0.099 ± 0.001°, c = 0.405, 30.2% ee, ether).

The cycloadducts were separated by preparative GLC on a 39 ft × 1/4 in. 20% Carbowax 20M on Chromosorb P column at 190 °C, providing milligram quantities of the pure cycloadducts. (Insufficient quantities were available to allow for the accurate measurement of the optical rotations.) The ee's of the cycloadducts were determined by the use of tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III) and integration the methyl resonances of the ester methyl groups (see Figure 2). The corresponding ee's are given under the structures.

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Use of Radical Ring-Opening for Introduction of Alkyl and Substituted Alkyl Groups with Stereochemical Control: A Synthetic Application of Cyclopropylcarbinyl Radicals

Derrick L. J. Clive* and Sylvain Daigneault

Chemistry Department, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

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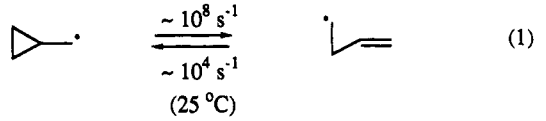
Cyclopropylcarbinols **2a** and **2b** (see Scheme I), which are accessible by a number of routes, can be converted into the corresponding radicals **3a** and **3b**, respectively. These radicals undergo peripheral ring-opening of the cyclopropyl substructure to afford substituted cycloalkenes **4a** and **4b**. The whole sequence represents a general method for attaching alkyl, and substituted alkyl, groups to an existing cyclic structure, and it can often be carried out with predictable stereo- and regiochemical control. Reaction conditions for the ring-opening depend on the substitution pattern of the cyclopropane: where the non-bridgehead carbon of the cyclopropane carries a strongly electron-withdrawing group, the ring-opening can be done at the reflux temperature of benzene. However, in the absence of such electron-withdrawing groups, a low temperature is best used in order to suppress ring expansion. Various methods that accommodate these requirements are available for generating the radicals.

We describe here details of a free radical method for attaching substituents to cyclic substructures.[1] The basic procedure, which is summarized in Scheme I, involves regioselective opening of cyclopropylcarbinyl radicals and allows placement of the substituent on either face of the starting material.[2,3]

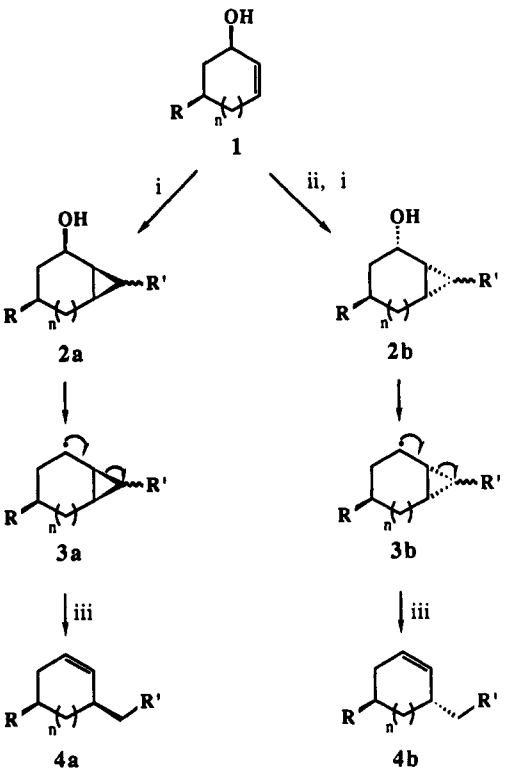
Although radical ring-closure is being investigated intensively[4] as a method for the construction of organic compounds, the synthetic applications of the reverse process—radical ring-opening—have received much less attention. In contrast, the physical organic chemistry of radical ring-opening is a well-studied area, particularly for carbocyclic systems. Most of the reported measurements[5] involve small rings, especially the cyclopropylcarbinyl system (eq 1), because opening of larger rings—at least in



(1)

the absence of substituents that stabilize the product radical—does not usually occur at an adequate rate.[5,6] The rate constants for the parent system of eq 1 are known over a range of temperatures[7,8a] and kinetic data are also availble for those cases in which substituents such as

Scheme I[a]



[a] (i) Cyclopropanation; (ii) Mitsunobu inversion; (iii) stannane. R' = H, alkyl group, or electron-withdrawing group.

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(2) Cf. Dauben, W. G.; Wolf, R. E. *J. Org. Chem.* **1970**, *35*, 2361.
(3) Cf. Degueil-Castaing, M.; Rahm, A.; Dahan, N. *J. Org. Chem.* **1986**, *51*, 1672. Renaud, P.; Fox, M. A. *J. Org. Chem.* **1988**, *53*, 3745.
(4) Reviews: Curran, D. P. *Synthesis* **1988**, 417 and 489. Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Oxford, 1986. Hart, D. J. *Science* **1984**, *223*, 883.
(5) E.g. *Landolt-Börnstein, Numerical Data and Functional Relationships in Science and Technology. New Series*; Fischer, H., Ed.; Springer-Verlag: Berlin, 1984; Vol. 13, subvol. a. Beckwith, A. L. J.; Ingold, K. U. In *Rearrangement in Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980; Vol. 1, Chapter 4.
(6) Fission of the C(9)–C(10) bond in the 9-decalinoxyl radical is fast but reversible: Beckwith, A. L. J.; Kazlauskas, R.; Syner-Lyons, M. R. *J. Org. Chem.* **1983**, *48*, 4718.
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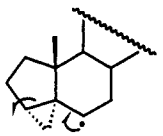
methyl,[8] ethoxycarbonyl,[8b] and phenyl[9] are attached to the basic skeleton. For the parent system itself the rate constant[7,8] for ring-opening is about 10^8 s^{-1} at 25 °C and the value for the reverse process about 10^4 s^{-1}. However, the nature of the substitution pattern can have a large effect on the absolute values and their relative magnitude.[7,8] The preferred regiochemistry of opening also depends on the substitution,[10] and a qualitative interpretation is provided[10a,b,c] by frontier molecular orbital theory. For the reaction shown in eq 2, the SOMO interacts preferentially

(2)

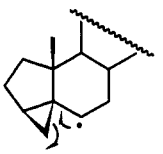
with the LUMO of the C(1)–C(3) bond because the corresponding orbital of the C(1)–C(2) bond is raised in energy by the attached (electron-releasing) methyl groups. Where the substituents on the three-membered ring are cis, steric effects can determine the outcome, and reaction takes place through that conformation in which nonbonded interactions are minimized.[10b,11]

The opening of conformationally unrestrained systems has a number of applications. Some types of cyclopropylcarbinyl radical have been used as radical clocks in mechanistic studies[12] and, in preparative chemistry, radical addition to vinylcyclopropanes represents a developing area[13,14] that is clearly useful.

Of particular relevance to the present work is the regiochemistry of ring-opening[15] when the cyclopropane is fused to another cyclic structure. The behavior of the steroidal radicals **5** and **6**[16] is typical of the available ev-



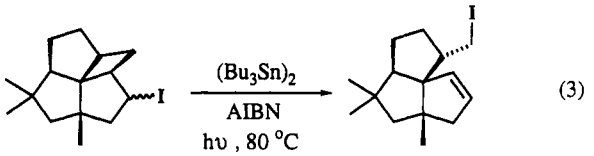
5



6

idence[17] and shows that stereoelectronic factors are usually a determining feature in such situations, because the cyclopropyl bond that breaks is the one that overlaps more effectively with the adjacent singly occupied orbital.

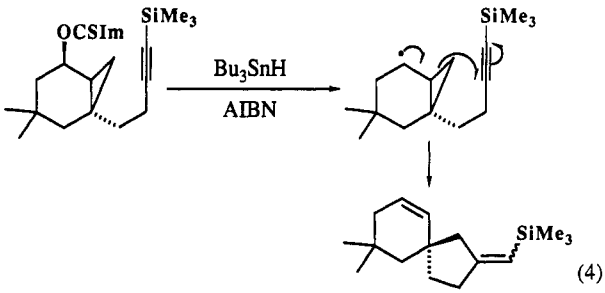
Four-membered rings have not been investigated as extensively as their lower homologues, in the present general context, but some rate data for ring-opening of cyclobutylcarbinyl radicals are available,[5,18] as well as information on the effect of substituents,[18a] and also the regiochemistry,[18a,19] and stereoelectronic[18a] features of the process. Ring-opening of the parent cyclobutylcarbinyl radical has a rate constant of 4.5×10^2 s^{-1} at 25 °C.[18a] A synthetic application is illustrated[20] in eq 3.



(3)

Five-membered rings do open if the resulting species is appropriately stabilized.[21,22]

The opening of cyclopropyl- and cyclobutylcarbinyl radicals in which the ring is a substructure of a polycyclic system has occasionally been used in synthesis,[20,23] but the present work, and spirocyclizations of the type illustrated in eq 4,[24] appear to be the first attempts to evaluate and generalize the synthetic potential of such reactions.



(4)

Although the present work is confined to carbocycles, it is relevant to mention that radical opening of epoxides[25] and aziridines[26] has also been studied. These reactions have synthetic utility,[25a,b,f,26] and the epoxide cleavage is useful as a diagnostic probe for radicals.[27]

Finally, there is evidence that cyclopropylcarbinyl radicals are involved in some biochemical transformations, and this possibility has been demonstrated by a number of model studies.[28-30]

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(12) Review on free-radical clocks: Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317.

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Table I. Formation of Cyclopropanes[a]

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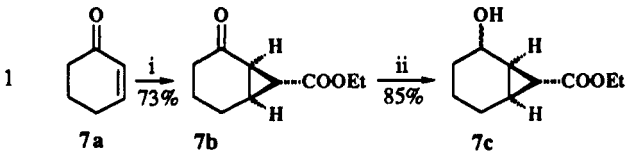
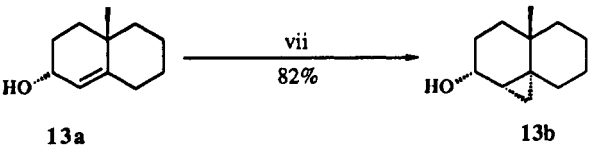
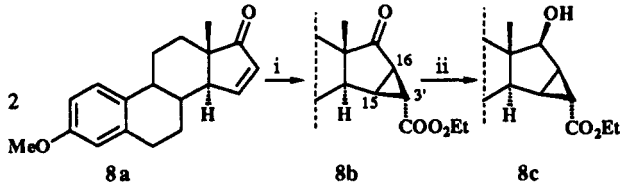
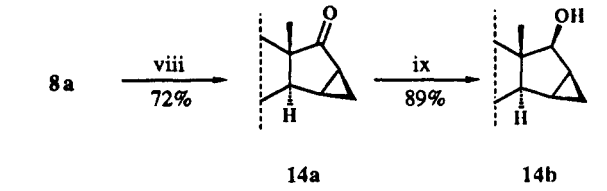
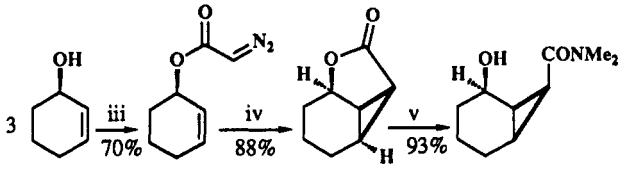
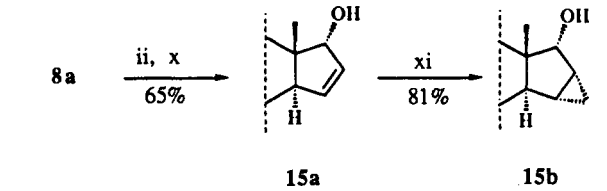
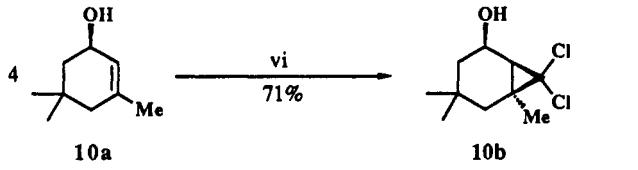
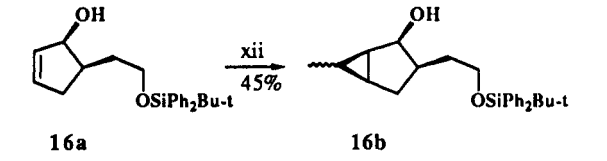
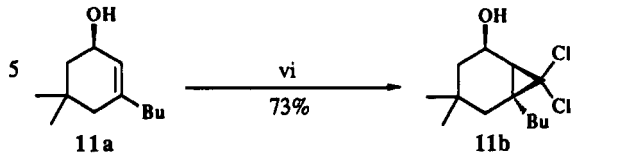
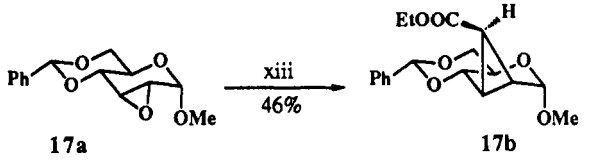
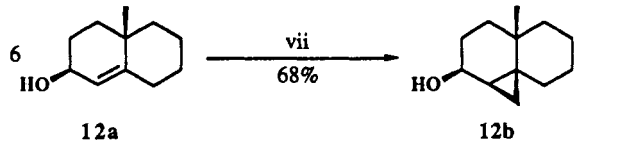
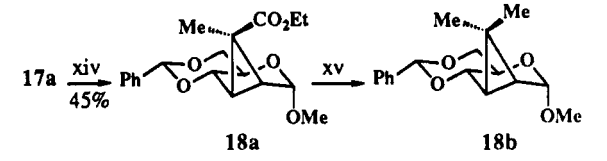
1		7	
2		8	
3		9	
4		10	
5		11	
6		12	

[a] (i) $Me_2S{=}CHCOOEt$; (ii) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH; (iii) $PhNMe_2$, $TsNHN{=}CHCOCl$, then Et_3N; (iv) bis(*N-tert*-butylsalicylaldiminato)copper(II); (v) Me_2AlNMe_2; (vi) aqueous NaOH, $PhCH_2N^+Et_3Cl^-$, $CHCl_3$; (vii) CH_2I_2, Zn, DME, sonication; (viii) $Me_3S^+(O)I^-$, NaH, DMSO; (ix) $LiAlH_4$; (x) Ph_3P, $EtOOCN{=}NCOOEt$, PhCOOH; aqueous NaOH (5 M); (xi) CH_2I_2, Zn(Cu); (xii) CH_3CHI_2, Sm, $HgCl_2$; (xiii) $EtOOCCH_2P(O)(OEt)_2$, NaH; (xiv) $EtOOCCH(Me)P(O)(OEt)_2$, NaH; (xv) see ref 37. Where stereochemical assignments are tentative, this fact is indicated in the Experimental Section.

Discussion

The sequence of Scheme I posed three chemical problems. First, we had to select the best routes to cyclopropanes with the desired stereochemistry and then a suitable method of generating the carbinyl radicals had to be found. Finally, it was necessary to establish what experimental conditions and/or substitution patterns favor in each case isolation of the product resulting from homolysis of the peripheral bond in the cyclopropane.

The cyclopropylcarbinols that we prepared are shown in Table I. We evaluated the classical Simmons–Smith reaction and used it for examples **12a** → **12b**, **13a** → **13b**, and **15a** → **15b**. A number of modifications of this stereoselective cyclopropanation have been reported.[31] We arbitrarily used the Zn/CH_2I_2/ultrasound system for **12b** and **13b** and the $Zn(Cu)/CH_2I_2$ reagent for the steroid **15b**. The methyl-substituted cyclopropane **16b** was prepared

(28) Ashwell, S.; Davies, A. G.; Golding, B. T.; Hay-Motherwell, R. S.; Mwesigye-Kibende, S. *J. Chem. Soc., Chem. Commun.* **1989**, 1483. Wollowitz, S.; Halpern, J. *J. Am. Chem. Soc.* **1988**, *110*, 3112. Davies, A. G.; Golding, B. T.; Hay-Motherwell, R. S.; Mwesigye-Kibende, S.; Ramakrishna Rao, D. N.; Symons, M. C. R. *J. Chem. Soc., Chem. Commun.* **1988**, 378.

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(30) Epoxide opening may be involved in the biosynthesis of Rifamycin S: Murphy, J. A.; Patterson, C. W.; Wooster, N. F. *J. Chem. Soc., Chem. Commun.* **1988**, 294.

(31) Tsuji, T.; Nishida, S. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: Chichester, 1987; p 307. Friedrich, E. C.; Lewis, E. J. *J. Org. Chem.* **1990**, *55*, 2491.

by using 1,1-diiodoethane and samarium metal.[32]

The decalin allylic alcohols **12a** and **13a** were not directly accessible by a highly stereoselective process: a mixture of the two (**12a**:**13a** = 87:13) was cyclopropanated, and the alcohols **12b** and **13b** could then be separated by column chromatography. However, compound **13a** was more conveniently obtained (as described below) from the major alcohol **12a**.

Compounds **10b** and **11b** were made by dichlorocarbene addition to the corresponding allylic alcohols **10a** and **11a**. In both cases the reaction should be stopped just short of completion for best results. The dichlorocarbene method is reported[33] to occur with stereochemical direction by the hydroxyl and, on this basis, the single product isolated in each case (71% yield for **10b** and 73% for **11b**) is assigned the indicated stereochemistry.

Formation of **9d** represents an example where the three-membered ring is generated by intramolecular delivery, which, of course, produces a predictable stereochemical result.

In those cases where a readily accessible allylic alcohol does not have the desired stereochemistry, Mitsunobu inversion gives[34] the alcohol required for hydroxyl-directed cyclopropanation, and this method was used in preparing **13a** and **15a**.

A different approach to cyclopropanes of predictable stereochemistry was used to construct the carbohydrate examples **17b**[35] and **18b**.[36] In both cases, an epoxide of appropriate stereochemistry was available by simple modifications of glucose. Conversion of epoxide **17a** into cyclopropane **18a** was effected by a more convenient procedure than that reported[36] in the literature (see Experimental Section).

We have also used enones as substrates for direct cyclopropanation (**7a** → **7b**; **8a** → **8b**; **8a** → **14a**) and in these cases the cyclopropyl ketone was then reduced to the corresponding alcohol (**7b** → **7c**; **8b** → **8c**; **14a** → **14b**). Of course, the procedure based on enones cannot be adjusted at will to place the cyclopropane on either face of the molecule.[37]

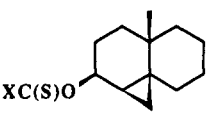
In this work all the cyclopropanes except for those in the steroid and carbohydrate series are racemic; we did not examine asymmetric cyclopropanation.[37]

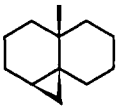
The second stage of the process shown in Scheme I involves generation of a carbon radical at the site occupied by the hydroxyl. In most cases we have replaced the hydroxyl by a phenylseleno group and then homolyzed the resulting selenium–aliphatic carbon bond.

Introduction of the phenylseleno group was first tried by the standard method,[38] which involves treatment of the alcohol with phenyl selenocyanate, followed by tributylphosphine. In some of our early experiments under these conditions the reaction did not go to completion; however, in these cases a very significant improvement was achieved by adding the selenocyanate slowly to a mixture of the alcohol and the phosphine, and we now prefer this modified procedure. Replacement of the hydroxyl by the selenium unit did not always involve clean inversion of stereochemistry, but this is of no consequence since both epimers at the selenium-bearing carbon afford the same radical. Compound **10c** was also made on a multigram scale and in this case it was more convenient to generate the selenide **10c** by nucleophilic displacement of the tosylate derived from alcohol **10b**. Lactone **9c** did not react with phenyl selenide anion[39] and so the lactone ring was first opened by conversion[40] to the hydroxy amide **9d**.

During preparation of the selenides used in this work, we often had to separate diphenyl diselenide from a cyclopropyl selenide. This was conveniently achieved by adding sodium borohydride and then bromoacetic acid to the crude material. The borohydride converts the diselenide into the phenyl selenide anion, which reacts with the bromoacetic acid to form (phenylseleno)acetic acid, and this can be removed by extraction into aqueous base.

The selenide unit turned out to be a general and very satisfactory source of the required carbon radicals,[41] and so we did not make a thorough examination of thiocarbonyl derivatives, which are an obvious alternative. With **20–22**,[42] as test cases, we found that the traditional thermal





23

20 X = Imidazolyl
21 X = OPh
22 X = SMe

deoxygenation[43] in refluxing benzene is unsuitable,[44] but we did not try to form the radicals at a low temperature using triethylborane and air.[45]

The carbohydrate examples were handled in a different way, but still with the use of readily accessible derivatives. In the case of **19a** the radical precursor was an anomeric bromide, which was prepared in the usual manner (see Experimental Section), and for **17c** and **18c** the required radical was formed by sensitized photolysis[46] of a benzoate at room temperature.

Radical generation and ring-opening was done under a number of different conditions that were determined by structural details of the substrate. Apart from examples **17c** and **18c**, where a photochemical process was used, those cyclopropanes carrying a strongly electron-with-

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(39) (a) Dowd, P.; Kennedy, P. *Synth. Commun.* **1981**, *11*, 935. (b) Ley, S.; O'Neil, I. A.; Low, C. M. R. *Tetrahedron* **1986**, *42*, 5363. (c) Liotta, D.; Sunay, U.; Santiesteban, H.; Markiewicz, W. *J. Org. Chem.* **1981**, *46*, 2605.
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(41) Clive, D. L. J.; Chittattu, G. J.; Farina, V.; Kiel, W. A.; Menchen, S. M.; Russell, C. G.; Singh, A.; Wong, C. K.; Curtiss, N. J. *J. Am. Chem. Soc.* **1980**, *102*, 4438.
(42) With the standard preparations given in ref 43 and in Robins and Wilson (Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 932) the yields of **24**, **25**, and **26** were 76%, 75%, and 45%, respectively.
(43) Barton, D. H. R.; McCombie, W. *J. Chem. Soc., Perkin Trans. I* **1975**, 1574.
(44) One of the problems we encountered was extensive formation of olefinic material, possibly as a result of ring expansion. However, for a very successful related use of the classical Barton deoxygenation, carried out in refluxing benzene, see ref 24.
(45) Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 6125. The presence of air is necessary. See: Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547 and ref 17 therein. Barton, D. H. R., Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* **1990**, *31*, 4681.
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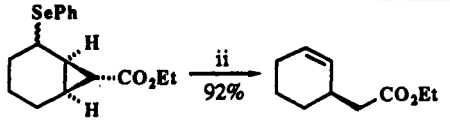
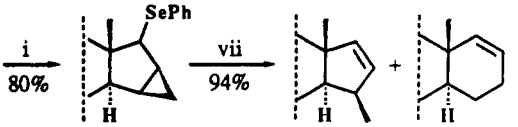
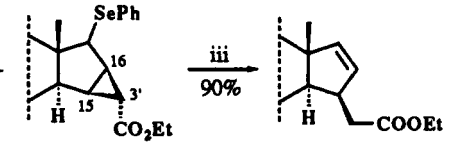
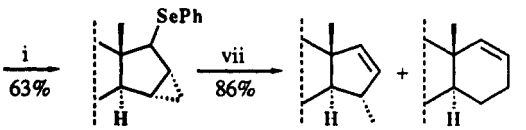
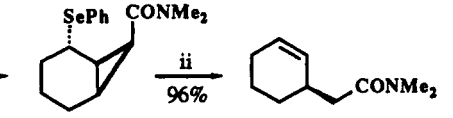
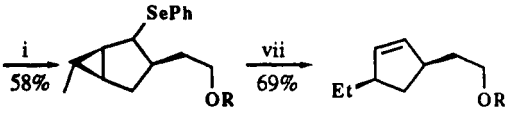
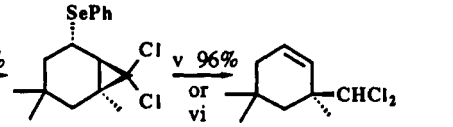
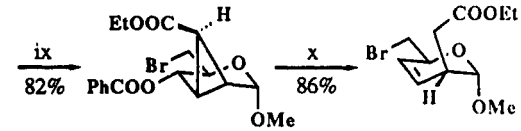
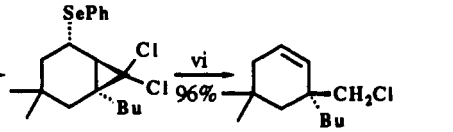
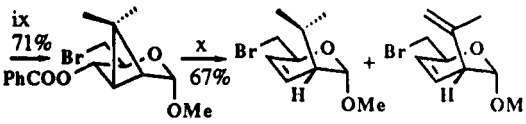
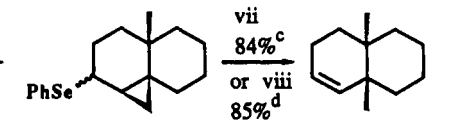
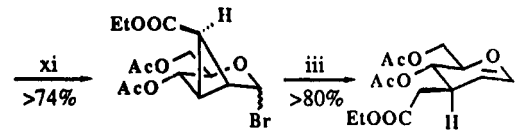
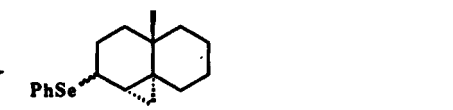
Table II. Cyclopropane Ring-Opening[a]

entry			entry		
1	7c	 7d 7e	8	14b	 14c 14d (84:16) 14e
2	8c	 8d 8e	9	15b	 15c 15d (84:16) 14e
3	9d	 9e 9f	10	16b	 16c R = $OSiPh_2Bu$-t 16d
4	10b	 10c 10d	11	17b	 17c 17d
5	11b	 11c 11d	12	18b	 18c 18d (1:1) 18e
6	12b	 12c 12d	13	17b	 19a 19b
7	13b	 13c[e]			

[a] (i) Bu_3P, PhSeCN; (ii) Ph_3SnH, AIBN; (iii) Bu_3SnH, AIBN; (iv) *p*-toluenesulfonyl chloride, DMAP, pyridine; then PhSeNa, HMPA; (v) Ph_3SnH, sunlamp; (vi) Ph_3SnH, Et_3B; (vii) Bu_3SnH, sunlamp; (viii) Bu_3SnH, Et_3B; (ix) NBS, $BaCO_3$; (x) *N*-methylcarbazole, $Mg(ClO_4)_2 \cdot 6H_2O$, $h\nu$; (xi) H_2, Pd–C; Ac_2O, pyridine; Ac_2O, H_2SO_4 (catalytic); Me_3SiBr. Where stereochemical assignments are tentative, this fact is indicated in the Experimental Section. [b] Overall from **8a**. [c] The material contains some impurities (7%). [d] The material contains some impurities (3%). [e] No ring-opening was observed (see text).

drawing group (**7d**, **8d**, **9e**, **19a**) gave the desired products when treated with a stannane and initiator (both added in one portion at the beginning of the experiment) in refluxing benzene. The whole process formally represents in these cases a radical equivalent of an Ireland ester–enolate rearrangement. In contrast, studies with **12c** and **14c** showed that cyclopropanes lacking an electrron-withdrawing group should be treated with stannane at a low or moderate temperature (−20 to 25 °C) in order to suppress the significant amount of ring expansion that is observed when the reaction is done in refluxing benzene. Compounds **10c**, **15c**, and **16c** were arbitrarily examined only under these mild conditions, and each case was conveniently dealt with by irradiating a cooled solution of the substrate and stannane with a domestic sunlamp. For **12c**, **14c**, and **15c**, which are our only examples where the cyclopropane lacks a substituent on the non-bridgehead carbon, the major product results from the desired opening of a peripheral bond, but some material from the ring expansion pathway was always formed (see Table II). With the dichloride **10c**, maintenance of a low temperature also serves to inhibit dechlorination, and the desired dichloro olefin was obtained in excellent yield, uncontaminated by the corresponding monochloro compound. With

11c we deliberately reduced the initial ring-opened product further so as to obtain the monochloride 11d.

In most experiments we have used triphenyltin hydride, but it is sometimes better to use the tributyl analogue. We have occasionally found that chromatographic separation of tin-containing byproducts is a little easier with one or other of the stannanes. In the case of the decalin derivative 12c, the use of tributyltin hydride, a poorer hydrogen donor,[47] gave a higher proportion of 12d to cyclopropane 23, which was always a minor byproduct with this decalin substrate.

As stated above, a photochemical method was used to form radicals from the carbohydrate benzoates 17c and 18c. The procedure[46] calls for photolysis at room temperature and so the method should be suitable even where an electron-withdrawing substituent is absent. In contrast to procedures based on stannane chemistry, the photochemical method is compatible with the presence of a bromine atom (see 17c → 17d and 18c → 18d + 18e).

From 18c the initial radical opening is apparently followed by disproportionation, as the product is a 1:1 mixture of carbohydrates (18d and 18e) containing an isopropyl and isopropenyl group, respectively. Such behavior has been noted for tertiary radicals under our experimental conditions.[46] The carbohydrate examples illustrate the fact that, in general, it will be possible to prepare carbohydrate cyclopropanes flanked on either side by a potential radical precursor, and so regiochemical control is possible, and the substituent resulting from cyclopropane opening can be placed at one or other of two sites.

Compound 13c was the only example we found that did not undergo ring opening under our standard conditions, and we attribute[48] this to the fact that the conformation of the molecule results in poor overlap between the radical center and the cyclopropane carbon–carbon bonds. The isomeric cyclopropane 12c did react in the required way to produce 12d, but, as mentioned above, some ring expansion product (about 4%) was formed even under optimized conditions. It should be noted that both compounds 12c and 13c have an additional feature in that ring expansion (internal homolysis) generates a tertiary radical; with the other unsubstituted cyclopropanes the competion is between primary and secondary radicals, for peripheral and internal homolysis, respectively.

Finally, in the case of 10c, 11c, and 12c we examined the use of triethylborane/air[45] to initiate the stannane reduction and found that the reaction works very well and represents an alternative to photochemical initiation.

Conclusions

The above results show that radical ring-opening of cyclopropane carbinols is a general method for attaching alkyl and substituted alkyl groups to an existing cyclic structure and can often be carried out with predictable stereo- and regiochemical control. Where the nonbridgehead carbon of the cyclopropane carries a strongly electron-withdrawing group, the ring opening can be done at the reflux temperature of benzene and proceeds efficiently. However, in the absence of such electron-withdrawing groups a low temperature is best used in order to suppress ring expansion.[49] Like many radical-based methods the procedure is compatible with a range of functionality and the required radicals can be generated by a number of different and complementary methods.

(47) Cf. Friedrich, E. C.; Holmstead, R. L. *J. Org. Chem.* **1971**, *36*, 971. Carlsson, D. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1968**, *90*, 7047.
(48) Shaffer, G. W. *J. Org. Chem.* **1973**, *38*, 2842.
(49) But cf. ref 24.

Experimental Section

General. Experimental procedures were the same as those used previously.[50] Isolated compounds were homogeneous as judged by ^{1}H NMR measurements. Gas chromatographic (GC) analyses were performed with an FID detector on a prepacked Hewlett-Packard 6 ft × $^1/_8$ in. o.d. stainless steel analytical column packed with 10% OV-1, 80/100 Chromosorb W-HP, and with nitrogen as the carrier gas. A Branson ultrasonic bath (Model B-12) was used as a source of ultrasound.

General Procedure for Photochemical Radical Ring-Opening. The substrate was placed in a 10- or 25-mL oven-dried Pyrex flask with an optically flat panel in its upper side and containing a Teflon-coated stirring bar. The system was flushed with argon, and dry solvent was injected. The flask was lowered into a cold-bath (−70 to 0 °C, depending on the experiment) and irradiated from above with a 275-W General Electric sunlamp. Ph_3SnH (or Bu_3SnH) (1.5 equiv) was injected over a period of 1 min and stirring was continued for 0.5 to 4 h at the specified temperature. The mixture was transferred to a round-bottomed flask and evaporated, and the residue was then processed as described for the individual examples.

General Procedure for Thermal Radical Ring-Opening. The substrate was placed in a 10- or 25-mL oven-dried round-bottomed flask containing a Teflon-coated stirring bar and equipped with a reflux condenser sealed by a rubber septum. The system was flushed with argon for 5–10 min, and dry benzene was injected. Ph_3SnH (or Bu_3SnH) (1.5 equiv) was injected over 1 min and AIBN (0.1 equiv) was added in one portion. The flask was lowered into an oil bath preheated to 100 °C, and the mixture was refluxed for 0.25 to 3 h, after which it was cooled and evaporated. The residue was then processed as described for the individual examples.

Ethyl (1α,6α,7α)- and (1β,6β,7α)-2-Oxobicyclo[4.1.0]heptane-7-carboxylate (7b).[51] Ethyl (dimethylsulfuranylidene)-acetate[51] (2.94 g, 19.9 mmol) was injected over 4 h into a refluxing solution of 2-cyclohexen-1-one (957 mg, 9.95 mmol) in dry benzene (9 mL). Refluxing was continued for an additional 14 h, and the solvent was then evaporated. Flash chromatography of the residue over silica gel (6.5 × 20 cm) using first 10% EtOAc–hexane and then gradually increasing proportions of EtOAc (up to 40%) afforded slightly impure (TLC, silica, 25% EtOAc–hexane) 7b (1.44 g). Distillation (Kugelrohr; 100 °C, 0.08 mm) gave 7b as an apparently homogeneous (TLC, 25% EtOAc–hexane) white solid (1.32 g, 73%). The material was largely [>95% (^{13}C NMR)] one isomer, presumed to have the indicated stereochemistry.

Ethyl (1α,2β,6α,7α)- and (1α,2α,6α,7α)-2-Hydroxybicyclo-[4.1.0]heptane-7-carboxylate (7c). $NaBH_4$ (109 mg, 2.87 mmol) was added over 3 min to a cold (0 °C) and stirred suspension of 7b (476 mg, 2.61 mmol) and $CeCl_3 \cdot 7H_2O$ (1.09 g, 2.92 mmol) in MeOH (7 mL). Stirring was continued for 30 min. The mixture was quenched by addition of water (10 mL) and extracted with ether (2 × 25 mL). The combined organic extracts were washed with brine (1 × 15 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 20 cm) using 40% EtOAc–hexane gave alcohols 7c (410 mg, 85%) as a colorless oily mixture of two isomers in a ratio (^{1}H NMR) of ca. 1:2: FT-IR ($CHCl_3$ cast) 3430, 2940, 1720, 1700, 1300, 1175, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.07 (m, 1 H), 1.10–1.20 [m, including a t at 1.27 (J = 7.3 Hz), 11 H], 2.23 (br m, 0.41 H), 2.60 (br s, 0.61 H), 4.04 (br s, 0.8 H), 4.12 (two superimposed q, J = 7.3 Hz, 2 H), 4.21 (m, 0.2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) (major isomer) δ 14.22, 15.84, 21.97, 22.01, 24.21, 29.01, 30.21, 60.47, 65.80, 174.00; (minor isomer) δ.20.09, 21.89, 22.70, 23.99, 28.92, 29.75, 65.63, 174.11; exact mass, m/z calcd for $C_{10}H_{15}O_2$ 167.1052, found 167.1072. Anal. Calcd for $C_{10}H_{15}O_2$: C, 65.19; H, 8.76. Found: C, 65.38; H, 8.67.

Ethyl (1α,2α,6α,7α)- and (1α,2β,6α,7α)-2-(Phenylseleno)-bicyclo[4.1.0]heptane-7-carboxylate (7d). PhSeCN (982 mg, 5.4 mmol) and then Bu_3P (1.34 mL, 5.4 mmol) were added, each in one portion, to a cold (0 °C) and stirred solution of 7c (332 mg, 1.8 mmol) in dry THF (7 mL). Stirring was continued for 4 h at 0 °C. Evaporation of the solvent and flash chromatography

(50) Clive, D. L. J.; Boivin, T. L. B. *J. Org. Chem.* **1989**, *54*, 1997. Clive, D. L. J.; Boivin, T. L. B.; Angoh, A. G. *J. Org. Chem.* **1987**, *52*, 4943.
(51) Payne, G. B. *J. Org. Chem.* **1967**, *32*, 3351.

of the residue over silica gel (3 × 20 cm) using successively hexane, 50% CH_2Cl_2–hexane, and 5% EtOAc–hexane gave **7d** (468 mg, 80%) as a slightly yellow oil: FT-IR ($CHCl_3$ cast) 2935, 1720, 1575, 1300, 1182, 740, 685 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15 [m, including two superimposed t at 1.25 (J = 7.2 Hz), 5 H], 3.62 (m, 0.2 H), 3.79 (m, 0.8 H), 4.10 (two superimposed q, J = 7.2 Hz, 2 H), 7.25 (m, 3 H), 7.58 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) (major isomer only) δ 14.20, 21.88, 22.17, 24.89, 25.56, 27.60, 28.39, 39.22, 60.28, 127.50, 128.78, 135.15, 173.65; exact mass, m/z calcd for $C_{16}H_{20}O_2Se$ 324.0629, found 324.0629. Anal. Calcd for $C_{16}H_{20}O_2Se$: C, 59.44; H, 6.24; O, 9.90. Found: C, 59.74; H, 6.28.

Ethyl (2-Cyclohexen-1-yl)acetate (7e).[52] The general procedure for thermal radical ring-opening was followed, using **7d** (179 mg, 0.55 mmol) in dry benzene (5.5 mL), Ph_3SnH (183 μL, 0.72 mmol), and AIBN (4 mg, 0.03 mmol). Refluxing was continued for 1 h, and the mixture was then evaporated. Kugelrohr distillation (90 °C, 1.5 mm) of the residue afforded **7e**[52] (85.4 mg, 92%) as a colorless oil.

Ethyl (15α,16α)-15,16-Dihydro-3-methoxy-17-oxo-3′*H*-cycloprop[15,16]estra-1,3,5(10),15-tetraene-3′-carboxylate (8b).[53] Ethyl (dimethylsulfuranylidene)acetate[51] (663 mg, 4.48 mmol) was added with stirring over 3 h (syringe pump) to a warm (55 °C) solution of **8a** (633 mg, 2.24 mmol) in dry DMSO (7.4 mL). Stirring at 55 °C was continued for 18 h, and water (20 mL) was added. The mixture was extracted with CH_2Cl_2 (50 mL), and the organic extract was washed with 1:1 brine–water (1 × 50 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3.0 × 20 cm) using 20% EtOAc–hexane afforded impure **8b** (546 mg), which was used directly in the next step.

Ethyl (15α,16α)-15,16-Dihydro-17-hydroxy-3-methoxy-3′*H*-cycloprop[15,16]estra-1,3,5(10),15-tetraene-3′-carboxylate (8c).[53,54] $NaBH_4$ (66 mg, 1.75 mmol) was added over 3 min to a stirred suspension of crude **8b** (536 mg, 1.45 mmol) and $CeCl_3·7H_2O$ (652 mg, 1.75 mmol) in MeOH (7 mL). Stirring was continued at room temperature for 2 h. Further portions of $CeCl_3·7H_2O$ (325 mg, 0.88 mmol) and of $NaBH_4$ (33 mg, 0.88 mmol) were then added, and stirring was continued for 1 h. The mixture was quenched by addition of water (1 × 10 mL) and extracted with EtOAc (2 × 20 mL). The combined extracts were washed with water (1 × 10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm) using first 20% EtOAc–hexane and then 25% EtOAc–hexane gave crude **8c** (471 mg), which was used directly in the next step.

Ethyl (15α,16α)-15,16-Dihydro-3-methoxy-17-(phenylseleno)-3′*H*-cycloprop[15,16]estra-1,3,5(10),15-tetraene-3′-carboxylate (8d).[53] PhSeCN (263 mg, 1.45 mmol) in dry THF (1 mL) was added with stirring over 2 h (syringe pump) to a warm (45 °C) solution of crude **8c** (268 mg, 0.723 mmol) and Bu_3P (361 μL, 1.45 mmol) in dry THF (4 mL). Stirring was continued at 45 °C for 16 h, and the solvent was evaporated. Flash chromatography of the residue over silica gel (2.0 × 20.0 cm) using first 30% CH_2Cl_2–hexane (to remove diphenyl diselenide) followed by 15% EtOAc–hexane afforded a mixture of selenides **8d** in a ratio of 95:5 [^1H NMR (300 MHz)] (218 mg, 59% based on **8a**) as a gummy white solid: FT-IR ($CHCl_3$ cast) 2932, 1722, 1500, 1282, 1172, 1037, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.91 (s, 0.3 H), 1.0 (s, 2.7 H), 1.21 (t, J = 7.3 Hz, 3 H), 1.36–1.68 (m, 4 H), 1.74–2.46 (m, 8 H), 2.82–3.0 (m, 2 H), 3.74 (s, 3 H), 3.80 (s, 1 H), 4.06 (q, J = 7.3 Hz, 2 H), 6.63 (d, J = 2.9 Hz, 1 H), 6.70 (dd, J = 8.5, 2.9 Hz, 1 H), 7.14 (d, J = 8.5 Hz, 1 H), 7.20–7.32 (m, 3 H), 7.50–7.69 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) (major peaks only) δ 14.22, 24.36, 26.46, 26.75, 28.09, 28.40, 29.57, 31.34, 37.06, 41.07, 42.04, 44.08, 52.83, 55.19, 56.78, 60.51, 111.45, 113.87, 125.90, 127.20, 129.13, 130.23, 132.30, 133.83, 137.72, 157.60, 172.72; exact mass, m/z calcd for $C_{29}H_{34}O_3Se$ 510.1674, found 510.1672. Anal. Calcd for $C_{29}H_{34}O_3Se$: C, 68.36; H, 6.73; O, 9.43. Found: C, 68.17; H, 6.82; O, 9.37.

Ethyl (3-Methoxyestra-1,3,5(10),16-tetraen-15β-yl)acetate (8e).[55] With one modification, the general procedure for thermal radical ring-opening was followed, using selenides **8d** (129 mg, 0.252 mmol) in benzene (2.5 mL), Bu_3SnH (88 μL, 0.33 mmol), and AIBN (3 mg, 0.02 mmol). In this particular experiment, further portions of Bu_3SnH (88 μL, 0.33 mmol) and AIBN (3 mg, 0.02 mmol) were added after 4 h, since the reaction had stopped (TLC control, silica, 10% EtOAc–hexane). Stirring under reflux was continued for 12 h more. The mixture was cooled and evaporated. Flash chromatography of the residue over silica gel (1.5 × 20.0 cm) using 10% EtOAc–hexane afforded pure **8e** (80 mg, 90%) as a white solid: FT-IR ($CHCl_3$ cast) 3248, 1733, 1500, 1255; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.97 (s, 3 H), 1.28 (t, J = 7.2 Hz, 3 H), 1.43–1.70 (m, 4 H), 1.71–1.88 (m, 2 H), 1.95–2.09 (m, 1 H), 2.20–2.41 (m, 3 H), 2.56 (dd, J = 15.6, 3.6 Hz, 1 H), 2.80–2.98 (m, 2 H), 2.98–3.08 (m, 1 H), 3.78 (s, 3 H), 4.15 (q, J = 7.2 Hz, 2 H), 5.89 (dd, J = 6.0, 3.0 Hz, 1 H), 5.97 (d, J = 6.0 Hz, 1 H), 6.66 (d, J = 2.9 Hz, 1 H), 6.72 (dd, J = 8.8, 2.9 Hz, 1 H), 7.18 (J = 8.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.30, 22.26, 26.02, 27.61, 29.58, 35.20, 35.42, 37.58, 40.83, 45.12, 46.39, 55.21, 55.79, 60.35, 111.34, 113.84, 125.70, 132.95, 133.12, 137.62, 143.67, 157.58, 173.32; exact mass, m/z calcd for $C_{23}H_{30}O_3$ 354.2195, found 354.2193. Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 77.96; H, 8.25.

2-Cyclohexen-1-yl Diazoacetate (9b). The procedure is based on a general literature method.[56] Dry *N,N*-dimethylaniline (1.55 mL, 12.24 mmol) was added to a cold (0 °C) and stirred solution of 2-cyclohexen-1-ol (1.0 g, 10.2 mmol) and [(*p*-toluenesulfonyl)hydrazono]acetyl chloride[57] (3.31 g, 12.75 mmol) in dry CH_2Cl_2 (68 mL). After 20 min at 0 °C, dry triethylamine (7.1 mL, 51 mmol) was injected over about 1 min and stirring was continued for 15 min. The cold bath was removed, and, after a further 30 min, the mixture was quenched with water (30 mL) and concentrated. The residue was extracted with 10% EtOAc–hexane (2 × 65 mL), and the combined extracts were washed with saturated aqueous citric acid (2 × 30 mL). The combined aqueous layers were extracted with 10% EtOAc–hexane (1 × 30 mL), and the organic extract was washed with saturated aqueous citric acid (1 × 5 mL). All the organic extracts were combined, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 × 20 cm) using 8% EtOAc–hexane afforded **9b** (1.19 g, 70%) as a bright yellow oil, containing trace impurities. The material was distilled (Kugelrohr, 45 °C, 0.05 mm) for characterization: FT-IR ($CHCl_3$ cast) 3120, 2950, 2055, 1690, 1380, 1180; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.55–1.81 (m, 3 H), 1.81–2.18 (m, 3 H), 4.74 (br s, 1 H), 5.35 (m, 1 H), 5.72 (ddt, J = 10.0, 3.8, 2.1 Hz, 1 H), 5.96 (ddt, J = 10.0, 3.8, 1.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.60, 24.86, 28.49, 68.61, 125.68, 132.67; exact mass, m/z calcd for $C_8H_{10}N_2O_2$ 166.0742, found 166.0725. Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.06; N, 16.86. Found: C, 57.81; H, 5.98; N, 16.81.

(2aα,2bα,5aα,5bα)-Hexahydrocyclopropa[*cd*]benzofuran-2(2a*H*)-one (9c). A solution of **9b** (1.09 g, 6.56 mmol) in dry toluene (40 mL) was injected over 12 h into a refluxing solution of bis(*N-tert*-butylsalicylaldiminato)copper(II)[58] (136 mg, 0.328 mmol) in dry toluene (210 mL) contained in a 500-mL round-bottomed flask equipped with a condenser and heated by an oil bath set at 135 °C. After the addition was complete, the mixture was cooled and evaporated. Flash chromatography of the residue over silica gel (3 × 18 cm) using 40% EtOAc–hexane afforded **9c** (798 mg, 88%) as a slightly yellow oil: FT-IR ($CHCl_3$ cast) 2950, 1760, 1340, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40–1.78 (m, 5 H), 1.85 (m, 1 H), 2.08 (m, 2 H), 2.36 (dt, J = 8.0, 6.2 Hz, 1 H), 4.92 (dt, J = 6.0, 2.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.61, 18.07, 18.52, 22.60, 24.07, 24.70, 74.03, 175.69; exact mass, m/z calcd for $C_8H_{10}O_2$ 130.0681, found 130.0682. Anal. Calcd for $C_8H_{10}O_2$: 69.54; H, 7.29. Found: C, 69.18; H, 7.31.

(1α,2β,6α,7β)-2-Hydroxy-*N,N*-dimethylbicyclo[4.1.0]heptane-7-carboxamide (9d). The procedure is based on a general literature method.[40] Cold (−70 °C) Me_2NH (30 μL, 0.456 mmol)

(52) Pitteloud, R.; Petrzilka, M. *Helv. Chim. Acta* **1979**, *62*, 1319.
(53) Stereochemistry shown at C(3′) is an arbitrary assignment; that at C(15) and C(16) is made by analogy to the transformation **8a** → **14a**.
(54) Stereochemistry shown at C(17) is made by analogy to the transformation **14a** → **14b**.
(55) Stereochemistry at C(15) follows from the sense of cyclopropanation.
(56) Corey, E. J.; Meyers, A. G. *Tetrahedron Lett.* **1984**, *25*, 3559.
(57) Blankley, C. J.; Sauter, F. J.; House, H. O. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 258.
(58) Charles, R. *J. Org. Chem.* **1957**, *22*, 677. See also: Sacconi, L.; Ciampolini, M. *J. Chem. Soc.* **1964**, 276.

and then Me_3Al (2 M in toluene, 0.217 mL, 0.434 mmol) were added to dry CH_2Cl_2 (1 mL). The mixture was stirred for 30 min at room temperature, and lactone **9c** in dry CH_2Cl_2 (0.2 mL, plus 0.2 mL as a rinse) was injected over about 5 min. Stirring was continued for 3 h at room temperature and then at reflux for 5 h. The mixture was cooled in ice and quenched by careful addition of aqueous HCl (1 M, 0.5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 7 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Kugelrohr distillation (90 °C, 0.05 mm) afforded **9d** (37 mg, 93%) as a white solid: FT-IR ($CHCl_3$ cast) 3287, 2943, 2870, 1615, 1451, 1048, 711 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.82 (m, 1 H), 0.97 (m, 1 H), 1.13 (ddq, J = 13.0, 4.5, 2.2 Hz, 1 H), 1.43 (dm, J = 13.0 Hz, 1 H), 1.77 (m, 2 H), 1.94 (m, 2 H), 3.03 (s, 3 H), 3.17 (s, 3 H), 4.12 (tt, J = 11.0, 7.0 Hz, 1 H), 5.30 (d, J = 11.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.79, 20.00, 20.21, 22.53, 25.84, 31.71, 35.41, 37.57, 66.65, 171.16; exact mass, m/z calcd for $C_{10}H_{17}NO_2$ 183.1259, found 183.1256. Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.41; H, 9.20; N, 7.84.

In a similar experiment on a larger scale [**9c** (150 mg)], **9d** (180 mg, 90%) was obtained.

(1α,2α,6α,7β)-*N*,*N*-Dimethyl-2-(phenylseleno)bicyclo[4.1.0]heptane-7-carboxamide (9e). PhSeCN (236 μL, 1.75 mmol) in dry THF (0.5 mL) was added over 15 min (syringe pump) to a refluxing solution of **9d** (168 mg, 0.874 mmol) and Bu_3P (436 μL, 1.75 mmol) in dry THF (3.9 mL). Stirring was continued for 14 h, and the mixture was cooled and evaporated. Flash chromatography of the residue over silica gel (2 × 20 cm) using 40% EtOAc–hexane gave **9e** (232 mg, 78%) as an orange oil. The material contained slight impurities [^1H NMR (200 MHz)] but was suitable for the next stage: FT-IR ($CHCl_3$ cast) 2930, 2855, 1841, 1580, 1140, 740, 685 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.2 (m, 1 H), 1.34–1.63 (m, 5 H), 1.75 (m, 2 H), 1.88 (m, 1 H), 2.93 (s, 3 H), 3.04 (s, 3 H), 4.0 (ddd, J = 8.1, 5.1, 2.3 Hz, 1 H), 7.25 (m, 3 H), 7.61 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.18, 19.57, 20.34, 21.50, 22.85, 28.97, 34.89, 36.17, 37.02, 127.08, 128.98, 130.37, 133.97, 170.24; exact mass, m/z calcd for $C_{16}H_{21}NOSe$ 323.0789, found 323.0791. Anal. Calcd for $C_{16}H_{21}NOSe$: C, 59.62; H, 6.57; N, 4.34. Found: C, 59.45; H, 6.51; N, 4.45.

***N*,*N*-Dimethyl-2-cyclohexene-1-acetamide (9f).** With one exception, the general procedure for thermal radical ring-opening was followed, using selenide **9e** (221 mg, 0.685 mmol) in benzene (6.8 mL), Ph_3SnH (262 μL, 1.02 mmol), and AIBN (11 mg, 0.07 mmol). In this particular experiment a second portion of AIBN (11 mg, 0.07 mmol) was added after 30 min at reflux temperature. Refluxing was continued for 2 h after the second addition of initiator, and the mixture was then cooled and evaporated. Kugelrohr distillation of the residue (90 °C, 0.4 mm) afforded **9f** (109 mg, 96%) as a colorless oil.

(1α,2β,6α)-7,7-Dichloro-4,4,6-trimethylbicyclo[4.1.0]heptan-2-ol (10b).[59] Benzyltriethylammonium chloride (35 mg) was added to a cold (0 °C) and stirred solution of 3,5,5-trimethyl-2-cyclohexen-1-ol (1.0 g, 7.13 mmol) in $CHCl_3$ (15 mL). Aqueous NaOH 50% w/w (7.1 mL) was then added over a period of 5 min.[33] The course of the reaction was closely monitored by TLC (silica, 20% EtOAc–hexane),[60] and, after 40 min at 0 °C, the reaction was stopped by addition of water (15 mL), and ether (25 mL) was added. The aqueous layer was extracted with ether (2 × 25 mL) and the combined organic layers were dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3.0 × 20.0 cm) using 15% EtOAc–hexane gave **10b** (1.14 g, 71%) as a white solid: mp 84–84.5 °C; FT-IR ($CHCl_3$ cast) 3220, 2956, 1050, 843 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (s, 3 H), 0.95 (s, 3 H), 1.24 (dd, J = 12.3, 11.8 Hz, 1 H), 1.41 (s) and 1.44 (dd, J = 14.5, 2.1 Hz) [both signals together correspond to 4 H], 1.61 (ddd, J = 13.1, 7.5, 2.1 Hz, 1 H), 1.69 (d, J = 7.5 Hz) and 1.75 (dd, J = 14.5, 0.7 Hz) [both signals together correspond to 2 H], 1.97 (br s, 1 H), 4.32 (dt, J = 11.2, 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 25.21, 25.99, 30.95, 32.04, 32.56, 36.66, 39.79, 42.04, 65.75, 71.25; exact mass, m/z calcd for $C_{10}H_{16}Cl_2O$ 222.0578, found 222.0576. Anal. Calcd for $C_{10}H_{16}Cl_2O$: C, 53.82; H, 7.23; Cl, 31.78. Found: C, 53.68; H, 7.30; Cl, 32.01.

(1α,5α,6α)-7,7-Dichloro-1,3,3-trimethyl-5-(phenylseleno)bicyclo[4.1.0]heptane (10c). Method a. PhSeCN (342 mg, 1.88 mmol) in dry THF (1 mL) was added by syringe pump over 1 h to a refluxing solution of dichlorocyclopropane alcohol **10b** (210 mg, 0.94 mmol) and Bu_3P (0.47 mL, 1.88 mmol) in dry THF (2 mL). After 16 h the mixture was cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (2 × 20 cm) using 10% EtOAc–hexane gave **10c** (539 mg) contaminated with diphenyl diselenide. This material was dissolved in dry THF–EtOH (4:1) (10 mL) and cooled to −20 °C. $NaBH_4$ (100 mg) was added and the mixture was stirred at −20 °C for 10 min. Bromoacetic acid (400 mg) was then added, the cold bath was removed, and stirring was continued for 30 min. The mixture was then diluted with ether (15 mL) and quenched with saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with ether (1 × 15 mL), and the combined extracts were washed with water (1 × 10 mL) and brine (1 × 10 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 20 cm) using 3% EtOAc–hexane gave selenide **10c** (282 mg, 82%) as a very slightly yellow solid: mp 52–58 °C; FT-IR ($CHCl_3$ cast) 2953, 1580, 1478, 1437, 734, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (s, 3 H), 1.08 (s, 3 H), 1.43 (s, 3 H), 1.44–1.59 (m, 3 H), 1.63 (dd, J = 15.1, 7.3 Hz, 1 H), 1.70 (d, J = 1.4 Hz, 1 H), 3.66 (dm, J = 7.0 Hz, 1 H), 7.32 (m, 3 H), 7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 26.88, 28.05, 29.33, 30.21, 32.14, 32.76, 33.16, 33.58, 38.58, 40.34, 40.78, 72.74, 128.11, 130.06, 131.82, 133.10; exact mass, m/z calcd for $C_{16}H_{20}Cl_2Se$ 362.0107, found 362.0064. Anal. Calcd for $C_{16}H_{20}Cl_2Se$: C, 53.05; H, 5.57. Found: C, 52.93; H, 5.59.

Method b. (i) (1α,2β,6α)-7,7-Dichloro-4,4,6-trimethylbicyclo[4.1.0]heptan-2-yl 4-Methylbenzenesulfonate. Freshly recyrstallized *p*-toluenesulfonyl chloride (2.15 g, 11.25 mmol) and then 4-(dimethylamino)pyridine (0.10 g, 0.73 mmol) were added in one portion to a solution of **10b** (2.03 g, 9.18 mmol) in dry pyridine (9 mL). The mixture was stirred at room temperature for 40 h and then concentrated under reduced pressure. The residue was diluted with EtOAc (30 mL), and the solution was washed with 1 N aqueous HCl (2 × 15 mL), saturated aqueous $NaHCO_3$ (15 mL), water (10 mL), and brine (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4.0 × 17.0 cm) using 8% EtOAc–hexane afforded the required tosylate (2.0 g, 57%) as a white solid: FT-IR ($CHCl_3$ cast) 2958, 2931, 2870, 1600, 1362, 1188, 924, 556 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.85 (s, 3 H), 0.92 (s, 3 H), 1.38 (s) and 1.44–1.57 (m) [both signals together correspond to 7 H], 1.75 (d, J = 13.4 Hz, 1 H), 2.46 (s, 3 H), 5.22 (ddd, J = 10.8, 8.8, 7.6 Hz, 1 H), 7.38 (d, J = 8 0 Hz, 2 H), 7.88 (d, J = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 22.15, 25.57, 26.32, 31.19, 33.24, 33.39, 34.67, 38.90, 40.07, 70.46, 77.39, 128.16, 130.41, 135.30, 145.09; exact mass, m/z calcd for $C_{17}H_{22}Cl_2O_3$ 376.0633, found 376.0633. Anal. Calcd for $C_{17}H_{22}Cl_2O_3$: C, 54.11; H, 5.88; Cl, 18.79. Found: C, 54.39; H, 5.82; Cl, 18.53.

The tosylate is rather unstable to silica gel and for larger scale work it is best to crystallise the crude product from cold (0 °C) 1:8 CH_2Cl_2–hexane solution and to purify material from the mother liquors by chromatography. In this way overall yields of 80 to 90% were obtained. The compound should not be exposed directly to sunlight. When kept in a refrigerator in the dark, no sign of decomposition was observed after 1 month.

(ii) (1α,5α,6α)-7,7-Dichloro-1,3,3-trimethyl-5-(phenylseleno)bicyclo[4.1.0]heptane (10c). NaH (0.128 g, 60% in oil, 3.2 mmol) was washed under argon with THF (3 × 2 mL). The residue was then covered with dry THF (5 mL), and diphenyl diselenide (0.50 g, 1.60 mmol) was added. The mixture was refluxed for 60 min, yielding a light yellow suspension of sodium phenyl selenide,[39a] which was allowed to cool to room temperature. Dry hexamethylphosphoramide (HMPA) (0.6 mL) was injected with stirring and the solid tosylate (1.15 g, 3.05 mmol) was added to the resulting homogeneous solution. The mixture was refluxed for 18 h, cooled to room temperature, and poured into ether (40 mL). The solution was washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), saturated aqueous $CuSO_4$ (10 mL), and 1:1 brine–water solution (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.0 × 17 cm) with 5% EtOAc–hexane afforded **10c** (1.0 g, 91%) as a slightly yellow

(59) The steric course of the cyclopropanation is based on precedent (see ref 33).

(60) The desired product is slowly transformed into a less polar (TLC) compound. It is best to stop the reaction a little short of completion.

oil, containing about 3 mol % of diphenyl diselenide [by ^{1}H NMR (200 MHz)]. The material can be used directly in the next step.

3-(Dichloromethyl)-3,5,5-trimethylcyclohexene (10d). (a) Photochemical Method. The general photochemical method for radical ring-opening was followed, using Ph_3SnH (161 μL, 0.63 mmol) and selenide **10c** (208 mg, 0.573 mmol) in dry toluene (3.8 mL). The mixture was stirred and irradiated at −23 to −10 °C for 1.5 h and then at −10 °C for 1 h. CCl_4 (0.5 mL) was added and stirring was continued at 25 °C for 1 h (without irradiation). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 20 cm) using hexane gave **10d** (116 mg), contaminated (TLC, silica, 2% EtOAc–hexane) by traces of impurity. Kugelrohr distillation of a portion (43.9 mg) of this material gave pure [^{1}H NMR (300 MHz)] **10d** (43.2 mg) as a colorless oil. Corrected yield (that would correspond to distillation of the total product): 114 mg (96%): FT-IR ($CHCl_3$ cast) 2954, 1456, 1365, 1213, 760, 733 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98 (s, 3 H), 1.02 (s, 3 H), 1.28 (s, 3 H), 1.45, (dm, J = 14.2 Hz, 1 H), 1.70 (d, J = 14.2 Hz, 1 H), 1.80 (m, 2 H), 5.53 (dm, J = 10.0 Hz) and 5.55 (s) [both signals together correspond to 2 H], 5.80 (ddd, J = 10.0, 4.9, 3.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 22.55, 28.18, 30.13, 31.76, 38.46, 44.02, 44.62, 83.33, 128.34, 129.54. Anal. Calcd for $C_{10}H_{16}Cl_2$: C, 57.98; H, 7.79. Found: C, 58.27; H, 7.66.

(b) Thermal Method Using Triethylborane. Et_3B (1 M in hexane, 5.0 mL, 5.0 mmol) and then Ph_3SnH (21.93 g, 62.0 mmol) were added dropwise over about 1 min to a cold (−10 °C) and stirred solution of **10c** (18.0 g, 50.0 mmol) in dry hexane (500 mL).[45] After 50 min at −10 °C, CCl_4 (5 mL) was added and the solvents were evaporated. The residue was filtered through a short pad (5 × 7 cm) of silica gel, using hexane (500 mL), in order to remove triphenyl(phenylseleno)stannane. The solution was evaporated and Kugelrohr distillation [125–140 °C (27 mm)] of the residue gave **10d** (9.50 g, 92%) as a colorless, homogeneous liquid.

(1α,2β,6α)-6-Butyl-7,7-dichloro-4,4-dimethylbicyclo[4.1.0]heptan-2-ol (11b).[59] Treatment of 3-butyl-5,5-dimethyl-2-cyclohexen-1-ol[61] (1.3 g, 7.22 mmol) in $CHCl_3$ (15 mL) with benzyltriethylammonium chloride (36 mg) and aqueous NaOH 50% w/w (7.1 mL), under identical conditions with those described for **10b**, gave **11b** (1.39 g, 73%) as a white solid.

(1α,5α,6α)-1-Butyl-7,7-dichloro-3,3-dimethyl-5-(phenylseleno)bicyclo[4.1.0]heptane (11c). Addition of PhSeCN (1.46 g, 8.06 mmol) in THF (4 mL) to **11b** (1.06 g, 4.03 mmol) and Bu_3P (2.0 mL, 8.06 mmol) in THF (9 mL), as described for **10b**, gave **11c** (1.50 g, 92%) as a yellowish oil.

3-Butyl-3-(chloromethyl)-5,5-trimethylcyclohexene (11d). Et_3B (1 M in hexane, 0.7 mL, 0.7 mmol) and then Ph_3SnH (187 μL, 0.734 mmol) were added dropwise over about 1 min to a cold (0 °C) and stirred solution of **11c** in dry hexane (6 mL).[45] After 45 min at 0 °C, some starting material still remained (TLC control, silica, hexane). A further portion of Ph_3SnH (60 μL, 0.235 mmol) was added, and stirring was continued for 15 min at 0 °C. At this point, no starting material remained (TLC control), and the mixture contained mainly the dichloride corresponding to the desired ring-opening, with traces (<5%) of the monochloride **11d** (GC, 220 °C). Ph_3SnH (250 μL, 0.98 mmol) was added in one portion to the cold (0 °C) solution and the cold bath was left in place. The mixture was stirred for 14 h and the solvent was then evaporated. Flash chromatography of the residue over silica gel (2 × 21 cm) using hexane afforded the monochloride **11d** (144 mg, 96%) as a colorless liquid: FT-IR ($CHCl_3$ cast) 2953, 1450, 747 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, J = 6.8 Hz, 3 H), 0.96 (s, 6 H), 1.10–1.60 (m, 8 H), 1.80 (dd, J = 4.0, 2.1 Hz, 2 H), 3.46 (s, 2 H), 5.48 (dt, J = 10.2, 1.2 Hz, 1 H), 5.74 (dt, J = 10.2, 4.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.13, 23.35, 25.66, 29.36, 29.72, 31.05, 38.34, 39.08, 39.61, 43.06, 53.01, 127.31, 130.14. Anal. Calcd for $C_{13}H_{23}Cl$: C, 72.70; H, 10.79. Found: C, 73.12; H, 10.78.

(1aα,2β,4aβ)-Decahydro-4a-methylcyclopropa[*d*]naphthalen-2-ol (12b).[63] A mixture of Zn powder (BDH Chemicals, 1.96 g, 30 mmol) and dry DME (10 mL), maintained under a static atmosphere of argon and contained in a 100-mL round-bottomed flask equipped with a condenser, was sonicated[64] for 20 min at 55 °C. A mixture[63] of alcohols **12a** and **13a** (in a ratio of 87:13, respectively) (500 mg, 3.0 mmol) was then added in one portion, followed by dropwise addition of CH_2I_2 over 15 min. Sonication was continued and, after a few min, an exothermic reaction began, causing the DME to reflux gently. Sonication was continued for 6 h after the CH_2I_2 had been added. [This experiment was done several times and, in some instances, heating at reflux for a few hours was necessary in order to complete the reaction.] The mixture was then diluted with ether (30 mL), followed by slow addition of saturated aqueous NH_4Cl (20 mL). The mixture was filtered through a pad of Celite (4.0 × 4.0 cm). The pad was washed with ether (3 × 20 mL) and the combined organic layers were washed with 5% w/v aqueous $Na_2S_2O_3$ (1 × 20 mL), water (1 × 20 mL), and brine (1 × 20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 20 cm) using 20% EtOAc–hexane afforded **12b** and **13b** (372 mg, 68%) as a brownish solid, which contained the two isomers in a ratio of 87:13, respectively [^{1}H NMR, (300 MHz)].

A mixture of **12b** and **13b** (87:13, about 2.4 g), obtained from a different experiment, was separated by chromatography over neutral alumina (grade III) (3.5 × 20 cm) using ether–benzene mixtures (2 to 20% ether–benzene). Pure **12b** (1.7 g, 70% of the original mixture) and a mixture of **12b** and **13b** (20:80, respectively; 0.65 g, 30% of the original mixture) were obtained. We later found that the compounds could be separated more conveniently by flash chromatography over silica gel, using 12% EtOAc–hexane.

Alcohol **12b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.08 (dd, J = 9.2, 4.7 Hz, 1 H), 0.55 (br d, J = 13.5 Hz, 1 H), 0.62 (t, J = 4.9 Hz, 1 H), 0.90 (m, 1 H), 1.02 (s, 3 H), 1.10–1.33 (m, 5 H), 1.48–1.79 (m, 6 H), 1.94 (dt, J = 13.0, 3.9 Hz, 1 H), 4.17 (br t, J = 13.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 10.22, 22.36, 25.52, 25.58, 26.83, 27.46, 28.00, 30.29, 31.10, 34.66, 35.15, 63.85. The GC retention times at 170 °C were 5.71 and 6.21 min for **12b** and **13b**, respectively.

(1aα,2α,4aβ)- and (1aα,2β,4aβ)-Decahydro-4a-methyl-2-(phenylseleno)cyclopropa[*d*]naphthalene (12c). The general method reported in the literature[38] was followed, but with some modifications. PhSeCN (511 mg, 2.79 mmol) in dry THF (1 mL) was added over 1 h to a cold (−78 °C), stirred solution of cyclopropyl alcohol **12b** (251 mg, 1.39 mmol) and Bu_3P (695 μL, 2.79 mmol) in dry THF (4 mL). The cold bath was left in place and stirring was continued for 12 h, during which time the mixture attained room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 20 cm) using 4% EtOAc–hexane afforded a yellow oil consisting of **12c** and diphenyl diselenide. This material was dissolved in a mixture of dry THF (8 mL) and absolute EtOH (2 mL), and the solution was cooled to −20 °C. $NaBH_4$ (100 mg) was added in one portion. Bubbling was observed and the yellow coloration due to diphenyl diselenide disappeared. Stirring was continued for 5 min at −20 °C, and bromoacetic acid (500 mg) was added in one portion. The cold bath was removed and the mixture was stirred for 1 h and diluted with ether (30 mL). The reaction was quenched with saturated aqueous $NaHCO_3$ (1 × 15 mL). The aqueous layer was extracted with ether (1 × 30 mL) and the combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ (1 × 15 mL), water (1 × 15 mL), and brine (1 × 15 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 × 20 cm) using 0.5% EtOAc–hexane afforded a mixture of selenides **12c** (366 mg, 82%) as a colorless oil: FT-IR ($CHCl_3$ cast) 2928, 1580, 740, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.27 (m, 2 H), 0.48 (dm, J = 13.5 Hz, 1 H), 0.99 (s, 3 H), 1.0–1.27 (m, 6 H), 1.41–1.81 (m, 7 H), 1.86 (dt, J = 13.9, 3.5 Hz, 1 H), 3.41 (dd, J = 11.0, 7.4 Hz, 1 H), 7.21–7.32 (m, 3 H), 7.53–7.63 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.04, 22.61, 25.57, 25.61, 25.80, 27.43, 27.91, 30.28, 35.32, 35.89, 39.46, 126.95, 128.91, 130.53, 133.81; exact mass, m/z calcd for $C_{18}H_{24}Se$,

(61) Prepared in 80% yield by conjugate addition (see ref 62) of butyl(phenylthio)copper to 3-bromo-5,5-dimethyl-2-cyclohexen-1-one, followed by reduction to the corresponding allylic alcohol using $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ in methanol.

(62) Cf. Piers, E.; Cheng, K. F.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 1256.

(63) Dauben, W. G.; Laug, P., Berezein, G. *J. Org. Chem.* **1966**, *31*, 3869.

(64) Repič, O.; Vogt, S. *Tetrahedron Lett.* **1982**, *23*, 2729.

320.1043, found 320.1040. Anal. Calcd for $C_{18}H_{24}Se$: C, 67.70; H, 7.57. Found: C, 68.21; H, 7.55.

***cis*-1,2,3,4,4a,5,6,8a-Octahydro-4a,8a-dimethylnaphthalene (12d). (a) Photochemical Method.** The general photochemical method for radical ring-opening was followed, using the selenides **12c** (57 mg, 0178 mmol) in dry hexane (0.9 mL) and Bu_3SnH (72 μL, 0.267 mmol). The mixture was stirred and irradiated for 2 h at −5 to 5 °C and evaporated. Flash chromatography of the residue over silica gel (1 × 20 cm) using hexane afforded, after careful evaporation of the solvent,[65] an oil (26.0 mg). Kugelrohr distillation (80 °C, 15 mm) (to effect complete removal of solvent) gave **12d** (25 mg, 84%) as a colorless oil: FT-IR ($CHCl_3$ cast) 2970, 2923, 2859, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (s, 3 H), 0.88 (s, about 3 H), 1.05–1.55 (m, 10 H), 2.0 (m, 2 H), 5.28 (dt, J = 10.0, 2.0 Hz, 1 H), 5.51 (dt, J = 10.0, 3.4 Hz, 1 H), 5.55–5.72 [m, 0.12 H (from an olefinic byproduct, which amounted to 6% of the total)]; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 22.20, 22.79, 23.25, 23.33, 33.80, 37.18, 37.48, 124.00, 131.57, 138.15; exact mass, m/z calcd for $C_{12}H_{20}$ 164.1565, found 164.1562.

The ^1H NMR spectrum shows that the oil contains the desired material (93%), an olefinic byproduct (6%), and the product of reduction without ring-opening (1%). The ^1H NMR chemical shifts of **12d** were identical with those reported for material synthesized[66] by another route. We are not certain if the ^{13}C NMR signals at 124.00 and 131.57 correspond to **12d** or to the olefinic byproduct.

(b) Thermal Method Using Triethylborane. Bu_3SnH (328 μL, 1.22 mmol) and then Et_3B (1M in hexanes, 121 μL, 0.121 mmol) were each added in one portion to a cooled (−5 °C) and stirred solution of selenides **12c** in dry hexane (2 mL), and then air (12 mL) was injected into the solution over a period of 2 h (syringe pump). CCl_4 (0.5 mL) was then injected and the solvent was evaporated. The residue was processed as described above and gave **12d** (58 mg, 85%) as a colorless oil, whose ^1H NMR spectrum showed the desired material **12d** (97%), the olefinic byproduct (2%), and product of reduction without ring opening (1%).

(1aβ,2α,4aβ)-Decahydro-4a-methylcyclopropa[*d*]naphthalen-2-ol (13b). The procedure described for **12b** was followed, using Zn powder (6.96 g, 107.4 mmol) in dry DME (40 mL), a mixture[67] of **13a** and **12a** (**13a**:**12a** = 79:21) (1.78 g, 10.74 mmol), and CH_2I_2 (3.03 mL, 37.6 mmol), except that, after sonication at 55 °C for 6 h, more Zn powder (1.39 g, 21.4 mmol) and CH_2I_2 (0.86 mL, 10.74 mmol) were added, followed by refluxing for 30 min and sonication for 6 h at 55 °C. This modification was necessary to ensure complete reaction. Flash chromatography over silica gel (3 × 20 cm) using 20% EtOAc–hexane afforded **13b** and **12b** (1.58 g, 82%) as a mixture of isomers in a 79:21 ratio, respectively [^1H NMR (300 MHz)]. The components were separated by flash chromatography over silica gel using 12% EtOAc–hexane.

(1aα,2β,4aα)- and (1aα,2α,4aα)-Decahydro-4a-methyl-2-(phenylseleno)cyclopropa[*d*]naphthalene (13c). The procedure described for selenide **12c** was followed, using alcohol **13b** (240 mg, 1.39 mmol) in dry THF (4.5 mL), Bu_3P (690 μL, 2.78 mmol), and PhSeCN (510 mg, 2.78 mmol) in dry THF (0.5 mL). Diphenyl diselenide was removed as described for **12c**, using $NaBH_4$ (100 mg) and bromoacetic acid (500 mg). After workup, flash chromatography of the residue over silica gel (2 × 20 cm) using 1% EtOAc–hexane afforded a mixture of selenides **13c** (304 mg, 72%) as a slightly yellow oil. The material contained the isomers in a ratio of 75:25, based on ^1H NMR (300 MHz) signals at δ 3.65 and 4.06.

(15α,16α)-15,16-Dihydro-3-methoxy-17-(phenylseleno)-3′*H*-cycloprop[15,16]estra-1,3,5(10),15-tetraene (14c).[68] Bu_3P (83 μL, 0.334 mmol) was added dropwise over 1 min to a stirred solution of PhSeCN (61 mg, 0.334 mmol) and cyclopropyl alcohol **14b**[69] (50 mg, 0.167 mmol) in dry THF (0.6 mL). Stirring was continued for 4 h and another portion of PhSeCN (30 mg, 0.16 mmol) and of Bu_3P (42 μL, 0.16 mmol) were added. The mixture was stirred for 12 h at room temperature and was then diluted with CH_2Cl_2 (20 mL) and water (5 mL). The organic layer was washed with brine (1 × 5 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.2 × 15 cm) using 30% CH_2Cl_2–hexane gave **14c** (59 mg, 80%) as a gummy solid free of diphenyl diselenide: FT-IR ($CHCl_3$ cast) 2920, 1605, 1578, 1500, 1255, 1039, 737 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.35 (dd, J = 14.0, 8.2 Hz, 1 H), 0.95 (m, including a s at 1.0, 4 H), 1.38–1.72 (m, 6 H), 1.90 (dt, J = 12.5, 3.2 Hz, 1 H), 2.03–2.38 (m, 4 H), 2.93 (m, 2 H), 4.78 (s, 1 H), 7.66 (d, J = 3.2 Hz) and 7.71 (dd, J = 8.4, 3.2 Hz) [both signals together corresponds to 2 H], 7.16 (d, J = 8.4 Hz, 1 H), 7.28 (m, 3 H), 7.60 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 11.03, 18.31, 20.88, 26.74, 26.85, 28.55, 29.76, 37.43, 41.25, 41.91, 44.08, 52.39, 55.19, 57.61, 111.35, 113.86, 125.95, 126.68, 128.97, 131.26, 132.76, 133.28, 137.90, 157.50; exact mass, m/z calcd for $C_{26}H_{30}OSe$ 438.1462, found 438.1459. Anal. Calcd for $C_{26}H_{30}OSe$: C, 71.38; H, 6.91; O, 3.66. Found: C, 71.53; H, 6.88; O, 3.69.

In a similar experiment, done on a larger scale (593 mg of starting material), the selenide was obtained in 75% yield.

(15β)-3-Methoxy-15-methylestra-1,3,5(10),16-tetraene (14d). The general photochemical method for radical ring-opening was followed, using cyclopropyl selenide **14c** (275 mg, 0,981 mmol) in toluene (5.0 mL) and Bu_3SnH (396 μL, 1.47 mmol). The mixture was stirred and irradiated for 2.5 h at 0 °C. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 × 15 cm) using 20% CH_2Cl_2–hexane gave a mixture of **14d** and **14e** (167 mg, 94%; corresponding to a 79% yield of **14d** after correction for the fact that the material contains [^1H NMR (200 MHz)] 16 mol % of the ring expansion product **14e**[70]) as a white semisolid.

The results were slightly different when the reaction was done with Ph_3SnH at −30 °C (16% ring expansion) or in refluxing benzene (with Ph_3SnH) (22% ring expansion).

(17α)-3-Methoxyestra-1,3,5(10),15-tetraen-17-ol (15a). (a) (17β)-3-Methoxyestra-1,3,5(10),15-tetraen-17-ol. $CeCl_3 \cdot 7H_2O$[72] (1.58 g, 4.25 mmol) was added in one portion to a cooled (−23 °C) and stirred suspension of **8a** (0.98 g, 3.54 mmol) in dry MeOH (18 mL) and dry THF (4 mL). $NaBH_4$ (161 mg, 4.25 mmol) was then added in portions over 5 min. Stirring was continued for 30 min at −23 °C. The cold bath was replaced by an ice bath and, after 30 min, this was removed. Stirring was continued for an additional 45 min. The mixture was diluted with CH_2Cl_2 (20 mL) and quenched with saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (1 × 20 mL), and the combined organic extracts were washed with water (1 × 10 mL) and brine (1 × 10 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 20 cm) using 5% EtOAc–CH_2Cl_2 gave the desired alcohol (969 mg, 98%) as a white solid: FT-IR ($CHCl_3$ cast) 3460, 2927, 1605, 1502, 1237, 1037 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.86 (s, 3 H), 1.40–1.51 (m, 1 H), 1.53–1.73 (m, 4 H), 1.98–2.13 (m, 3 H), 2.23–2.39 (m, 2 H), 2.91 (m, 2 H), 3.78 (s, 3 H), 4.41 (br s, 1 H), 5.73 (ddd, J = 5.9, 3.1, 1.3 Hz, 1 H), 6.04 (br d, J = 5.9 Hz, 1 H), 6.65 (d, J = 2.5 Hz, 1 H), 6.72 (dd, J = 8.5, 2.5 Hz, 1 H), 7.21 (d, J = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.24, 26.14, 27.64, 29.63, 34.74, 36.42, 44.43, 51.36, 55.24, 56.76, 85.72, 111.50, 113.92, 126.13, 131.61, 132.58, 134.68, 137.87, 157.57; exact mass, m/z calcd for $C_{19}H_{24}O_2$ 284.1777, found 284.1778.

(b) (17α)-3-Methoxyestra-1,3,5(10),15-tetraen-17-yl Benzoate. Ph_3P (1.74 g, 6.6 mmol) and $PhCO_2H$ (806 mg, 6.6 mmol) were added successively to a magnetically stirred solution of the above alcohol (940 mg, 3.31 mmol) in dry THF (27 mL). Diethyl azodicarboxylate (1.04 mL, 6.6 mmol) in dry THF (6 mL) was

(65) The evaporation was done at 25 °C under water pump vacuum, and the residual oil was kept under water pump vacuum for a maximum of 2 min.

(66) Heathcock, C. H.; DelMar, E. G.; Graham, S. L. *J. Am. Chem. Soc.* **1982**, *104*, 1907.

(67) Marshall, J. A.; Flynn, K. E. *J. Am. Chem. Soc.* **1982**, *104*, 7430.

(68) Stereochemistry at C(17) was not determined.

(69) For preparation of **14b** from estrone, see: (a) Schmidt, O.; Prezewowsky, K.; Schulz, G.; Wiechert, R. *Chem. Ber.* **1968**, *101*, 939. (b) Johnson, W. S.; Johns, W. F. *J. Am. Chem. Soc.* **1957**, *79*, 2005. (c) Nambara, T.; Sudo, K.; Sudo, M. *Steroids* **1976**, *27*, 111.

(70) The byproduct **14e** was identified by comparison of its ^1H and ^{13}C NMR spectra with those of an authentic sample prepared (see ref 71) from 3-methoxy-D-homoestra-1,3,5(10)-triene-17β,17aβ-diol.

(71) Clive, D. L. J.; Keshava Murthy, K. S.; Zhang, C.; Hayward, W. D.; Daigneault, S. *J. Chem. Soc., Chem. Commun.* **1990**, 509.

(72) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

then added dropwise over 30 min and stirring was continued for 2 h.[73] At this point, the reaction was still incomplete (TLC control, silica, 30% EtOAc–hexane). Further portions of Ph_3P (1.74 g, 6.6 mmol), $PhCO_2H$ (806 mg, 6.6 mmol), and diethyl azodicarboxylate (1.04 mL, 6.6 mmol) were then added and, after an additional 1 h, the solvent was evaporated and the residue was taken up in CH_2Cl_2 (150 mL). The solution was washed with saturated aqueous $NaHCO_3$ (1 × 50 mL), water (1 × 50 mL), and brine (1 × 50 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (4 × 20 cm) using 25% EtOAc–hexane gave the desired benzoate (1.10 g, 86%) as a gummy solid, which contained slight impurities (TLC).

(c) (17α)-3-Methoxyestra-1,3,5(10),15-tetraen-17-ol (15a).[74] MeOH (21 mL) and 20% w/v aqueous NaOH (9 mL) were added to a magnetically stirred solution of the above benzoate (1.06 g, 2.73 mmol) in THF (7 mL). Stirring was continued for 16 h and the mixture was then quenched with saturated aqueous NH_4Cl (15 mL). Most of the THF was evaporated (water pump vacuum) and the residue was extracted with CH_2Cl_2 (1 × 100 mL). The organic phase was washed with water (2 × 20 mL) and brine (1 × 20 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 15 cm) afforded **15a** (592 mg, 76%) as a white solid: mp 135–138 °C; FT-IR ($CHCl_3$ cast) 3300, 2929, 1610, 1501, 1258, 1053, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84 (s, 3 H), 1.42–1.75 (m, 5 H), 1.96 (m, 1 H), 2.10 (m, 1 H), 2.28 (dt, J = 10.5, 4.4 Hz, 1 H), 2.36–2.53 (m, 2 H), 2.90 (m, 2 H), 3.78 (s, 3 H), 4.15 (br d, J = 2.0 Hz, 1 H), 6.0 (m, 1 H), 6.22 (dd, J = 4.2, 1.4 Hz, 1 H), 6.63 (d, J = 2.8 Hz, 1 H), 6.72 (dd, J = 8.5, 2.8 Hz, 1 H), 7.21 (d, J = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.50, 25.75, 28.19, 29.58, 30.56, 36.04, 44.46, 46.15, 54.80, 55.20, 82.47, 111.45, 113.89, 126.06, 132.68, 133.19, 137.20, 137.79, 157.50; exact mass, m/z calcd for $C_{19}H_{24}O_2$ 284.1777, found 284.1777. Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 79.95; H, 8.52.

(15β,16β,17α)-15,16-Dihydro-3-methoxy-3′*H*-cycloprop[15,16]estra-1,3,5(10),15-tetraen-17-ol (15b). The procedure is based on a literature method.[75] Allylic alcohol **15a** (200 mg, 0.7 mmol) and then dry ether (5 mL) were added to a suspension of Zn(Cu) couple (436 mg, 6.7 mmol)[76] in dry DME (5 mL) maintained under a static atmosphere of argon. CH_2I_2 (324 μL, 4.02 mmol) was then added dropwise and the mixture was stirred at reflux temperature (oil bath at 60 °C) for 18 h. At this point the reaction was still incomplete (TLC, silica, 30% EtOAc–hexane). Zn(Cu) couple (218 mg, 3.3 mmol) and then CH_2I_2 (162 μL, 2.01 mmol) were added and the mixture was stirred at reflux temperature for an additional 18 h. Saturated aqueous NH_4Cl (10 mL) was added followed by EtOAc (10 mL). The resulting slurry was filtered through a pad of Celite (2.0 × 2.0 cm) and the pad was washed with EtOAc (5 × 6 mL). The organic filtrate was washed with water (1 × 10 mL), saturated aqueous $NaHCO_3$ (1 × 10 mL), water (1 × 10 mL), and brine (1 × 10 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 × 20.0 cm) using 20% EtOAc–hexane afforded **15b** (171 mg, 81%; 86% based on conversion) and starting material **15a** (11 mg). Compound **15b**: FT-IR ($CHCl_3$ cast) 3440, 1600, 1570, 1255, 1230, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.9–1.08 (m, including a s at 0.95, 6 H), 1.20–1.80 (m, 8 H), 2.13 (m, 2 H), 2.28 (m, 1 H), 2.88 (m, 1 H), 3.77 (s, 3 H), 3.96 (d, J = 5.5 Hz, 1 H), 6.64 (d, J = 2.8 Hz, 1 H), 6.70 (dd, J = 8.5, 2.8 Hz, 1 H), 7.20 (d, J = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.31, 19.32, 21.12, 25.32, 25.85, 28.78, 29.92, 30.47, 37.98, 43.96, 54.66, 55.21, 56.14, 77.99, 111.41, 113.88, 126.24, 132.78, 138.12, 157.45, 180.97; exact mass, m/z calcd for $C_{20}H_{26}O_2$ 298.1933, found 298.1933. Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.26; H, 8.94.

(15β,16β)-15,16-Dihydro-3-methoxy-17-(phenylseleno)-3′*H*-cycloprop[15,16]estra-1,3,5(10),15-tetraene (15c).[68] Bu_3P (0.41 mL, 334 mg, 1.65 mmol) was added to a stirred solution of **15b** (214 mg, 0.72 mmol) in dry THF (4 mL) at 50 °C contained in a flask equipped with a condenser. PhSeCN (303 mg, 1.65 mmol) in dry THF (0.8 mL) was then added over 3 h (syringe pump) via the condenser, and stirring was continued for 12 h. The mixture was allowed to cool to room temperature and the solvent was evaporated. Flash chromatography of the residue over silica gel (2 × 20.0 cm) using 25% CH_2Cl_2–hexane gave **15c** (197 mg, 63%) as a viscous oil: FT-IR ($CHCl_3$ cast) 2930, 1620, 1590, 1500, 1260, 1050, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.63 (dd, J = 7.8, 3.7 Hz, 1 H), 0.82 (dd, J = 11.0, 5.1 Hz, 1 H), 1.12 (s, 3 H), 1.2–1.93 (m, 8 H), 2.21 (m, 3 H), 2.75 (d, J = 4.8 Hz, 1 H), 2.91 (m, 2 H), 3.80 (s, 3 H), 6.67 (d, J = 2.8 Hz, 1 H), 6.73 (dd, J = 8.5, 2.8 Hz, 1 H), 7.11–7.32 [m, including a d at 7.20 (J = 8.5 Hz), 4 H], 7.60 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) (major peaks only) δ 17.20, 20.74, 26.02, 27.15, 27.25, 28.54, 29.81, 35.63, 38.21, 44.34, 55.13, 57.34, 57.91, 60.16, 111.40, 113.85, 126.16, 128.90, 132.04, 132.13, 132.52, 138.03, 157.52; exact mass, m/z calcd for $C_{26}H_{30}OSe$ 438.1462, found 438.1460. Anal. Calcd for $C_{26}H_{30}OSe$: C, 71.38; H, 6.91; O, 3.66. Found: C, 71.28; H, 6.92; O, 3.95.

(15α)-3-Methoxy-15-methylestra-1,3,5(10),16-tetraene (15d). The general photochemical method for radical ring-opening was followed, using Bu_3SnH (110 μL, 0.411 mmol), which was added to a cold (0 °C) solution of **15c** (115 mg, 0.262 mmol) in dry toluene (2.8 mL). The mixture was stirred and irradiated at 0–20 °C for 3 h. At this point, the reaction was still incomplete (TLC control, silica, 5% EtOAc–hexane). Bu_3SnH (44 μL, 0.164 mmol) was added at 0 °C and the mixture was stirred and irradiated at 0–25 °C for 1 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm) using 20% CH_2Cl_2–hexane gave a mixture of **15d** and **14e** in a ratio [^1H NMR (300 MHz)] of 84:16, respectively (64 mg, 86%).

***cis*-5-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2-cyclopenten-1-ol (16a). (a) *cis*-3,3a,4,6a-Tetrahydro-2*H*-cyclopenta[*b*]furan-2-one.** $NaHCO_3$ (66.4 g, 0.70 mol) and I_2 (120.7 g, 0.47 mol) were added with vigorous stirring to a cooled (0 °C) solution of 2-cyclopentene-1-acetic acid (20.0 g, 0.158 mol) in 75% THF–water. The cold bath was left in place and allowed to attain room temperature. After 16 h, the reaction mixture was diluted with ether (1000 mL) and washed with water (1 × 250 mL). The organic layer was washed with 10% aqueous $Na_2S_2O_3$ (1 × 200 mL), water, (1 × 200 mL), and brine (1 × 200 mL) and dried ($MgSO_4$). Evaporation of the solvent gave the desired iodo lactone (38.4 g) as a red-brown oil, which was used without further purification.

1,8-Diazabicyclo[5.4.0]undec-7-ene (27.8 mL, 0.185 mol) was added in one portion to a stirred solution of the crude iodo lactone (36.12 g, 0.143 mol) in dry benzene (650 mL). The mixture was stirred and refluxed for 4 h, cooled to room temperature, and filtered through a sintered glass funnel to remove insoluble salts. The filtrate was diluted with ether (1000 mL), washed with water (1 × 250 mL) and brine (1 × 250 mL), and dried ($MgSO_4$). Evaporation of the solvent gave crude *cis*-3,3a,4,,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one (12.7 g, 71.3%). The combined aqueous layers were saturated with NaCl and continuously extracted with ether for 4 h. The ether was dried and evaporated to afford more product (7.2 g, 40.4%): ^1H NMR ($CDCl_3$, 80 MHz) δ 1.90–3.40 (m, 7 H), 5.40 (d, J = 7.0 Hz, 1 H), 5.50–5.90 (m, 1 H), 5.90–6.20 (m, 1 H). The material was used directly in the next step.

(b) *cis*-5-(2-Hydroxyethyl)-2-cyclopenten-1-ol. The crude lactone from the previous step (10.0 g, 0.08 mol) was added over 5 min to a cold (0 °C) and stirred suspension of $LiAlH_4$ (6.11 g, 0.161 mol) in ether (300 mL). The cold bath was removed and stirring was continued for 2 h. The mixture was then quenched by slow addition of saturated aqueous NH_4Cl (200 mL). The organic layer was separated, and the aqueous layer was saturated with NaCl and extracted continuously with ether for 16 h. The combined organic extracts were dried ($MgSO_4$) and evaporated to afford the required diol (10.0 g). Flash chromatography over silica gel (7 × 30 cm) using 50% EtOAc–hexane gave the pure diol (8.6 g, 86% based on 2-cyclopentene-1-acetic acid): ^1H NMR ($CDCl_3$, 80 MHz) δ 1.30–2.50 (m, 5 H), 3.0–3.95 (m, 4 H), 4.65 (br s, 1 H), 5.75–6.15 (m, 2 H).

(c) *cis*-5-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-ethyl]-2-cyclopenten-1-ol (16a). Imidazole (233 mg, 3.43 mmol) and *tert*-butylchlorodiphenylsilane[77] (440 μL, 1.72 mmol) were

(73) Mitsunobu, O. *Synthesis* **1981**, 1.
(74) Cf. *Chem. Abstr.* **1976**, *84*, 165115p. [Hofmeister, H.; Annen, K.; Wiechert, R.; Laurent, H. Ger. Offen. 2,439,082.]
(75) Wiechert, R.; Bittler, D.; Hoyer, G.-A. *Chem. Ber.* **1973**, *106*, 888.
(76) For preparation, see: Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A. *Org. React.* **1973**, *20*, 1.

added to a cold (0 °C) and stirred solution of the above diol (200 mg, 1.56 mmol) in dry DMF (3.2 mL). The cold bath was left in place and allowed to attain room temperature. After 11 h, the mixture was quenched by addition of saturated aqueous NH_4Cl (5 mL) and diluted with ether (25 mL). The organic layer was washed with water (1 × 10 mL) and brine (1 × 10 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.0 × 18.0 cm) using 15% EtOAc–hexane gave **16a** (442 mg, 77%) as a thick, colorless oil: FT-IR ($CHCl_3$ cast) 3400, 2930, 2857, 1472, 1427, 1112, 1084, 701, 505 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.06 (s, 9 H), 1.68 (ddd, J = 14.4, 9.5, 4.4 Hz, 1 H), 1.96–2.30 (m, 3 H), 2.38 (dddd, J = 15.6, 7.4, 2.8, 1.6 Hz, 1 H), 2.81 (d, J = 4.1 Hz, 1 H), 3.67 (dt, J = 9.7, 3.9 Hz, 1 H), 3.81 (m, 1 H), 4.72–4.81 (br m, 1 H), 5.92 (m, 1 H), 6.01 (br dt, J = 6.0, 2.2 Hz, 1 H), 7.32–7.49 (m, 6 H), 7.60–7.80 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.05, 26.82, 31.58, 37.54, 41.63, 64.36, 76.32, 127.77, 129.79, 132.82, 133.08, 133.17, 135.29, 135.60; exact mass, m/z calcd for $C_{19}H_{21}O_2Si$ [$(M - C_4H_9)^+$] 309.1311, found 309.1311. Anal. Calcd for $C_{23}H_{30}O_2Si$: C, 75.36; H, 8.25. Found: C, 75.27; H, 8.39.

(1α,2β,3β,5α,6α)- and (1α,2β,3β,5α,6β)-3-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-6-methylbicyclo[3.1.0]hexan-2-ol (16b).[78] The procedure is based on a general literature method.[32,79] Sm metal (Research Chemicals, Pheonix, AZ, 1.15 g, 7.65 mmol) was flame-dried in a 50-mL round-bottomed flask equipped with a Teflon-coated stirring bar and purged with a stream of argon. The flask was allowed to cool to room temperature and dry THF (18 mL) was added, followed by a solution of $HgCl_2$ in THF (1.5 M, 407 μL, 0.6 mmol). Stirring was continued for 10 min at room temperature and then allylic alcohol **16a** (650 mg, 1.77 mmol) in dry THF (2 mL) was introduced via a cannula over about 10 min. The mixture was cooled to −78 °C and 1,1-diiodoethane (2.0 g, 7.08 mmol) was injected dropwise over about 5 min. The cold bath was left in place and allowed to attain room temperature. After 8 h, the mixture was diluted with CH_2Cl_2 (20 mL) and quenched with saturated aqueous NH_4Cl (15 mL). Stirring was continued for 3 min, and the aqueous layer was separated and extracted with CH_2Cl_2 (1 × 25 mL). The combined organic extracts were washed with water (1 × 15 mL) and brine (1 × 15 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 20 cm) with 15% EtOAc–hexane afforded **16b** (313 mg, 45%; 69% based on conversion) and recovered starting material **16a** (230 mg). Compound **16b**: FT-IR ($CHCl_3$ cast) 3460, 2929, 2858, 1595, 1428, 1112, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.0 (s, 3 H), 1.0–1.1 (m, including a s at 1.05, 11 H), 1.17–1.27 (m, 1 H), 1.32 (ddd, J = 14.3, 9.5, 4.5 Hz, 1 H), 1.42 (m, 1 H), 1.88 (m, 1 H), 2.06 (ddd, J = 13.0, 9.2, 6.3 Hz, 1 H), 2.21 (m, 1 H), 2.70 (br s, 1 H), 3.54 (dt, J = 10.0, 4.0 Hz, 1 H), 3.67 (dt, J = 10.0, 4.0 Hz, 1 H), 4.63 (br t, J = 6.5 Hz, 1 H), 3.67 (dt, J = 10.0, 4.0 Hz, 1 H), 7.35–7.48 (m, 6 H), 7.63–7.71 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.08, 19.02, 19.57, 26.83, 26.92, 32.35, 34.61, 35.49, 48.77, 64.66, 73.95, 127.75, 129.75, 133.10, 133.20, 135.58, 135.63; exact mass, m/z calcd for $C_{21}H_{25}O_2Si$ [$(M - C_4H_9)^+$] 337.1624, found 337.1622. Anal. Calcd for $C_{25}H_{34}O_2Si$: C, 76.09; H, 8.68. Found: C, 75.77; H, 8.58.

(1,1-Dimethylethyl)[2-[6-methyl-2-(phenylseleno)bicyclo[3.1.0]hex-3-yl]ethoxy]diphenylsilane (16c).[80] PhSeCN (137 mg, 0.75 mmol) in dry THF (0.5 mL) was added dropwise over about 5 min to a stirred solution of cyclopropyl alcohol **16b** (197 mg, 0.5 mmol) and Bu_3P (187 μL, 0.75 mmol) in dry THF (5 mL). Stirring at room temperature was continued for 4 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 20 cm) using 20% CH_2Cl_2–hexane (to remove diphenyl diselenide) followed by 5% EtOAc–hexane gave the selenide **16c** as a single isomer (154 mg, 58%) and an olefinic byproduct (48 mg, 26%). Selenide **16c**: FT-IR ($CHCl_3$ cast) 2929, 1580, 1111, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.52 (d of septets, J = 6.0, 3.2 Hz, 1 H), 0.91 (d, J = 6.0 Hz, 3 H), 1.02 (s, 9 H), 1.06–1.50 (m, 5 H), 1.52 (m, 1 H), 2.14 (ddd, J = 13.0, 9.7, 5.5 Hz, 1 H), 2.33 (m, 1 H), 3.27 (d, J = 3.8 Hz, 1 H), 3.48 (t, J = 8.0 Hz, 1 H), 7.15 (m, 3 H), 7.30–7.45 (m, 6 H), 7.45–7.57 (m, 2 H), 7.60–7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 17.76, 19.19, 23.00, 26.93, 28.72, 33.74, 34.70, 40.77, 45.69, 50.67, 62.75, 126.95, 127.66, 128.94, 129.60, 131.10, 133.72, 133.97, 135.64; exact mass, m/z calcd for $C_{31}H_{38}OSeSi$ 534.1857, found 534.1855. Anal. Calcd for $C_{31}H_{38}OSeSi$: C, 69.77; H, 7.18. Found: C, 69.61; H, 7.34.

***cis*-(1,1-Dimethylethyl)[2-(4-ethyl-2-cyclopenten-1-yl)ethoxy]diphenylsilane (16d).** The general photochemical method for radical ring-opening was followed, using selenide **16c** (107 mg, 0.2 mmol) in dry hexane (3 mL) and Bu_3SnH (81 μL, 0.3 mmol). The mixture was stirred and irradiated at 0–10 °C for 45 min and then at 10–30 °C for 1.5 h. At this stage, some starting material still remained (TLC, silica, 5% EtOAc–hexane). Bu_3SnH (25 μL) was added[81] and the mixture was stirred and irradiated for 40 min at 10–30 °C. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 × 20 cm) using 1% EtOAc–hexane afforded **16d** (52 mg 69%) as a slightly yellow oil:[82] FT-IR ($CHCl_3$ cast) 2957, 2930, 2857, 1582, 1472, 1428, 1112, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.9 (t, J = 7.5 Hz, 3.6 H), 1.07 (s, 9 H), 1.18–1.60 (m, 3.4 H), 1.75 (dq, J = 13.5, 7.0 Hz, 1 H), 2.18 (dt, J = 12.7, 8.0 Hz, 1 H), 2.52 (m, 1 H), 2.75 (m, 1 H), 3.71 (t, J = 6.9 Hz, 1 H), 5.62 (m, 2 H), 7.32–7.45 (m, 6 H), 7.62–7.73 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.31, 19.25, 26.95, 29.54, 37.04, 39.79, 42.41, 47.52, 62.96, 127.64, 129.54, 134.16, 134.69, 135.64; exact mass, m/z calcd for $C_{21}H_{25}OSi$ [$(M - C_4H_9)^+$] 321.1675, found 321.1678. Anal. Calcd for $C_{25}H_{34}OSi$: C, 79.30; H, 9.05. Found: C, 79.39; H. 9.03.

Ethyl [1*R*-(1α,2α,4β,5α,6α,7α)]-5-(Benzoyloxy)-4-(bromomethyl)-2-methoxy-3-oxabicyclo[4.1.0]heptane-7-carboxylate (17c). The procedure is based on a general literature method.[83] $BaCO_3$ (533 mg, 2.7 mmol) and then *N*-bromosuccinimide (freshly recyrstallised from water; 354 mg, 1.99 mmol) were each added in one portion to a hot (50 °C) solution of sugar **17b**[35] (596 mg, 1.8 mmol) in dry CCl_4 (32 mL). The oil bath temperature was then rasied to 90 °C and the mixture was allowed to reflux for 2 h. The hot solution was filtered through a sintered glass funnel and the insoluble material was washed with hot CCl_4 (4 × 5 mL). The combined filtrates were evaporated and the residue was diluted with EtOAc (100 mL). The solution was washed with water (2 × 10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 × 20 cm) using 15% EtOAc–hexane afforded **17c** (611 mg, 82%) as a white solid: mp 82–82.5 °C; FT-IR ($CHCl_3$ cast) 1723, 1285, 712 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, J = 7.0 Hz, 3 H), 1.8 (m, J = 14.5, 4.0 Hz, 2 H), 1.93 (dd, J = 9.9, 5.0 Hz, 1 H), 3.37 (dd, J = 11.3, 7.5 Hz, 1 H), 3.55 (s) and 3.56 (dd, J = 11.5, 2.5 Hz) [both signals together correspond to 4 H], 4.0–4.2 [m, including q at 4.13 (J = 7.0 Hz) and at 4.14 (J = 7.0 Hz), 3 H], 4.96 (s, 1 H), 5.07 (d, J = 9.2 Hz, 1 H), 7.47 (m, 2 H), 7.62 (m, 1 H), 8.07 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.18, 21.97, 23.09, 24.45, 32.68, 55.68, 61.07, 66.79, 67.13, 96.84, 128.56, 129.32, 129.85, 133.60, 165.55, 171.89; exact mass, m/z calcd for $C_{18}H_{21}O_6Br$ 414.0501, found 414.0526. Anal. Calcd for $C_{18}H_{21}BrO_6$: C, 52.31; H, 5.12; O, 23.23; Br, 19.34. Found: C, 52.04; H, 5.26; O, 23.18; Br, 20.08.

Ethyl [2*S*-(2α,3β,6β)]-6-(Bromomethyl)-3,6-dihydro-2-methoxy-2*H*-pyran-3-acetate (17d). The procedure is based on a general literature method.[46] $Mg(ClO_4)_2 \cdot 6H_2O$ (152 mg, 0.46 mmol) in water (1 mL) and water (7 mL) were added to a solution of *N*-methylcarbazole (87 mg, 0.482 mmol) and **17c** (181 mg, 0.438 mmol) in distilled THF (80 mL). The mixture was then distributed among four 50-mL test tubes [using distilled THF (3 mL) as a rinse for each tube]. The tubes were capped with septa, flushed with argon, and maintained under a static pressure of argon. The tubes were irradiated simultaneously for 10 h at room temperature, using a Hanovia 200-W high pressure mercury lamp

(77) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975. Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1977**, *55*, 562.

(78) The samarium-mediated cyclopropanation proceeds with syn direction by the hydroxyl (see ref 32). The stereochemistry at C(6) was not determined.

(79) Samarium metal (about 40 mesh) from Research Chemicals (Phoenix, AZ) gave better results than other material we tried.

(80) Stereochemistry at C(2) and C(6) was not determined.

(81) Addition of the supplementary amount of hydride was arbitrarily done: it might not be necessary.

(82) The ^1H NMR spectrum (200 MHz) showed a byproduct (about 6 mol % of the total). The corrected yield is 65%.

(83) Hanessian, S.; Plessas, N. R. *J. Org. Chem.* **1969**, *34*, 1035.

surrounded by a Pyrex filter. The reaction mixtures were then transferred to a 500-mL round-bottomed flask containing a mixture of saturated aqueous $NaHCO_3$ (20 mL) and THF (50 mL). The resulting mixture was evaporated. The residue was extracted with EtOAc (2 × 75 mL), and the extracts were washed with saturated aqueous $NaHCO_3$ (1 × 40 mL) and 50% brine–water (1 × 40 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 20 cm) using 10% EtOAc–hexane afforded **17d** (110 mg, 86%) as a colorless oil: FT-IR ($CHCl_3$ cast) 1733, 1370, 1265, 1170, 1120, 1040, 935, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, J = 7.2 Hz, 3 H), 2.37–2.64 (m, 3 H), 3.44 (dd, J = 10.8, 5.5 Hz), 3.50 (s), 3.51 (dd, J = 10.8, 4.5 Hz) [the signals at 3.44, 3.50 and 3.51 together correspond to 5 H], 4.16 (q, J = 7.2 Hz, 2 H), 4.43 (m, 1 H), 5.71 (br d, J = 10.0 Hz, 1 H), 5.89 (dm, J = 10.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.19, 34.95, 35.42, 37.40, 55.67, 60.56, 61.02, 67.37, 100.55, 126.30, 127.39, 171.65; exact mass, m/z calcd for $C_{10}H_{14}BrO_3$ [$(M - CH_3O)^+$] 263.0106, found 263.0085. Anal. Calcd for $C_{11}H_{17}BrO_4$: C, 45.06; H, 5.85; O, 21.83. Found: C, 45.27; H, 6.02; O, 21.87.

Methyl (2*R*,4*R*)-2,3-Dideoxy-2,3-[1-(ethoxycarbonyl)-ethylidene]-4,6-*O*-(phenylmethylene)-α-D-mannopyranoside (18a).[36] The literature procedure[36] was followed, but with some modifications. NaH (7.56 g, 60% suspension in oil, 0.189 mol) was added in several portions over a period of 15 min to a stirred solution of triethyl 2-phosphonopropionate (45.0 g, 0.189 mol) in dry triglyme (150 mL) contained in a flask equipped with a condenser. Stirring was continued for 30 min at room temperature, and methyl 2,3-anhydro-4,6-*O*-(phenylmethylene)-α-D-allopyranoside (**17a**)[84] (10.1 g, 0.0378 mol) was added in one portion. The flask was lowered into an oil bath preheated to 140 °C. Heating at 140 °C was continued for 4 days. The brown solution was allowed to cool to room temperature and was poured into saturated aqueous NH_4Cl (100 mL). The mixture was extracted with ether (2 × 200 mL), and the combined organic extracts were washed with water (3 × 50 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue (which was applied to the column dissolved in a minimum amount of CH_2Cl_2) over silica gel (6 × 20 cm) using 20% EtOAc–hexane afforded **18a**[36] (5.99 g, 45%) as a thick oil containing traces of impurities (TLC, silica, 20% EtOAc–hexane).

[1*R*-(1α,2α,4β,5α,6α)]-5-(Benzoyloxy)-4-(bromomethyl)-2-methoxy-7,7-dimethyl-3-oxabicyclo[4.1.0]heptane (18c). $BaCO_3$ (571 mg, 2.89 mmol) and then *N*-bromosuccinimide (freshly recrystallized from water, 377 mg, 2.12 mmol) were added to a hot (65 °C) and stirred solution of methyl 4,6-*O*-(phenylmethylene)-2,3-dideoxy-2,3-*C*-isopropylidene-α-D-mannopyranoside (**18b**)[85] (555 mg, 1.93 mmol) in CCl_4 (34 mL). Stirring at 65 °C was continued for 1 h and the hot suspension was filtered through Whatman filter paper (no. 1). The insoluble material was washed with hot CCl_4 (10 mL) and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (4.0 × 20 cm) with 10% EtOAc–hexane afforded **18c** (501 mg, 71%) as a thick, colorless oil: FT-IR ($CHCl_3$ cast) 2950, 1722, 1274, 1111, 1027 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (d, J = 9.1 Hz, 1 H), 1.04 (dd, J = 9.1, 1.9 Hz, 1 H), 1.10 (s, 3 H), 1.25 (s, 3 H), 3.52 (s, J = 11.1, 8.0 Hz, 1 H), 3.58 (dd, J = 11.1, 2.3 Hz, 1 H), 3.89–3.98 (m, 1 H), 4.79 (s, 1 H), 4.85 (dd, J = 8.0, 1.9 Hz, 1 H), 7.43–7.51 (m, 1 H), 7.57–7.63 (m, 1 H), 8.02–8.11 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.42, 17.33, 23.31, 26.09, 27.77, 32.77, 55.18, 67.02, 67.26, 97.52, 128.54, 129.72, 129.80, 133.39, 165.58; exact mass, m/z calcd for $C_{17}H_{21}BrO_4$ 370.0603, found 370.0599. Anal. Calcd for $C_{17}H_{21}BrO_4$: C, 55.42; H, 5.75; O, 17.37. Found: C, 55.23; H, 5.72; O, 17.47.

[2*S*-(2α,3β,6β)]-6-(Bromomethyl)-3,6-dihydro-3-(1-methylethyl)-2-methoxy-2*H*-pyran (18d) and [2*S*-(2α,3β,6β)]-6-(Bromomethyl)-3,6-dihydro-3-(1-methylethenyl)-2-methoxy-2*H*-pyran (18e). $Mg(ClO_4)_2 \cdot 6H_2O$ (308 mg, 0.932 mmol) in water (2 mL) and water (7 mL) were added to a solution of *N*-methylcarbazole (169 mg, 0.932 mmol) and **18c** in distilled THF (104 mL). The mixture was then distributed among among four 50-mL test tubes [using distilled THF (3 mL) as a rinse for each tube]. The tubes were capped with septa, flushed with argon, and maintained under a static pressure of argon. The tubes were irradiated simultaneously for 7 h at 25 °C using a Hanovia 400-W high pressure mercury lamp surrounded by a Pyrex filter. The mixtures were then transferred to a 500-mL round-bottomed flask containing saturated aqueous $NaHCO_3$ (50 mL) and the resulting mixture was evaporated. The residue was extracted with ether (2 × 75 mL) and the extracts were washed with water (1 × 40 mL), dried ($MgSO_4$), and evaporated. [In this particular run the crude material was kept at −5 °C for 48 h.] Flash chromatography of the residue over silica gel (3 × 20 cm) using mixtures of 2%, 5%, and 40% EtOAc–hexane afforded a 1:1 mixture [^1H NMR (300 MHz)] of **18d** and **18e** (140 mg, 67%) as a colorless oil, as well as unidentified material (29 mg). Mixture of **18d** and **18e**: FT-IR ($CHCl_3$ cast) 2959, 1192, 1117, 1048, 973, 961 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, J = 7.3 Hz, 3 H), 1.71–1.87 (m, 2.5 H), 1.87–2.03 (m, 1 H), 3.39–3.53 (m, including s at 3.46 and 3.48, 5 H), 4.32–4.44 (m, 1 H), 4.715 (s, 0.5 H), 4.735 (s, 0.5 H), 5.70–5.89 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.67, 20.53, 21.49, 30.74, 34.71, 34.97, 45.10, 46.95, 55.19, 55.40, 66.87, 67.12, 100.45, 100.48, 113.96, 125.95, 126.02, 126.88, 127.08, 143.74; mass for $C_{10}H_{17}{}^{81}BrO$ and $C_{10}H_{15}{}^{81}BrO$ (chemical ionization, NH_3) 268 $(M + 18)^+$.

(*R*)-4,6-Di-*O*-acetyl-2,3-dideoxy-2,3-[(ethoxycarbonyl)-methylene]-α-D-mannopyranosyl Bromide and (*R*)-4,6-Di-*O*-acetyl-2,3-dideoxy-2,3-[(ethoxycarbonyl)methylene]-β-D-mannopyranosyl Bromide (19a). (a) Methyl (*R*)-2,3-Dideoxy-2,3-[(ethoxycarbonyl)methylene]-α-D-mannopyranoside. A stirred suspension of 5% Pd on C (0.5 g) in glacial AcOH (8 mL) was saturated with hydrogen and **17b**[35] (1.01 g, 3.04 mmol)[86] was added in one portion. Stirring under 1 atm of H_2 was continued for 17 h. The catalyst was then removed by filtration through a pad of Celite and the pad was washed with EtOAc (5 × 5 mL). The combined filtrates were evaporated and traces of AcOH were removed by azeotropic evaporation with toluene (15 mL). This evaporation was repeated twice more to afford a white solid, which was used without further purification.

(b) Methyl (*R*)-4,6-Di-*O*-acetyl-2,3-dideoxy-2,3-[(ethoxycarbonyl)methylene]-α-D-mannopyranoside. Ac_2O (0.75 mL, 9.12 mmol) and then 4-(dimethylamino)pyridine (37 mg, 0.3 mmol) were added, each in one portion, to a cold (0 °C) and stirred solution of the above diol (736 mg, 3.04 mmol) in dry pyridine. Stirring was continued for 4 h at room temperature. The mixture was diluted with CH_2Cl_2 (70 mL), washed with 1 M aqueous HCl (2 × 25 mL), saturated aqueous $NaHCO_3$ (1 × 20 mL), water (1 × 20 mL), and brine (1 × 20 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 20 cm) using 30% EtOAc–hexane followed by azeotropic evaporation of the new residue with toluene (2 × 15 mL), for removal of traces of pyridine, afforded the required diacetate (881 mg, 88% from the diol) as a white solid.

(c) Methyl (*R*)-1,4,6-Tri-*O*-acetyl-2,3-dideoxy-2,3-[(ethoxycarbonyl)methylene]-α-D-mannopyranose and Methyl (*R*)-1,4,6-Tri-*O*-acetyl-2,3-dideoxy-2,3-[(ethoxycarbonyl)-methylene]-β-D-mannopyranose. A solution of H_2SO_4 (15 μL) in Ac_2O (1 mL) was injected over 5 min into a cold (0 °C) and stirred solution of the above mannopyranoside (438 mg, 1.34 mmol) in Ac_2O (4 mL). Stirring was continued for 4 h at 0 °C. The mixture was diluted with CH_2Cl_2 (20 mL) and stirred for 10 min which saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (1 × 20 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (1 × 10 mL) and water (1 × 10 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 × 20 cm) using 40% EtOAc–hexane afforded a mixture of the required triacetates in a ratio of 8:1 [^1H NMR (200 MHz)] (469 mg, 99%) as a colorless oil.

(d) (*R*)-4,6-Di-*O*-acetyl-2,3-dideoxy-2,3-[(ethoxycarbonyl)methylene]-α-D-mannopyranosyl Bromide and (*R*)-4,6-Di-*O*-acetyl-2,3-dideoxy-2,3-[(ethoxycarbonyl)-methylene]-β-D-mannopyranosyl Bromide (19a). Me_3SiBr (37 μL, 0.28 mmol) was injected into a stirred solution of the above

(84) Richtmyer, N. K. *Methods in Carbohydrate Chemistry* Wiley: New York, 1962, Vol. 1, 107.

(85) Prepared from **18a** according to the literature procedure; see ref 36.

(86) The starting material was contaminated with 6% of the corresponding epoxide.

triacetates (51 mg, 0.14 mmol) in dry benzene (1.4 mL) contained in a 10-mL round-bottomed flask equipped with a condenser.[87] The mixture was lowered into a bath preheated at 65 °C and stirring was continued for 8 h. The mixture was cooled and evaporated (oil pump vacuum) to give the crude bromides **19a**, which were used without purification for the next step. The bromides are rather unstable, and, therefore, were kept under argon and protected from moisture.

4,6-Di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-3-(2-ethoxy-2-oxoethyl)-D-*arabino*-hex-1-enitol (19b). The general procedure for thermal radical ring-opening was followed, using the crude bromides **19a** (about 0.143 mmol) in dry benzene (1.4 mL), Bu_3SnH (94 μL, 0.35 mmol), and AIBN (2 mg, 0.012 mmol). Refluxing was continued for 2 h, and the mixture was cooled and evaporated. Flash chromatography (twice) of the residue over silica gel (1 × 15 cm) using 25% EtOAc–hexane afforded **19b** [34.0 mg, 79% based on the anomeric acetates (see part c above)]: FT-IR ($CHCl_3$ cast) 2980, 1744, 1651, 1374, 1237, 1062, 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, J = 7.2 Hz, 3 H), 2.09 (s, 6 H), 2.21 (dd, J = 16.0, 9.5 Hz, 1 H), 2.49 (dd, J = 16.0, 5.0 Hz, 1 H), 2.88 (m, 1 H), 3.99 (ddd, J = 10.0, 5.0, 2.4 Hz, 1 H), 4.14 (q, J = 7.2 Hz) and 4.17 (d, J = 12.3 Hz) [both signals together correspond to 3 H], 4.36 (dd, J = 12.3, 5.0 Hz, 1 H), 4.68 (dd, J = 6.0, 2.0 Hz, 1 H), 4.97 (t, J = 9.4 Hz, 1 H), 6.38 (dd, J = 6.0, 2.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.21, 20.76, 20.85, 35.32, 37.29, 60.63, 62.12, 68.83, 74.86, 102.14, 143.06, 170.09, 170.76, 171.68; exact mass, m/z calcd for $C_{12}H_{17}O_5$ [$(M - C_2H_3O_2)^+$] 255.0869, found 255.0865; mass (chemical ionization, NH_3) 318 [$(M + 18)^+$]. Anal. Calcd for $C_{14}H_{20}O_7$: C, 55.99; H, 6.71. Found: C, 55.78; H, 6.86.

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Supplementary Material Available: Appropriate spectroscopic and analytical data for **7b**, **7e**, **8b**, **8c**, **9f**, **11b**, **11c**, **13b**, **13c**, **14d**, (17α)-3-methoxyestra-1,3,5(10),15-tetraen-17-yl benzoate, a mixture of **15d** and **14e**, **18a**, methyl (*R*)-4,6-di-*O*-acetyl-2,3-dideoxy-2,3-[(ethoxycarbonyl)methylene]-α-D-mannopyranoside, methyl (*R*)-1,4,6-tri-*O*-acetyl-2,3-dideoxy-2,3-[(ethoxycarbonyl)-methylene]-α-D-mannopyranose, and methyl (*R*)-1,4,6-tri-*O*-acetyl-2,3-dideoxy-2,3-[(ethoxycarbonyl)methylene]-β-D-mannopyranose (6 pages). Ordering information is given on any current masthead page.

Microbiological Transformations. 19. Asymmetric Dihydroxylation of the Remote Double Bond of Geraniol: A Unique Stereochemical Control Allowing Easy Access to Both Enantiomers of Geraniol-6,7-diol

X. M. Zhang, A. Archelas, and R. Furstoss*

Laboratoire de Chimie Organique et Bioorganique, URA CNRS 1320, Faculte des Sciences de Luminy, 163, Avenue de Luminy, case 901, 13288 Marseille, Cedex 9, France

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The microbiological oxygenation of the geraniol *N*-phenylcarbamate **1** by *Aspergillus niger* is described, which leads regiospecifically to a formal dihydroxylation of its C(6)=C(7) double bond. By use of different pH values of the incubation medium, it is possible to modulate the stereochemical outcome of this reaction. Thus, 6*S* diol **3** (ee > 95%) is obtained at pH 2, whereas 6*R* diol **3** (ee > 95%) is formed at pH 6–7. The mechanism of this reaction has been studied by $^{18}O_2$ labeling. It is shown that, in a first step, the 6*S* epoxide **2** is almost exclusively formed. The second step involves hydrolysis of this key intermediate via a spontaneous acid-catalyzed hydrolysis at pH 2 or an enzymatic hydrolysis at pH 6–7.

Asymmetric dihydroxylation reactions of simple olefins are, at the present time, a widely used approach to prepare chiral building blocks.[1] Although these methods lead in some cases to diols showing ee values as high as 95%, the reactions seem to be limited to monoolefins of quite simple structure. We have recently[2] described an asymmetric biooxidation of the remote double bond of geraniol *N*-phenylcarbamate (**1**) by the fungus *Aspergillus niger*, which led to diol (6*S*)-**3** (49% yield, ee 95%) (Figure 1). Since this diol is a valuable chiral synthon,[3] it would be of great synthetic interest to obtain its 6*R* enantiomer stereospecifically. Whereas the challenge of obtaining a specific enantiomer of product can often be accomplished by asymmetric chemical reactions by using the appropriate enantiomer of catalyst, achieving such selectivity is less predictable in the case of bioconversions, although various options exist, i.e., by chemically modifying the substrate[4] or searching for other microorganisms (or enzymes) of opposite stereoselectivity.[5] We report here a more direct approach in which the stereochemical outcome is controlled simply by modifying the bioconversion conditions.

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