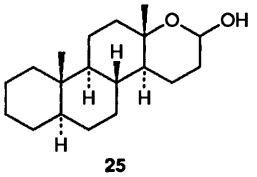

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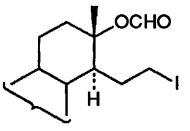


26 (*cf.* 30)

β-scission of the alkoxyl radical generated from the hypoiodite of the bishomoallyl tertiary alcohol **23** should therefore be even faster.

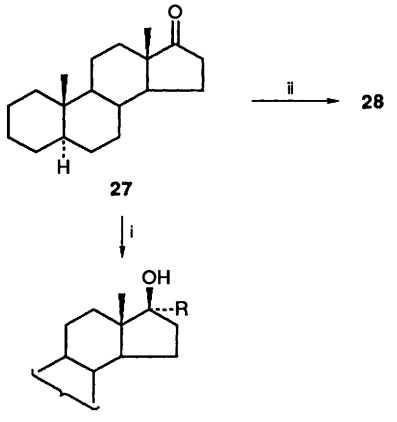
We therefore decided to examine whether the formation of spirotetrahydrofurans in preference to the β-scission products is general in alkoxyl radicals generated from bishomoallyl alcohols, where the β-scission of alkoxyl radicals is assumed to be especially easy, using several model substrates, including the unsaturated alcohol **23**.[5]

We have found that spirotetrahydrofuran derivatives are generally formed from homoallyl alcohol hypoiodites prepared *in situ* with excess of mercury(II) oxide and iodine in benzene *via* an *ionic process without light*, and that spirotetrahydrofuran derivatives (produced from bishomoallyl alcohol hypoiodites which are very susceptible to β-scission upon generation of the corresponding alkoxyl radical) are formed *via* this *ionic addition*, but not *via* the radical addition, as has been claimed by Kraus and Thurston.[5] We report here our results in full.

Results

Preparation of a Model Substrate for Testing the Formation of Spirotetrahydrofurans vs. β-*Scission of Alkoxyl Species.*—We have chosen 17α-(but-3-enyl)-5α-androstan-17β-ol **28** for examining the intramolecular addition *vs.* a β-scission, since the photoinduced reaction of the hypoiodite of the parent 5α-androstan-17β-ol **29** in the presence of mercury(II) oxide and iodine in benzene has been known readily to cause a β-scission to give an iodo formate **30** exclusively.[7]

Reaction of 5α-androstan-17-one **27** with but-3-enylmagnesium bromide in diethyl ether gave 17α-(but-3-enyl)-5α-androstan-17β-ol **28** and 5α-androstan-17β-ol **29** in 9 and 47% yield, respectively. The poor yield of bishomoallyl alcohol **28** in this Grignard reaction was improved to 69%, without concomitant formation of by-product **28**, by carrying out the

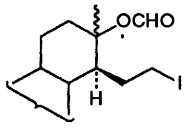


28 R = but-3-enyl
29 R = H

Scheme 4 *Reagents and conditions:* i, CH_2=$CHCH_2CH_2MgBr$–diethyl ether; ii, CH_2=$CHCH_2CH_2MgBr$–$CeCl_3$–THF

reaction in the presence of cerium trichloride[8] (Scheme 4). The assigned stereochemistry is based solely on a consideration of the reaction stereochemistry.

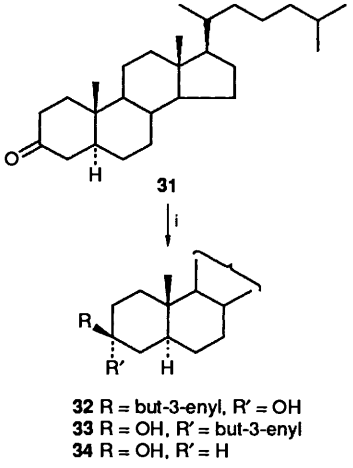
3β- and 3α-(But-3-enyl)-5α-cholestan-3-ol **32** and **33** were



30 (*cf.* **26**)

similarly prepared by the reaction of 5α-cholestan-3-one **31** with but-3-enylmagnesium bromide in 44 and 22% yield (Scheme 5), though these bishomoallyl alcohols, **32**, and **33**, are not suitable models for studying the β-scission *vs.* addition, since the alkoxyl radical generated from the parent alcohol **33** is known to be unsusceptible to β-scission.[7] We were unable to assign the configurations of the butenyl groups of bishomoallyl alcohols **32** and **33** by spectroscopy.

The stereochemistry at C-3 of the epimeric alcohols **32** and **33** was, however, assignable (as depicted in Scheme 5) on the basis

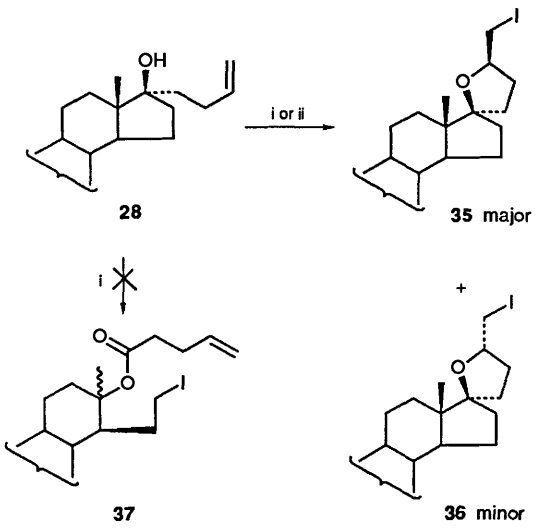


32 R = but-3-enyl, R′ = OH
33 R = OH, R′ = but-3-enyl
34 R = OH, R′ = H

Scheme 5 *Reagents and conditions:* i, CH_2=$CHCH_2CH_2MgBr$–diethyl ether

of their polarity difference. Hence, the more mobile epimer on a TLC plate, compound **32**, should have an axial hydroxy group.[9]

Ionic Formation of Spirotetrahydrofurans in the Reaction of Hypoiodites of Bishomoallyl Alcohols **28**, **32** *and* **33** (*Schemes* 6, 8 *and* 9).—A solution of the bishomoallyl alcohol **28** in benzene containing mercury(II) oxide and iodine (each 2 mol equiv.) was stirred in the dark under nitrogen at room temperature for 15 min. Virtually no starting bishomoallyl alcohol **28** remained unchanged at this point, as revealed by TLC. Two isomeric products, **35** and **36**, were obtained in 64 and 29% yield, respectively, by preparative TLC (PLC) (Scheme 6). Combustion and mass spectrometric analyses of the two epimers indicated that the molecular formula of these epimers is $C_{23}H_{37}IO$. The IR and the ^1H NMR spectra (see Experimental section), in conjunction with pathways for the formation of the product, indicated that the epimers were spirotetrahydrofurans **35** and **36**. We were unable to determine the configuration of the iodomethyl group of the epimers unambiguously by spectral analysis. The configuration of the iodomethyl group of the major epimer **35** was, however, tentatively assigned to be β on the basis of consideration of the reaction stereochemistry. We confirmed that no iodo pentenoate **37**, arising from a β-scission, was formed in this reaction. The spirotetrahydrofuran derivatives, **35** and **36**, were formed in high yields, even when the reaction of the hypoiodite of the bishomoallyl alcohol **28** was



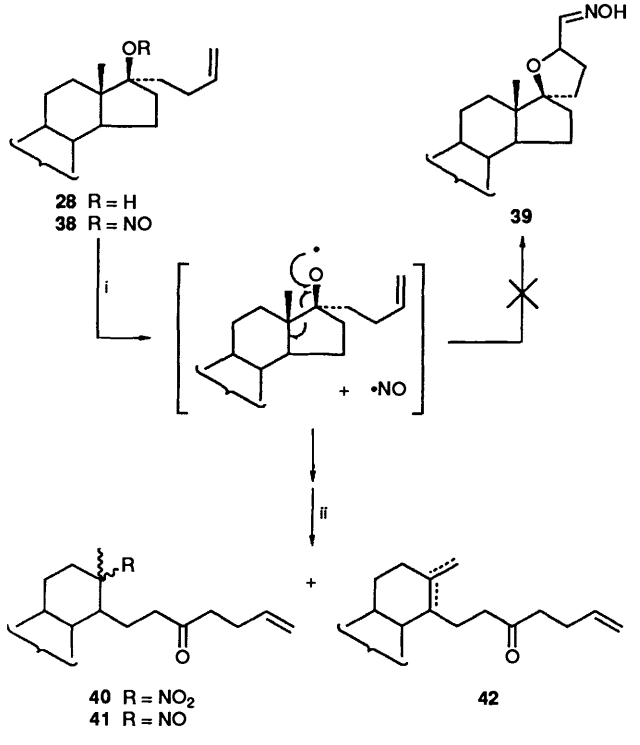
Scheme 6 *Reagents and conditions:* i, $HgO–I_2$–benzene, room temp.; ii, $HgO–I_2$, **29** (1 mol equiv.), benzene, room temp.

carried out in the presence of a radical scavenger, such as 2,2′-diphenyl-1-picrylhydrazyl (DPPH).

These results have indicated that spirotetrahydrofurans **35** and **36** are produced *via* a thermal ionic cyclization of the hypoiodite of the bishomoallyl alcohol **28**.

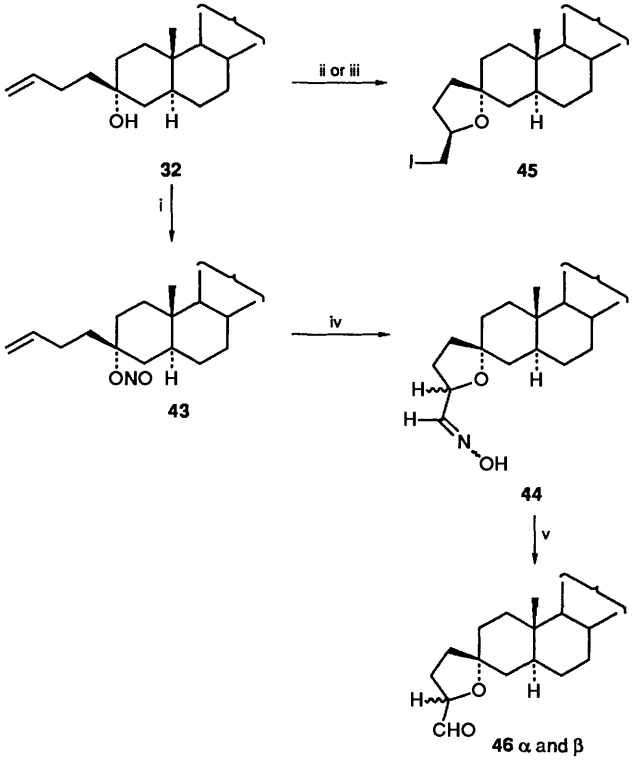
In order further to confirm this conclusion we examined the products from the photolysis of the nitrite **38** of the bishomoallyl alcohol **28** prepared by reaction with nitrosyl chloride in pyridine by the standard method. Photolysis of nitrite **38** in benzene with a high-pressure mercury arc through a Pyrex filter afforded none of the tetrahydrofurans **39** expected from an intramolecular addition of the corresponding alkoxyl radical, but did afford a mixture of ill defined products from which a mixture of products **40**, **41** and **42**, arising from β-scission, were isolated in poor yields (Scheme 7). These results are parallel to those reported by Irmscher[10] a long time ago.

Similar photolysis of nitrite **43**, prepared from 3α-alcohol **32**



Scheme 7 *Reagents and conditions:* i, *hν*–benzene; ii, PLC separation

by the standard method,[11] on the other hand, gave a stereoisomeric mixture of spirotetrahydrofuran oximes **44** arising from an intramolecular radical addition[12] in a combined yield of 64%, as outlined in Scheme 8. The ^1H NMR spectrum of



Scheme 8 *Reagents and conditions:* i, NOCl–pyridine; ii, $HgO–I_2$, benzene; iii, $HgO–I_2$–DPPH–benzene; iv, *hν*–benzene; v, $NaHSO_3$, aq. EtOH, reflux

the mixture exhibited a doublet signal at δ 6.90 and two double doublet signals at δ 7.35 and 7.36 assignable to –CH=N– protons of a *Z* and two *E* isomers, respectively.

Deoximation of this mixture **44** with $NaHSO_3$ in aq. ethanol gave a 2.3:1 mixture of the corresponding aldehyde **46** in 58% yield as estimated by ^1H NMR spectroscopy. Analysis of the mixture by ^1H NMR spectroscopy, details of which are described in the Experimental section, indicated that it was a mixture of two stereoisomers of aldehydes, differing at the α-position of the tetrahydrofuran ring.

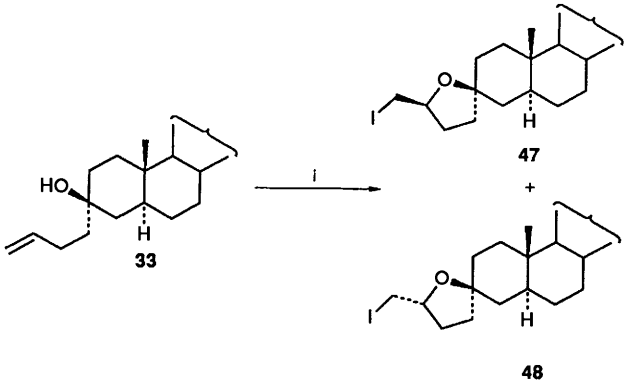
These results clearly indicate that the β-scission takes place in preference to an intramolecular addition from the alkoxyl radical generated from the bishomoallyl alcohol **28**.

It is of interest to note that cyclization to give spirotetrahydrofurans **35** and **36** takes place even under the standard photolytic conditions of hypoiodites. The above mentioned failure regarding the cyclization of the alkoxyl radical generated from the nitrite **38** indicates that the formation of spirotetrahydrofurans **35** and **36** under photolytic conditions takes place by ionic addition, and not by radical addition.

This conclusion was further confirmed by the following control experiment: the above-mentioned intramolecular addition of 17α-(but-3-enyl)-5α-androstan-17β-ol **28** to spirotetrahydrofurans **35** and **36** was carried out by the addition of an equivalent amount of 5α-androstan-17β-ol **29**. This experiment was undertaken under otherwise exactly the same conditions as those for the reaction of 17-(but-3-enyl)-5α-androstan-17β-ol **28** alone. This experiment gave two epimeric spirotetrahydrofurans, **35** and **36**, in 51 and 25% yield, but gave no iodo formate **30**, a product produced from β-scission of the 17β-alkoxyl radical. The added 17β-ol **29** was recovered unchanged.

The results are entirely parallel to those obtained in the reaction of the hypoiodite of 17α-butenyl-17β-ol **28** in the absence of 17β-ol **29**, clearly indicating that no alkoxyl radicals are involved in the formation of spirotetrahydrofurans **35** and **36** in cyclization of the hypoiodite of 17β-ol **28** under the conditions mentioned above.

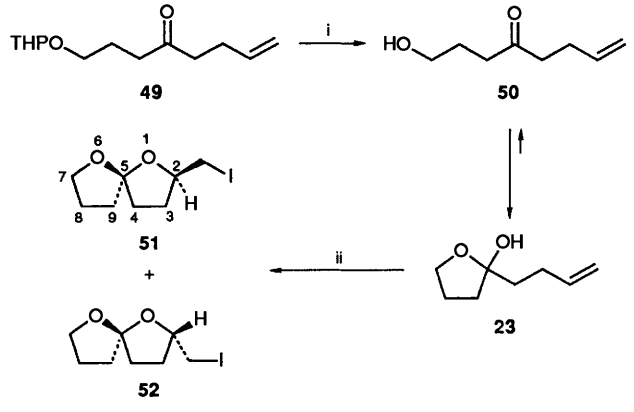
The reaction of 3β-(but-3-enyl)-5α-cholestan-3-α-ol **32** in benzene containing mercury(II) oxide and iodine under the same conditions as those for the bishomoallyl alcohol **28** in the dark gave the corresponding crystalline spirotetrahydrofuran derivative **45** in 93% yield as a single product. The assigned β-configuration of the iodomethyl group attached to the tetrahydrofuran ring is based merely on steric considerations, and is not unambiguous. The analogous reaction of 3α-(3-butenyl)-5α-cholestan-3β-ol **33** gave an inseparable 1:1 mixture of epimers of the tetrahydrofuran derivative, **47** and **48**, as expected (Scheme 9).



Scheme 9 *Reagents and conditions:* i, $HgO–I_2$, benzene

Formation of Spiroketals by the Halogenoetherification of 2-Hydroxy-2-(but-3-enyl)tetrahydrofuran via *its Hypoiodite* (*Scheme* 10).—We finally repeated the formation of spiroketal **24** from 2-hydroxy-2-(but-3-enyl)tetrahydrofuran **23** through its hypoiodite, reported by Kraus and Thurston.[5]

Thus, treatment of 1-(tetrahydropyran-2-yloxy)oct-7-en-4-one **49**[13,14] with toluene-*p*-sulfonic acid (PTSA) in a mixed solvent of methanol and water at 50 °C for 1 h gave the corresponding alcohol **50** in 61% yield. This alcohol **50** was set aside for 5 days at room temperature; column chromatography through Florisil gave lactol **23** in 65% yield as a thick liquid.

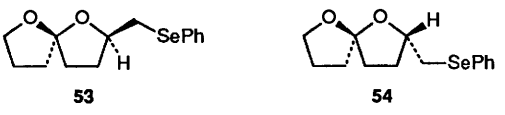


Scheme 10 *Reagents and conditions:* i, PTSA, aq. MeOH, 50 °C; ii, $HgO–I_2$–benzene, 20 °C

To a solution of lactol **23** in benzene in a vessel covered by aluminium foil were added mercury(II) oxide and iodine (each 2 mol equiv.). This solution was stirred for 105 min at room temperature in the dark to give a 1:2 mixture of two products, **51** and **52**, in 67% yield by the usual work-up of the solution and product separation by PLC. The ^1H NMR spectrum indicated that the products comprised a mixture of the diastereoisomers of spirotetrahydrofurans. The EI mass spectrum exhibited a molecular ion peak at *m/z* 268, and fragments at *m/z* 141 (23%) and 127 (100%), assignable to the $(M - I)^+$ and $(M - CH_2I)^+$ ions, respectively. The IR spectrum exhibited the absence of hydroxy and carbonyl groups as well as the presence of an ether linkage.

An analysis of a mixture of the diastereoisomers by ^1H NMR (400 MHz) spectroscopy, by comparison of the spectrum with those of the diastereoisomers of the closely related spirotetrahydrofurans **53** and **54**,[14] aided by a double-resonance technique, enabled us to determine it to be a 1:2 mixture of *cis* and *trans* spirotetrahydrofurans, **51** and **52**.

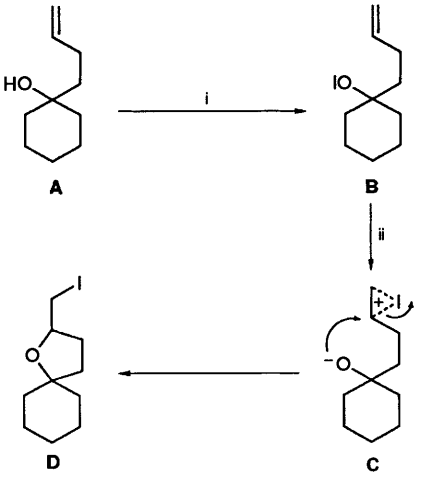
Our experiments thus confirmed that, in contrast to the previous report,[5] *a mixture of diastereoisomers* **53** *and* **54** is obtained as the product by *an ionic reaction in the dark.*



Discussion

The foregoing results have indicated that spirotetrahydrofurans are produced in high yield when a solution of a bishomoallyl alcohol, such as **28**, containing mercury(II) oxide and iodine (each 2 mol equiv.) is stirred at room temperature in the dark under nitrogen. The foregoing experiments also indicated that the formation of the spirotetrahydrofurans takes place *via an ionic* reaction of the hypoiodite of the bishomoallyl alcohol **28**, as outlined in Scheme 11, and not *via* a cyclization of the corresponding alkoxyl radical generated from the hypoiodites.

The pathway for the formation of the spirotetrahydrofurans from the bishomoallyl alcohols is outlined in Scheme 11;



Scheme 11 *Reagents:* i, $HgO–I_2$ (→ $[I_2O]$), benzene; ii, ROI

hypoiodite **B** is formed by the reaction of the bishomoallyl alcohol **A** with iodine oxide generated *in situ* from mercury(II) oxide and iodine in benzene.

An intramolecular reaction of iodonium ion **C** generated by the reaction of hypoiodite **B** with another hypoiodite molecule gives spirotetrahydrofuran **D**. This pathway is entirely analogous to that regarding the addition of acyl hypoiodites to olefins,[15] in which the acyl hypoiodite attacks the olefin to form an iodonium ion that is, in turn, attacked by a carboxylate ion, resulting in an overall *trans* addition.

The cyclization to iodotetrahydrofurans found in the

photolysis of hypoiodites in benzene (reported in the past) is considered to consist mostly of ionic reactions.

There have been a number of reports concerning the formation of cyclic ethers by electrophilic halogenocyclization of unsaturated alcohols involving halogenonium and other ions. The variety of reagents used include: (a) NBS–Bu^{t}OH–water;[16a] NBS–CCl_4;[16b] Br_2–CCl_4;[16c] Br_2–pyridine–CCl_4;[16d] (b) I_2–aq. KI;[17] (c) I_2–$NaHCO_3$–Et_2O–H_2O;[18a,b] KI_3–$NaHCO_3$–Et_2O–water;[18b] (d) $Pb(OAc)_4$–NaI or $ZnBr_2$–DME,[19] (e) *N*-phenylselenophthalimide (NPSP)–$ZnBr_2$–CH_2Cl_2,[14] (f) PhSSPh + e ⟶ PhS^+–CH_2Cl_2,[20] (g) I_2–MeCN.[21]

The electrophilic cyclization of unsaturated alcohols *via* their hypoiodites generated *in situ* with mercury(II) oxide and iodine (described in this paper) is complementary to these methods; the procedure is simple and the reaction takes place at room temperature under essentially neutral conditions, giving high yields of functionalized tetrahydrofuran derivatives.

Experimental

M.p.s were determined with a Yanagimoto m.p. apparatus and are uncorrected. The IR spectra were determined for Nujol mulls with a JASCO IR 810 infrared spectrophotometer. The ^1H NMR spectra were determined in $CDCl_3$ ($SiMe_4$ as internal reference) with a JEOL EX-400 spectrometer operated at 400 MHz unless stated otherwise. The *J*-values are in Hz. High- and low-resolution mass spectra were recorded with a JEOL JMS-DX303 mass spectrometer (70 eV) at the faculty of Pharmaceutical Sciences of this University. PLC was carried out on Merck silica gel 60 PF_{254}.

17α-(*But*-3-*enyl*)-5α-*androstan*-17β-*ol* **28**. (a) *In the Presence of Cerium Trichloride*.—Cerium trichloride hydrate ($CeCl_3$·$7H_2O$) (560 mg, 1.5 mmol) was dried at ~140 °C *in vacuo* (0.1 mmHg) for 3 h. To this dehydrated cerium chloride, cooled at 0 °C in an ice-bath, was added tetrahydrofuran (THF) (5 cm^3). The solution was stirred for 16 h. To this suspension, cooled at 0 °C by ice-bath, was added a solution of but-3-enylmagnesium bromide prepared by the reaction of magnesium (61 mg, 2.54 mmol) with 4-bromobut-1-ene (0.2 cm^3, 1.9 mmol) in THF (5 cm^3). The solution was stirred for 80 min at 0 °C. To this solution at 0 °C was added a solution of 17-ketone **27** (274 mg, 1 mmol) in THF (5 cm^3). The solution was stirred for 17 h at room temperature. After 10% acetic acid (10 cm^3) had been added, the solution was extracted with diethyl ether. The organic layer was washed successively with 5% aq. sodium hydrogen carbonate, water, and finally brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a product, which was purified by PLC [(6:1) hexane–ethyl acetate] to give 17β-*ol* **28** (228 mg, 69%) m.p. 138–140 °C (from acetone) (Found: C, 83.4; H, 11.5. $C_{23}H_{38}O$ requires C, 38.57; H, 11.59%); ν_{max}/cm^{-1} 3496 (OH), 1641 (C=C) and 905; δ (400 MHz) 0.79 (3 H, s, 19-H_3), 0.85 (3 H, s, 18-H_3), 4.93–5.10 (2 H, m, CH=CH_2); *m/z* 330 (M^+, 13), 312 [$(M - H_2O)^+$, 12], 297 [$(M - H_2O - Me)^+$, 17], 275, [$(M - C_4H_7)^+$, 75] and 109 (100%).

(b).—To a solution of 5α-cholestan-17-one **27** (1.0 g, 3.65 mmol) and magnesium (175 mg, 7.20 mmol) in diethyl ether (15 cm^3) was added dropwise a solution of 4-bromobut-1-ene (1 cm^3, 9.86 mmol) in dry diethyl ether (1 cm^3). The solution was stirred for 24 h at room temperature. After the addition of ammonium chloride (195 mg) and 0.5 mol dm^{-3} sulfuric acid (5 cm^3) to the solution, the organic layer was washed successively with water and brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a product mixture, which was subjected to PLC [(7:1) hexane–ethyl acetate] to give three fractions (A, B and C). The most mobile fraction (382 mg, 38%) was the starting 17-one **27**. The second mobile fraction (112 mg, 9%) was 17β-ol **28**.

The most polar fraction (C) was 5α-androstan-17β-ol **29** (471 mg, 47%) identical with an authentic sample.

3α- *and* 3β-(*But*-3-*enyl*)-5α-*cholestan*-3-*ols* **32** *and* **33**.—To a solution of 5α-cholestan-3-one **31** (670 mg, 1.74 mmol) and magnesium (281 mg, 11.56 mmol) in dry diethyl ether (8 cm^3) was added dropwise a solution of 4-bromobut-1-ene (1 cm^3, 9.85 mmol) in dry diethyl ether (2 cm^3). The solution was stirred for 2 h at room temperature. To the solution were added ammonium chloride (60 mg) and 0.5 mol dm^{-3} hydrochloric acid (3 cm^3). The organic layer was then washed with 2 mol dm^{-3} sodium hydroxide, water, and brine, successively, and then dried over anhydrous sodium sulfate. Evaporation of the solvent gave a mixture of products, which was subjected to PLC [(5:1) hexane–ethyl acetate] to give three fractions (A, B and C). The most mobile fraction (337 mg, 44%) was 3β-(*but*-3-*enyl*)-5α-*cholestan*-3α-*ol* **32**, m.p. 104–107 °C (from MeOH) (Found: M^+, 442.4147. $C_{31}H_{54}O$ requires *M*, 442.4174); ν_{max}/cm^{-1} 3496 (OH), 1641 (C=C), 1163, 943, 947 and 905; δ (400 MHz) 0.65 (3 H, s, 18-H_3), 0.74 (3 H, s, 19-H_3), 4.90–5.07 (2 H, m, CH=CH_2) and 5.78–5.91 (1 H, m, C*H*=CH$_2$; *m/z* 442 (M^+, 2.2), 424 [$(M - H_2O)^+$, 2.4], 409 [$(M - H_2O - Me)^+$, 8] and 387 [$(M - C_4H_7)^+$, 100%].

The second mobile fraction (B) (182 mg, 24%) was 3α-(*but*-3-*enyl*)-5α-*cholestan*-3β-*ol* **33**, m.p. 38–42 °C (from MeOH) (Found: M^+, 442.4176); ν_{max}/cm^{-1} 3344 (OH), 1645 (C=C) and 905; δ (400 MHz) 0.65 (3 H, s, 18-H_3), 0.82 (3 H, s, 19-H_3), 4.90–5.10 (2 H, m, CH=CH_2) and 5.80–5.95 (1 H, m, C*H*=CH$_2$); *m/z* 442 ($M - H_2O - Me)^+$, 7.9] and 387 [$(M - C_4H_7)^+$, 100%].

The most polar fraction (115 mg, 17%) was identified as being 5α-*cholestan*-3β-*ol* **34**.

Intramolecular Addition of the Hypoiodite of 17α-(*But*-3-*enyl*)-5α-*androstan*-17β-*ol* **28**.—A solution of the 17β-ol **28** (52 mg, 0.158 mmol) in benzene (8 cm^3) containing red mercury(II) oxide (68 mg, 0.314 mmol) and iodine (80 mg, 0.315 mmol), placed in a vessel covered with aluminium foil, was flushed with nitrogen gas and stirred for 15 min at room temperature. After the solution had been filtered, the organic layer was washed successively with 5% aq. sodium thiosulfate, water, and finally brine and was dried over anhydrous sodium sulfate. Evaporation of the solvent gave products, which were subjected to PLC [(7:1) hexane–ethyl acetate] to give two products, **35** and **36**. The more mobile, major product (46 mg, 64%) was *spirotetrahydrofuran derivative* **35**, m.p. 121–122 °C (from acetone) (Found: C, 60.5; H, 8.3; I, 27.65. $C_{23}H_{37}IO$ requires C, 60.52; H, 8.17; I, 27.80%); ν_{max}/cm^{-1} 1197, 1055, 1024, 969 and 892; δ (400 MHz) 0.78 (3 H, s, 19-H_3), 0.85 (3 H, s, 18-H_3), 1.93–2.02 (1 H, m), 2.03–2.15 (2 H, m), 3.08 (1 H, dd, *J* 7.8 and 9.8, CH_2I), 3.27 (1 H, dd, *J* 4.4 and 9.8, CH_2I) and 3.91–4.00 (1 H, m, OCH); *m/z* 456 (M^+, 23), 441 [$(M - Me)^+$, 6], 329 [$(M - I)^+$, 4], 315 [$(M - CH_2I)^+$, 12] and 237 (100%).

The less mobile, minor product (21 mg, 29%) was the *epimeric spirotetrahydrofuran derivative* **36**, m.p. 116–117 °C (from acetone) (Found: M^+, 456.1910. $C_{23}H_{37}IO$ requires *M*, 456.1889); ν_{max}/cm^{-1} 1302, 1275, 1206, 1162, 1090, 1005, 967 and 895; δ (400 MHz) 0.79 (3 H, s, 19-H_3), 0.86 (3 H, s, 18-H_3), 1.85–1.94 (1 H, m), 2.03–2.15 (2 H, m), 3.06 (1 H, dd, *J* 7.8 and 9.8, CH_2I), 3.21 (1 H, dd, *J* 4.4 and 9.8, CH_2I) and 3.98–4.06 (1 H, m, OCH); *m/z* 456 (M^+, 27], 441 [$(M - Me)^+$, 7], 329 [$(M - I)^+$, 3], 315 [$(M - CH_2I)^+$, 12] and 237 (100%). The ratio of the two epimers **35** and **36** was 2.2:1.

Control Experiment of Intramolecular Addition of the

Hypoiodite of 17α-(*But*-3-*enyl*)-5α-*androstan*-17β-*ol* **28** *in the Presence of a Molar Equivalent of* 5α-*Androstan*-17β-*ol.* **29.**—A solution of the 17α-butenyl-17β-ol **28** (37 mg, 0.112 mmol) and the 17β-ol **29** (38 mg, 0.137 mmol) in benzene (25 cm^3) containing red mercury(II) oxide (108 mg, 0.499 mmol) and iodine (127 mg, 0.500 mmol), placed in a vessel covered by aluminium foil, was flushed with nitrogen and stirred for 10 min at room temperature. The solution was then worked up as described for the reaction of the hypoiodite of 17α-butenyl-17β-ol **28** alone. Separation of the product mixture obtained by PLC gave three fractions. The most mobile fraction (26 mg, 51%) was the spirotetrahydrofuran derivative **35**; the next fraction (13 mg, 25%) was its epimer **36**. The most polar fraction (37 mg, 97%) was the recovered starting 17β-ol **29**.

Attempted Photoaddition of the Alkoxyl Radical generated from 17α-(*But*-3-*enyl*)-5α-*androstan*-17β-*yl Nitrite* **38.**—The steroidal 17β-yl nitrite **38**, prepared from steroidal 17β-ol **28** (60 mg, 0.182 mmol) and nitrosyl chloride in pyridine by the standard method,[10] was dissolved in benzene (2.5 cm^3). The solution was flushed with nitrogen and was irradiated for 105 min with a 100 W high-pressure mercury arc (EIKOSHA-EHB-WU-100). After evaporation of the solvent, the product was subjected to PLC [(7:1) hexane–ethyl acetate] to give three fractions A, B and C in order of their mobility. The most mobile fraction, A (5 mg, 8%), was a mixture of secosteroids **42**, ν_{max}/cm^{-1} (neat) 1717 (C=O), 1644 (C=C) and 1447; δ (400 MHz) 0.70 and 0.72 [each 3 H, each s 19-H_3 of 13-ene and 13(18)-ene], 1.56 (s, 18-H_3 of 13-ene), 4.47 and 4.71 [each s, 18-H_3 of 13(18)-ene], 4.94–5.08 (2 H, m, CH=CH_2) and 5.74–5.88 (1 H, m, C*H*=CH_2); *m/z* 328 (M^+, 3.5), 230 [$(M - C_6H_{10}O)^+$, 100] and 55 (76).

The next mobile fraction, B (8 mg), was a blue coloured mixture of nitro and nitroso secosteroids **40** and **41**, ν_{max}/cm^{-1} (neat) 1717 (C=O), 1643 (C=C), 1550 (NO_2), 1535, 1468, 1448 and 1382; *m/z* 329 [$(M - NO_2)^+$ or $(M - NO)^+$, 11], 230 [$(329 - C_6H_{10}O)^+$, 57] and 55 (100%).

The most polar fraction (11 mg) was an intractable mixture.

Intramolecular Photoaddition of 3β-(*But*-3-*enyl*)-5α-*cholestan*-3α-*yl Nitrite* **43.**—The nitrite, prepared from hydroxy steroid **32** (51 mg, 0.115 mmol) and nitrosyl chloride in pyridine by the standard method,[10] was dissolved in a mixture of benzene (3 cm^3) and methanol (0.5 cm^3). The solution was flushed with nitrogen and irradiated through a Pyrex filter for 2 h with a 100 W high-pressure mercury arc. Evaporation of the solvent gave products, which were subjected to PLC [(7:1) hexane–ethyl acetate] to give a *mixture of isomeric tetrahydrofuran derivatives* **44** (34 mg, 64%) (Found: M^+, 471.4055. $C_{31}H_{53}NO_2$ requires *M*, 471.4076); ν_{max}/cm^{-1} (neat) 3330 (OH) and 1047; δ (270 MHz) 0.64 (3 H, s, 18-H_3), 0.76, 0.76 and 0.77 (each 3 H, each s, 19-H_3 of three stereoisomers), 4.4–4.6 and 4.9–5.1 (each 1 H, each m, OCH of stereoisomers), 6.90 (1 H, dd, *J* 1.7 and 4.6, CH=N of *Z*-isomer) and 7.35 and 7.36 (1 H, each d, *J* 6.6, CH=N of *E*-isomer); *m/z* 471 (M^+, 16), 454 [$(M - OH)^+$, 25], 438 (27), 427 [$(M - CHNOH)^+$, 18], 298 (82), 95 (85) and 81 (100%).

Hydrolysis of Spirotetrahydrofuran Oximes **44.**—To a solution of a mixture of stereoisomeric oximes (61 mg, 0.130 mmol), obtained as mentioned above, in a mixture of ethanol (17 cm^3) and water (5 cm^3) was added $NaHSO_3$ (90 mg, 0.865 mmol). The solution was heated for 25.5 h under reflux. Evaporation of the solvent gave a residue, which was dissolved in diethyl ether. The solution was washed successively with water and then brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave products, which were subjected to PLC [(7:1) hexane–ethyl acetate] to give a 2.3:1 mixture (by ^1H NMR spectroscopy) of two isomeric aldehydes **46** (34 mg, 58%) [Found: $(M - CHO)^+$, 427.3941. $C_{30}H_{51}O$ requires *m/z* 427.3940]; ν_{max}/cm^{-1} (neat) 1736 (C=O), 1215, 1061 and 1000; δ (270 MHz) 0.65 (3 H, s, 18-H_3), 0.76 and 0.78 (each 3 H, each s, 19-H_3), 4.23–4.34 (1 H, m, OCH of major product), 4.68 (1 H, br dt, *J* 5 and 7, OCH of minor product) and 9.68 (1 H, m, CHO); *m/z* 427 [$(M - CHO)^+$, 100], 409 (34) and 298 (57%).

Intramolecular Addition of the Hypoiodite of 3β-(*But*-3-*enyl*)-5α-*cholestan*-3α-*ol* **32**—(a) To a solution of steroidal 3α-ol **32** (50 mg, 0.113 mmol) in benzene (6 cm^3) placed in a vessel covered by aluminium foil were added red mercury(II) oxide (50 mg, 0.231 mmol) and iodine (62 mg, 0.244 mmol) in the dark. The solution was flushed with nitrogen and was then stirred for 140 min at room temperature in the dark. The filtered solution was washed successively with 5% aq. $Na_2S_2O_8$, water and brine, and then dried over anhydrous sodium sulfate. Evaporation of the solvent gave a product, which was purified by PLC (benzene) to give the *spirotetrahydrofuran derivative* **45** (60 mg, 93%), m.p. 88.5–90.0 °C (from acetone) (Found: C, 65.6; H, 9.3; I, 22.5. $C_{31}H_{53}IO$ requires C, 65.49; H, 9.39; I, 22.32%); ν_{max}/cm^{-1} 1160, 1040 and 900; δ (400 MHz) 0.64 (3 H, s, 18-H_3), 0.75 (3 H, s, 19-H_3), 3.13 (1 H, dd, *J* 9.8 and 8, CH_2I), 3.30 (1 H, dd, *J* 9.8 and 3.9, CH_2I) and 3.96–4.06 (1 H, m, OCH); *m/z* 568 (M^+, 54), 553 [$(M - Me)^+$, 20], 441 [$(M - I)^+$, 14], 413 (37), 263 (56), 250 (66), 238 (80), 95 (86), 81 (95) and 55 (100%).

(b) *In the presence of* 2,2′-*diphenyl*-1-*picrylhydrazyl* (*DPPH*). To a solution of the 3α-ol **32** (51 mg, 0.115 mmol) in benzene (6 cm^3) placed in a vessel covered by aluminium foil were added DPPH (136 mg, 0.345 mmol), red mercury(II) oxide (50 mg, 0.231 mmol) and iodine (59 mg, 0.232 mmol) successively. The solution was flushed with nitrogen and was then stirred for 2 h at room temperature in the dark. Work-up as described above gave the spirotetrahydrofuran derivative **45** (60 mg, 93%) as a single isomer.

Intramolecular Addition of the Hypoiodite of 3α-(*But*-3-*enyl*)-5α-*cholestan*-3β-*ol* **33.**—A solution of the 3β-ol **33** (58 mg, 0.131 mmol), red mercury(II) oxide (57 mg, 0.263 mmol) and iodine (67 mg, 0.264 mmol) in benzene (7 cm^3), made up as described above, was flushed with nitrogen and was then stirred for 40 min at room temperature in the dark. The solution was then worked up as described above to give a 1:1 *mixture of two isomers*, **47** and **48**: m.p. 101–103 °C (from acetone) (Found: C, 65.5; H, 9.5; I, 22.4. $C_{31}H_{53}IO$ requires C, 65.49; H, 9.39; I, 22.32%); ν_{max}/cm^{-1} 1171, 1078, 1051, 930 and 672; δ (400 MHz) 0.64 (3 H, s, 18-H_3), 0.81 (3 H, s, 19-H_3), 3.129 (1 H, dd, *J* 7.3 and 9.8, HC*H*I), 3.133 (1 H, dd, *J* 7.8 and 9.8, HC*H*I), 3.27 (1 H, dd, *J* 3.9 and 9.8, HC*H*I), 3.28 (1 H, dd, *J* 3.9 and 9.8, HC*H*I) and 3.96–4.07 (1 H, m, OCH); *m/z* 568 (M^+, 70), 553 [$(M - CH_3)^+$, 11], 441 [$(M - I)^+$, 15], 427 (40), 413 (15), 331 (56), 263 (84), 250 (100), 238 (93) and 237 (77%).

1-*Hydroxyoct*-7-*en*-4-*one* **50.**—To a solution of 1-(tetrahydropyran-2-yloxy)oct-7-en-4-one **49**[13] (122 mg, 0.54 mmol) in a mixture of methanol (1.2 cm^3) and water (1.2 cm^3) was added a catalytic amount of PTSA. The solution was stirred for 1 h at 50 °C. The reaction mixture was then extracted with diethyl ether. The extract was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a product, which was subjected to column chromatography (Florisil, 2 g). Elution with 10:1 hexane–ethyl acetate gave the alcohol **50** (47 mg, 61%). TLC indicated that it was almost a single product. The alcohol **50** was, however, unstable in $CDCl_3$.

2-(*But*-3-*enyl*)*tetrahydrofuran*-2-*ol* **23.**—The open-chain alcohol **50** (neat) was set aside for 5 days at room temperature,

and was then subjected to column chromatography (Florisil, 10 g). Elution with 5:2 hexane–ethyl acetate gave lactol **23** (237 mg, 65%), which was stable in benzene and gave a single spot on TLC. It was, however, unstable in $CDCl_3$ and the ^1H NMR spectrum of lactol **23** indicated that it existed as a 1:4 equilibrated mixture of tautomers **50** and **23**, δ (270 MHz) 3.38 (0.4 H, m, OCH_2 of **23**), 3.65 (0.2 H, t, $J \sim 6$, CH_2OH of **50**), 3.86 (0.4 H, m, OCH_2 of **23**), 4.93–5.06 (2 H, m, $CH{=}CH_2$) and 5.73–5.92 (1 H, m, $CH{=}CH_2$).

Formation of Spirotetrahydrofurans **51** *and* **52** (*Diastereoisomers of Compound* **24**) *from the Hypoiodite of Lactol* **23**.—To a solution of lactol **23** (237 mg, 1.67 mmol) in benzene (82 cm^3) placed in a vessel covered by aluminium foil were added red mercury(II) oxide (724 mg, 3.34 mmol) and iodine (849 mg, 3.34 mmol). This solution was stirred for 105 min at room temperature in the dark. The solution was then filtered, and the filtrate was washed successively with 5% aq. sodium thiosulfate, water and brine, and was then dried over anhydrous sodium sulfate. Evaporation gave a product mixture, which was subjected to PLC [(5:1) hexane–ethyl acetate] to give a 1:2 *mixture of diastereoisomers* **51** and **52** (301 mg, 67%) (Found: M^+, 267.9985. $C_8H_{13}IO_2$ requires M, 267.9960); ν_{max}/cm^{-1} (neat) 1166, 1152, 1112, 1052, 1008, 933 and 920; δ (400 MHz) 1.69–1.77 (1 H, m, 3-H of **52**), 1.82–2.16 (13 H, m), 2.20–2.30 (2 H, m, 3-H of **51** and **52**), 3.16 (1 H, dd, J 8.3 and 9.3, CH_2I of **51**), 3.22 (1 H, dd, J 6.3 and 9.8, CH_2I of **52**), 3.28 (1 H, dd, J 4.2 and 9.8, CH_2I of **52**), 3.36 (1 H, dd, J 5.9 and 9.3, CH_2I of **51**), 3.82–3.98 (4 H, m, 7-H_2 of **51** and **52**), 4.07–4.13 (1 H, m, 2-H of **52**) and 4.23–4.30 (1 H, m, 2-H of **51**). Assignments of the signals at δ 1.69–1.77 and 2.20–2.30 were achieved by irradiating signals at δ 4.07–4.13 (2-H of **52**), as well as those at δ 4.23–4.30 (2-H of **51**). All of the assignments are based on comparisons with the signals of diastereoisomers **53** and **54** of the phenylseleno spirotetrahydrofurans; m/z 268 (M^+, 6.3), 141 [$(M - I)^+$, 23], 127 [$(M - CH_2I)^+$, 100], 85 (48) and 55 (97%).

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