Synthetic Applications of Radical Ring-Opening: Use of Cyclopropylmethyl Radicals

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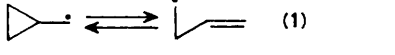
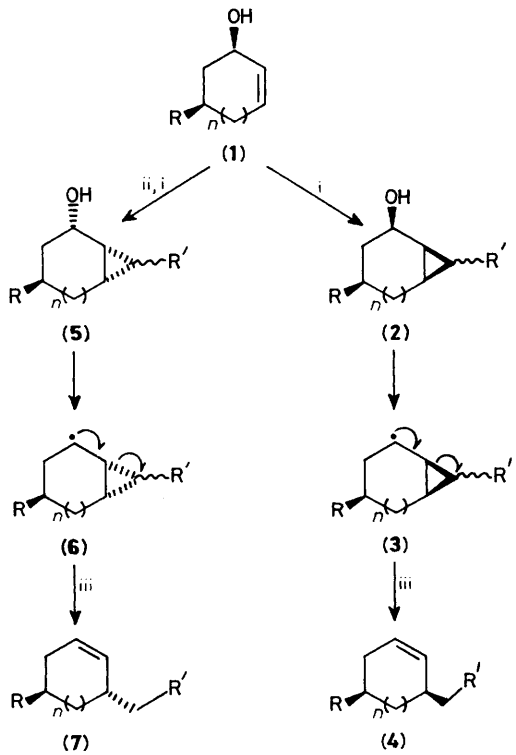
Cyclopropanation of cyclic allylic alcohols followed by radical deoxygenation leads, by peripheral ring-opening of the cyclopropylmethyl system, to alkyl-substituted cycloalkenes (Scheme 1); the alkyl group can itself be substituted (during the cyclopropanation stage), synthetic equivalents of allylic alcohols can be used, and the overall process occurs with predictable stereo- and regio-chemistry.

One of the conspicuous features of recent chemical literature is the speed with which the area of radical cyclisation is being developed by synthetic organic chemists.[1] In contrast, synthetic possibilities of the reverse process, radical ring-opening, have not yet been developed, although the physical organic chemistry[2] of these reactions has been studied in considerable detail and they have occasionally been used as mechanistic probes[3] and chronometric devices[4] for examination and detection of radical intermediates. In the area of carbocycles, a radical ring-opening that is very suitable for preliminary synthetic evaluation[5] is that shown in Equation (1).[6] The rate constants for this type of system are known[4,7] and some of the stereoelectronic[8,9] and conformational[9a,10] characteristics have been established.

We report that the preparation and opening of cyclopropylmethyl radicals constitutes a general synthetic method for attachment of alkyl and also substituted alkyl groups to existing cyclic structures (Scheme 1).[11] The procedure incorporates facilities to control stereochemistry [*cf.* (**1**)→(**4**) and (**1**)→(**7**), Scheme 1] and possess other useful characteristics that are described below.

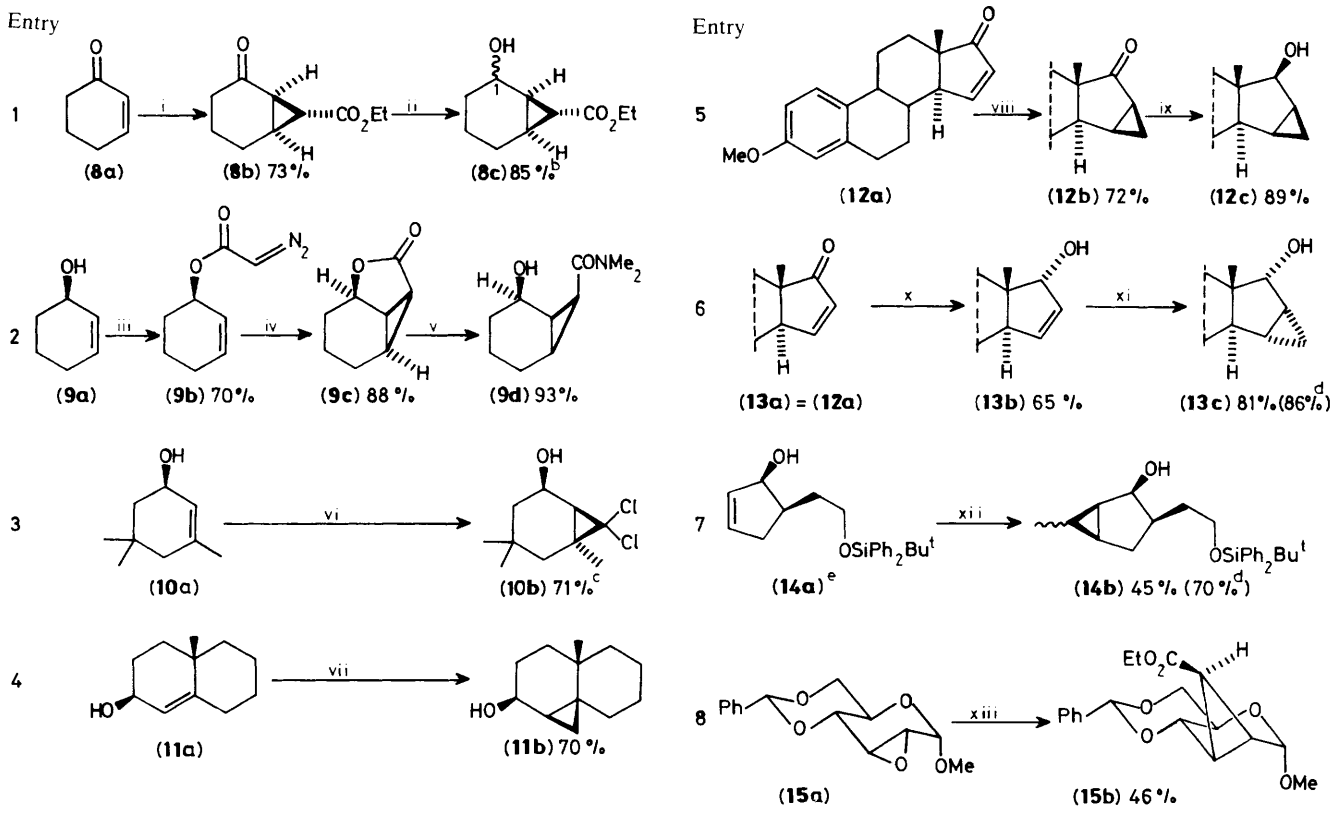
We normally prepare the cyclopropanes from allylic alcohols or from enones, and our experience is that some preliminary trials are necessary as no single method is always best for a particular class of starting material. Experimental variations of the classical Simmons–Smith process were applied in two cases (see Table 1, entries 4[12] and 6[13]) and these reactions occurred in the usual sense with direction by the hydroxy group. A phase–transfer approach[14] was used to make the geminal dichloride (**10b**), also by reaction *syn* to the hydroxy, and an organosamarium reagent[15] served for preparation of the methyl-substituted cyclopropane (**14b**), likewise with hydroxy-directed stereochemistry. In each of these cases the product is a cyclopropylmethanol, and so it is properly constituted for the radical deoxygenation step [*cf.* (**2**)→(**3**), Scheme 1]. When the substrate for cyclopropanation is an enone, however, then the stereochemistry is not controllable





Scheme 1. i, Cyclopropanation, ii, Mitsunobu inversion, iii, stannane. R′ = H, alkyl group, electron-withdrawing group

Table 1.[a]



Reagents and conditions: i, Slow addition (4 h) of $Me_2S{=}CHCO_2Et$ to refluxing benzene solution of (**8a**); reflux 16 h; ii, $NaBH_4$, $CeCl_3.7H_2O$, MeOH, room temp., 30 min; iii, $PhNMe_2$, $TsNHN{=}CHCOCl$, (Ts = *p*-$MeC_6H_4SO_2$), CH_2Cl_2, 0 °C, 20 min; then Et_3N, 0 °C, 15 min, room temp., 30 min.; iv, (**9b**) added over 12 h to bis-(*N*-t-butylsalicylaldiminato) copper(II) in toluene at reflux; v, Me_2AlNMe_2, CH_2Cl_2, reflux, 3 h; vi, aq. NaOH (12.5 M), $PhCH_2N^+Et_3Cl^-$, $CHCl_3$, 0 °C, 40 min; vii, CH_2I_2, Zn(Cu), ether, reflux, 16 h, or CH_2I_2, Zn, 1,2-dimethoxyethane (DME), sonication, 55 °C, 8 h; viii, Me_3S^+ (O) I^-, NaH, dimethyl suphoxide (DMSO), room temp., 30 min; then add (**12a**), 50 °C, 3 h; $LiAlH_4$, 1:4 tetrahydrofuran (THF)–ether, −15 °C to room temp., x, $NaBH_4$, $CeCl_3.7H_2O$, MeOH, −20 °C to room temp.; Ph_3P, EtO_2C–N=N–CO_2Et, $PhCO_2H$, THF, room temp., 3 h; aq. NaOH (5 M), 1:3 THF–MeOH, room temp, 16 h; xi, CH_2I_2, Zn(Cu), 1:1 DME–ether, reflux, 16 h; xii, CH_3CHI_2, Sm, $HgCl_2$, THF, −78 °C to room temp., xiii, $EtO_2CCH_2P(O)(OEt)_2$, NaH, dioxane, 80 °C, 3 days.

[a] Yields refer to pure, isolated compounds. [b] Two isomers, epimeric at C-1. [c] Reaction must be monitored closely by thin layer chromatography, (TLC) otherwise the yield is lower. [d] Yield corrected for recovered starting material. [e] Made by reduction ($LiAlH_4$) of (3, 3aα, 4,6aα)-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one and selective silylation.

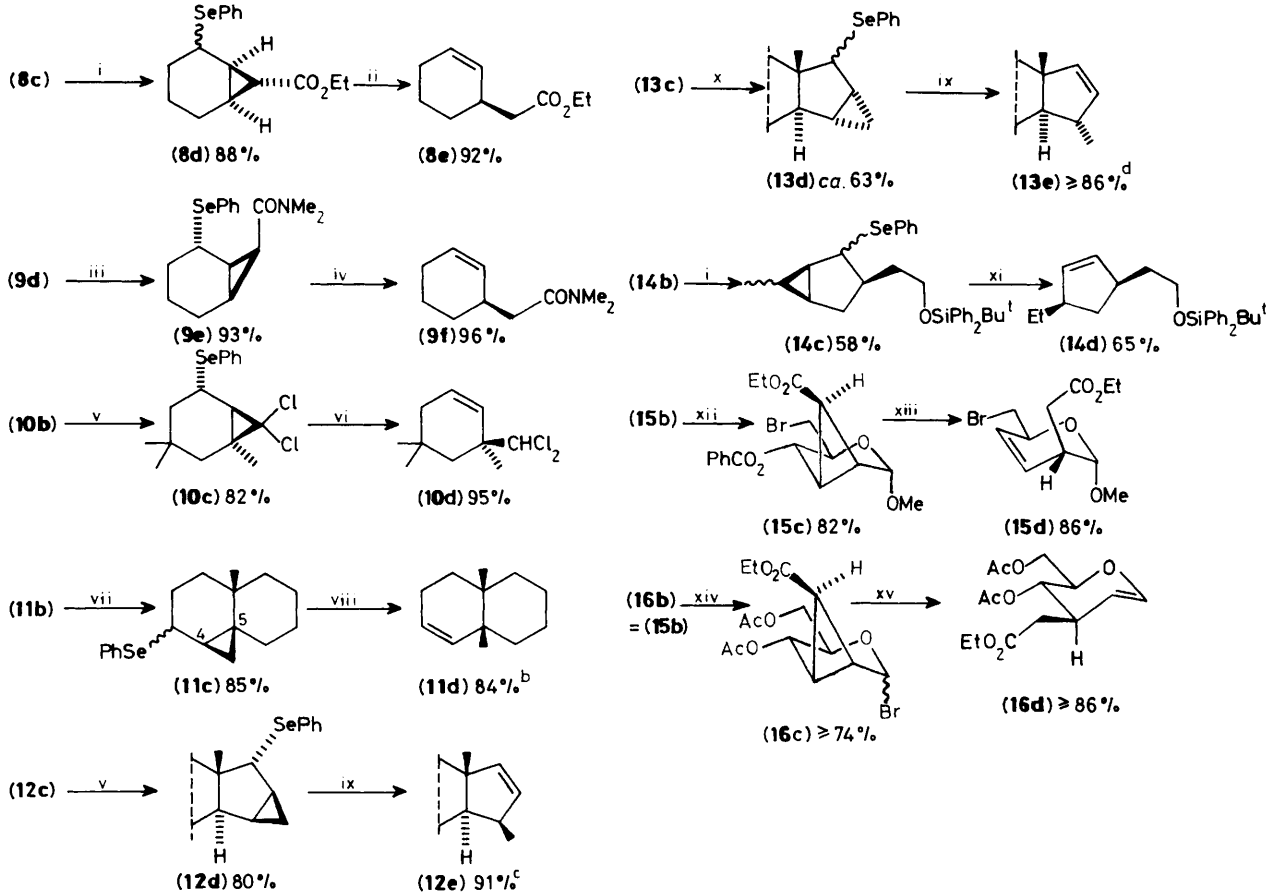
at will,[16] and the initial adduct [*e.g.*, (**8b**)[17] and (**12b**),[18] Table 1] must be reduced to the alcohol. However, if the enone is first reduced to an allylic alcohol (*cf.* entry 6 of Table 1) then such control can again be exercised and the examples of entries 5 and 6 (Table 1) show one way in which both of the required isomeric cyclopropanes can be made from the same starting material. We have also found (see Table 1, entry 2) that intramolecular cyclopropanation[19] (with its inherent stereocontrol) is suitable for the purposes of Scheme 1. Lastly, appropriate cyclopropanes can be made from epoxides as demonstrated with the sugar epoxide (**15a**),[20] which was converted, as shown, into cyclopropane (**15b**).

Generation of the initial radical [*cf.* (**2**)→(**3**), Scheme 1] was usually best done in two steps: replacement of the hydroxy by a benzeneseleno group and then treatment with a stannane.[21] Direct conversion of secondary alcohols into selenides has not often been reported and is a slow process. We find that cyclopropylmethanols react easily with the standard reagents,[22] phenyl selenocyanate and tributylphosphine, although we do not follow the procedure recommended[22] with this system. In our experiments we add the phenyl selenocyanate to a mixture of the alcohol and the phosphine, instead of introducing the phosphine last. The yields are usually high (see Table 2) but we have not determined whether this is a characteristic of cyclopropylmethanols or is a result of our experimental method. Formation of the phenyl selenides does not always occur in a stereochemically unique manner; however, this is of no consequence. The tricyclic lactone (**9c**) (Table 1) failed to react with phenyl selenide anion[23] and so the lactone ring was first opened by conversion to a hydroxy amide (**9d**) (Table 1).[24]

All of the selenides undergo homolysis in the presence of a stannane (Table 2) but the optimum conditions for ring opening depend on the substitution pattern of the cyclopropane. Where this unit carries an electron-withdrawing substituent, as in (**8d**), (**9e**), and (**16c**) (Table 2), a simple thermal reaction in refluxing benzene using triphenyl- or tributyl-tin hydride and AIBN (azoisobutyronitrile) is suitable.† In the case of the geminal dichloride (**10c**) we arbitrarily ran the

† In these cases [(**8d**), (**9e**), (**16c**)] the stannane and initiator are added in one portion.

Table 2.[a]



Reagents and conditions: i, Bu_3P, PhSeCN, THF, room temp.; 4 h, ii, Ph_3SnH, AIBN, benzene, reflux, 1 h; iii, Bu_3P, PhSeCN, THF, reflux, 14 h; iv, Ph_3SnH, AIBN, benzene, reflux, 3 h; v, Bu_3P, PhSeCN, THF, reflux, 16 h; vi, Ph_3SnH, sunlamp, Pyrex, toluene, −20 to −10 °C, 2.5 h; vii, Bu_3P, PhSeCN, THF, −78 °C to room temp., 16 h; viii, Bu_3SnH, sunlamp, Pyrex, hexane or THF −10°C, 2 h; ix, Bu_3SnH, sunlamp, Pyrex, toluene, 0 °C, 2.5 h; x, Bu_3P, PhSeCN, THF, reflux, 18 h; xi, Bu_3SnH, sunlamp, Pyrex, hexane, 10—30 °C, 2.5 h; xii, *N*-bromosuccinimide, $BaCO_3$, CCl_4, reflux, 2 h; xiii, *N*-methylcarbazole, $MgClO_4.6H_2O$, 9:1 THF–H_2O, 200 W medium pressure Hg lamp, Pyrex filter, room temp., 10 h; xiv, H_2, Pd–C, AcOH, room temp., 17 h; Ac_2O, pyridine, room temp., 4 h; Ac_2O, H_2SO_4 (catalytic), room temp, 7 h; Me_3SiBr, benzene, 65 °C, 8 h; xv, Bu_3SnH, AIBN, benzene, reflux, 2 h.

[a] Unless otherwise stated, yields refer to pure, isolated compounds. [b] Yield refers to a mixture 95:5 [(**11d**):ring-expanded olefin]. [c] Yield refers to a mixture 84:16 [(**12e**):ring-expanded olefin]. [d] Yield refers to a mixture 84:16 [(**13e**):ring-expanded olefin]. [e] Bromide not isolated; yield of its precursor was 87% [from (**16b**)]. Yield of (**16d**) from this precursor was 86%.

reaction at a low temperature in order to optimise the level of chemoselectivity. This necessitated photochemical initiation‡ and, in the event, the chlorine atoms were not attacked.§ A photochemically initiated reaction at low temperature was definitely needed for (**11c**), where the cyclopropane ring carries no electron-withdrawing group and, in this case, it was advantageous to use tributyltin hydride because it is a poorer hydrogen donor than the aromatic stannane.[25] These experimental conditions served (see Table 2, footnote[b]) to inhibit strongly two competing reactions: simple replacement of the benzeneseleno group by hydrogen and opening of the internal cyclopropane bond [*i.e.*, C(4)–C(5)]. However, when the three-membered ring is fused onto a cyclopentane [see (**12d**) and (**13d**), Table 2],¶ expansion (in this case to a cyclohexene) is not fully suppressed but the desired process is still by far (>84%) the major pathway. In some cases [*e.g.*, with (**12d**) and (**13d**), Table 2] chromatographic isolation of the products is a little easier if tributyltin hydride is used instead of the triphenyl compound, but this change in reagents is not obligatory for satisfactory ring opening.

The present method for attaching substituents to a cyclic structure has a number of useful characteristics. In particular, the benzeneseleno group, though tolerant of a wide range of reaction conditions both before and during the homolysis step, is not the only source of radicals that is appropriate; however, the Barton deoxygenation is generally not suitable because of

‡ Our photochemical reactions (Table 2) were carried out in toluene, hexane, or tetrahydrofuran (0.1—0.2 M in substrate and 0.1—0.3 M in stannane) using a Pyrex flask with an optically flat panel in its upper side. The flask was immersed in a cold-bath and irradiated from above with a 275 W General Electric Sunlamp.

§ We did not try other conditions.

¶ The results with (**12d**) were very little different when the reaction was done in refluxing benzene (22% ring expansion) or photochemically at −10 °C (16% ring expansion).

our requirement for low temperatures.[26] The photolysis[27] of a benzoate proved very efficient as illustrated by the conversion of (**15c**) into (**15d**). In the case of (**16c**) stannane reduction of a bromide was used. An additional feature is that both the benzoate (**15c**) and the bromide (**16c**) are available in a straightforward manner. A special point about the photochemical experiment with benzoate (**15c**) is the presence of bromine in the substrate. This substituent is not compatible with deoxygenation methods involving stannanes. The formation, at will, of either (**15d**) or (**16d**) from the same starting material demonstrates a type of regiochemical control that is easily achieved by the present method. In an analogous way, production of (**12e**) and (**13e**) illustrates stereochemical results that are not *both* readily accessible by organocopper methodology. Our results also show that functional groups not normally stable to organometallic reagents can be tolerated.[28] Formation of γ,δ-unsaturated esters, such as (**15d**) and (**16d**), by radical chemistry warrants further comment. In general, γ,δ-unsaturated esters can be made using the Ireland ester enolate rearrangement; however, this ionic process, under strongly basic conditions, is not applicable in the presence of other acetoxy or bromo substituents.

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