(28%) of the monoalkylated products **14a** (*ca.* 88%) and **15** (*ca.* 12%) eluted in the later benzene–ether fractions. Fractional distillation of the crude product from a comparable preparative run separated a fraction [bp 36° (0.13 mm), $n^{24.3}$D 1.4651; lit.[27] bp 85° (10 mm), n^{25}D 1.4590] which contained[10] primarily the thiobutyl ether **28a**. The fractions [bp 83–100° (0.1 mm), $n^{24.3}$D 1.4899–1.4927] from this distillation contained[10] 80–90% of the monoalkylated products **14a** and **15** accompanied by minor quantities of several lower boiling components. A collected[10] sample of the thiobutyl ether **28a** has infrared absorption[16] at 1740 cm^{-1} (ester C=O) with nmr peaks[16] at δ 3.71 (3 H, OCH_3) and 3.10 (2 H, SCH_2CO) with multiplets in the regions δ 2.4–2.8 (2 H, CH_2S) and 0.8–1.8 (7 H, aliphatic CH). The mass spectrum has a molecular ion peak at *m/e* 162 with abundant fragment peaks at *m/e* 89 (n-$C_4H_9S^+$), 74 $[CH_2{=}C(OH)OCH_3]^+$, 61, 55, 47, 45, and 41. This thiobutyl ether **28a** is apparently found during alkaline cleavage of the blocking group by reaction of the liberated butyl mercaptide anion with the excess methyl bromoacetate present. A collected[19] sample of the *cis*-keto ester **14a** was identified with the previously described sample by comparison of infrared and mass spectra. The small amount of *trans* isomer present was identified only by its gas chromatographic retention time.[19]

In subsequent experiments, the same alkylation procedure was followed but the crude product was investigated prior to cleavage of the blocking group. From reaction of a solution of 2.02 g (8.6 mmoles) of the ketone **6** in 50 ml of *t*-butyl alcohol with 34.5 mmoles of potassium *t*-butoxide followed by 5.54 g (36.2 mmoles) of methyl bromoacetate the crude neutral alkylated product consisted of 4.91 g of an orange oil. Successive chromatography on Florisil and on neutral alumina (activity grade III) separated a number of low boiling fractions from 1.55 g of liquid fractions which contained[28] mixtures of the methyl and *t*-butyl esters **13a** and **b**. Additional chromatography on neutral alumina (activity grade III) separated 241 mg of an early fraction, eluted with benzene–hexane mixtures, which contained[28] primarily the crude *t*-butyl ester **13b**. This sample has infrared absorption[16] at 1720 (br, ester and ketone C=O) and 1595 cm^{-1} (conjugated C=C) with an ultraviolet maximum[15] at 310 mμ (ϵ 16,500). The material has nmr absorption[16] at δ 7.26 (1 H multiplet, C=CHS), 5.60 (2 H multiplet, vinyl CH), and 1.38 [singlet, $(CH_3)_3CO$], as well as complex absorption in the region δ 0.8–3.1 (aliphatic CH). A later fraction (449 mg) from the chromatography, also eluted with benzene–hexane mixtures, contained mainly the methyl ester **13a**. Short-path distillation of this fraction afforded the methyl ester **13a** as a pale yellow liquid with infrared absorption[16] at 1740 (ester C=O), 1710 (C=O of a conjugated cyclopentanone derivative) and 1590 cm^{-1} (conjugated C=C) and an ultraviolet maximum[15] at 309.5 mμ (ϵ 20,600). The sample has nmr peaks[16] at δ 7.31 (1 H multiplet, C=CHS), 5.66 (2 H multiplet, vinyl CH), 3.58 (3 H singlet, OCH_3), and 2.87 (2 H triplet with J = 7 cps, CH_2S), as well as complex absorption in the region δ 0.8–2.6 (16 H, aliphatic CH). Although the general appearance of the nmr spectrum of this sample would suggest that it contains only the *cis* fused tetrahydroindan stereoisomer, we have no way to exclude the possibility that the *trans* fused stereoisomer is also present.

Anal. Calcd for $C_{17}H_{24}O_3S$: C, 66.21; H, 7.85; S, 10.26. Found: C, 66.40; H, 7.94; S, 10.45.

In an additional alkylation experiment, an aliquot of the crude alkylation product was mixed with a weighed amount of triphenylmethane as an internal standard and analyzed by gas chromatography.[11] The calculated yields of products were 1% starting ketone **6** and 31% methyl ester **13a**.[29] The remainder of the crude alkylated product was treated with potassium hydroxide in aqueous ethanol to remove the blocking group. An aliquot of this final product (after reesterification with diazomethane) was mixed with a weighed amount of acenaphthene and analyzed by gas chromatography.[19] The calculated yields were 35% *cis* isomer **14a** and 2% *trans* isomer **15**.

Registry No.—**6**, 10308-96-0; **10**, 10308-97-1; **11**, 10308-98-2; **12a**, 10308-99-3; **12b**, 10309-00-9; **13a**, 10309-01-0; **13b**, 10309-02-1; **14a**, 10309-03-2; **14b**, 10309-04-3; **15**, 10309-05-4; **16**, 10309-06-5; **17a**, 10309-07-6; **17b**, 10309-08-7; **18**, 10315-72-7; **19**, 10309-09-8; **20**, 10309-10-1; **23**, 10309-11-2; **24**, 10309-12-3; **25**, 10309-13-4; **28a**, 10309-14-5.

(27) Y. Uyeda and E. E. Reid, *J. Am. Chem. Soc.*, **42**, 2385 (1920).

(28) Thin layer chromatography plates coated with alumina and eluted with benzene–ether mixtures were employed for this analysis.

(29) The *t*-butyl ester **13b** could not be successfully eluted from our gas chromatography equipment apparently because of decomposition in the inlet system or on the column. The reason for the apparent low yield of alkylated products arises from the fact that the crude alkylated product contains both the methyl and *t*-butyl esters **13** but only the methyl ester fraction is being measured in this analysis.

Alane Reductions of 1-Phenylcyclopentene Oxide

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Received November 22, 1966

The title compound has been reduced by alane prepared from lithium aluminum hydride ($LiAlH_4$) and aluminum chloride in ether, according to Eliel and Ashby, or from $LiAlH_4$ and sulfuric acid in tetrahydrofuran, as described by Brown, with similar results. Three types of reaction occur, depending on ratios of reactants and order of addition, when alane-d_3 is used: excess alane gives *cis*-2-phenylcyclopentanol-2-*d* mainly; when alane-d_3 is added in great deficiency, *cis*- and *trans*-2-phenylcyclopentanol-1-*d* are the main products. A mechanistic rationale for these reactions is presented.

Several groups of investigators, notably Nystrom, *et al.*,[2] and Eliel and co-workers[3] have investigated the reducing properties of "mixed hydride" reagents, prepared from various ratios of lithium aluminum hydride ($LiAlH_4$) and aluminum chloride. These reagents can reduce aryl carbonyl groups to methylene groups[2] and react with unsymmetrical epoxides in several ways,[3] depending on which ratios of the two reagents are used, as illustrated in Scheme I.[3] The structures and position of deuterium in the products indicate whether rearrangement occurs during reduction but the stereochemical aspects of the epoxide ring opening cannot be determined from the acyclic products obtained. Recently, Ashby[4] has shown that the actual reducing agent obtained from $LiAlH_4$–$^1/_3AlCl_3$ is alane, whereas $LiAlH_4$–$3AlCl_3$ produces dichloroalane, $AlHCl_2$. Realizing that the latter reagent is a stronger Lewis acid and weaker hydride donor than AlH_3, Ashby rationalized[4] earlier results of Eliel[3] in terms of initially formed epoxide–alane complexes that col-

(1) Alfred P. Sloan Foundation Fellow, 1963–1967.

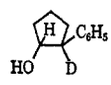
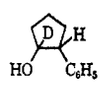
(2) R. F. Nystrom and C. R. A. Berger, *J. Am. Chem. Soc.*, **80**, 2896 (1958).

(3) E. L. Eliel, *Rec. Chem. Progr.*, **22**, 129 (1961); M. Rerick and E. L. Eliel, *J. Am. Chem. Soc.*, **84**, 2356 (1962).

(4) E. C. Ashby and J. Prather, *ibid.*, **88**, 729 (1966).

TABLE I

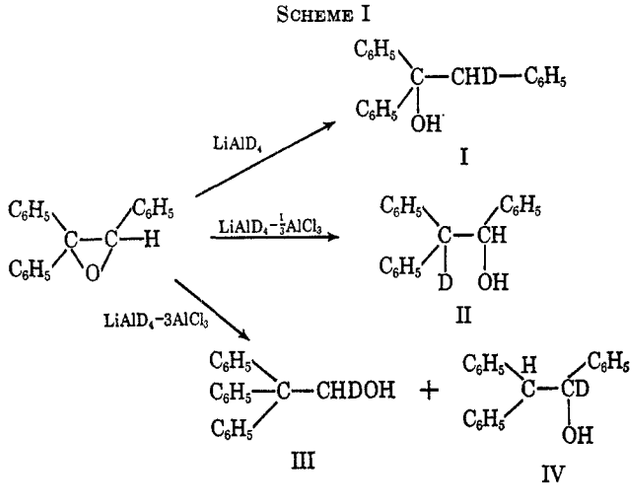
REDUCTIONS OF 1-PHENYLCYCLOPENTENE OXIDE (V) AND 2-PHENYLCYCLOPENTANONE (IX) WITH ALANE

Run	Mole ratio: 	AlD_3[a]	Mode of addn[b]				
1	1	2	Normal	62	13	4	21
2	1	1	Normal	19	8	17	56
3	1	1	Inverse	8	2	20	70
4	2	1	Normal	7	7	20	66
5	3	1	Inverse	8	5	18	69
6	1	2[c]	Combined in	60	1	5	29
7	2	1[c]	one portion[a]	20	2	20	58

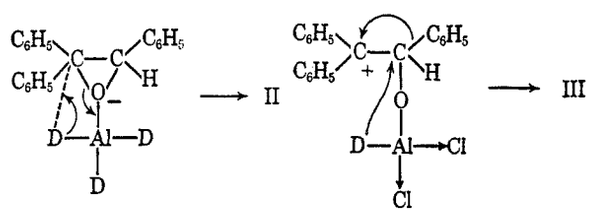
Run	Mole Ratio: 	AlH_3			
8	3	1	Inverse	40[d]	60[d]
9	1	3	Normal	18[d]	82[d]

[a] From $3LiAlD_4$ and $AlCl_3$ in diethyl ether unless otherwise noted. [b] "Normal" addition denotes V in solvent added to AlD_3; "inverse" addition involves AlD_3 solution *added to V*. [c] From $2LiAlD_4$ and sulfuric acid in tetrahydrofuran.[6] [d] Undeuterated.

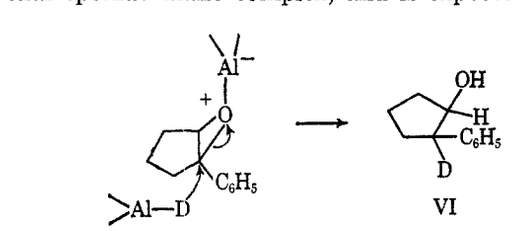
SCHEME I



lapsed intramolecularly (and presumably *cis*) with or without prior hydrogen or phenyl migration.



In connection with earlier synthetic studies, we found that 1-phenylcyclopentene oxide (V) gave mainly *cis*-2-phenylcyclopentanol-2-*d* (VI) when reduced by excess AlD_3.[5] This result involves *trans* opening of the epoxide, supposedly by intermolecular attack on the initial epoxide–alane complex, and is expected to predominate only with excess alane present. We have now undertaken a broader investigation of alane reductions of V, varying reagent ratios, order of addition, and even the method of preparing the alane, since Brown has recently reported on reductions of various substrates, using AlH_3 in tetrahydrofuran (THF) prepared from $LiAlH_4$ and 100% sulfuric acid.[6] As discussed below, it appears that $Al(OR)H_2$ and $Al(OR)_2H$ are important reductants when insufficient AlH_3 is employed and that such species produce results similar to chloroalanes.[3,4]



(5) P. T. Lansbury and V. A. Pattison, *Tetrahedron Letters*, 3073 (1966).

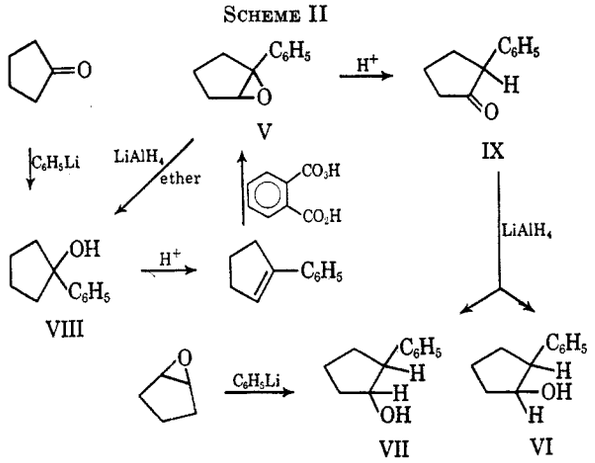
Results and Discussion

The model substrate used throughout this work was 1-phenylcyclopentene oxide (V), prepared by epoxidation of 1-phenylcyclopentene[7] with monoperphthalic acid. The three possible reduction products, 1-phenylcyclopentanol[7] and *cis*- and *trans*-2-phenylcyclopentanols,[7,8] were prepared by standard reactions shown in Scheme II, and could be clearly separated by alumina chromatography of reaction mixtures,[8] as well as analyzed by glpc. Reductions of V by AlH_3 or AlD_3 were run as described previously[3,5,8] and the alcohols VI–VIII were separated by chromatography.[9] VI and VII were then individually assayed for deuterium at the 1 and 2 positions by peak integration of the respective proton multiplets, relative to the hydroxyl proton and/or five-proton phenyl signals.

In VI, the benzylic proton resonance appeared at 2.75 ppm, and the carbinol proton appeared at 4.0 ppm, whereas in VII, the corresponding chemical shifts were 2.75 and 3.9 ppm. However, the deuterium analyses may have errors as high as ±5% since the integration curves for the broad multiplets were difficult to measure accurately and the results can be interpreted only qualitatively, although meaningfully. Table I shows the yields of the four deuterated 2-

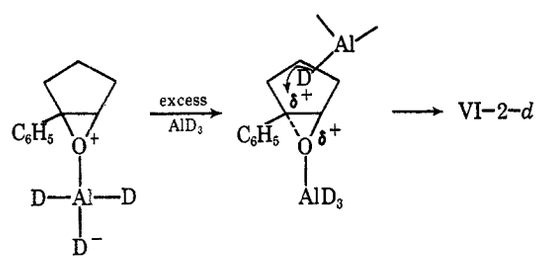
(6) H. C. Brown and N. M. Yoon, *J. Am. Chem. Soc.*, **88**, 1464 (1966).
(7) W. H. Tallent, *J. Org. Chem.*, **21**, 862 (1956).
(8) V. A. Pattison, Ph.D. Dissertation, State University of New York at Buffalo, 1964.
(9) Generally, VIII was present in 1–2% yield, if at all, the only exception being $LiAlH_4$ reduction of V, which produced VIII exclusively. Thus, no deuterium analyses of VIII were done when small quantities were present.

SCHEME II

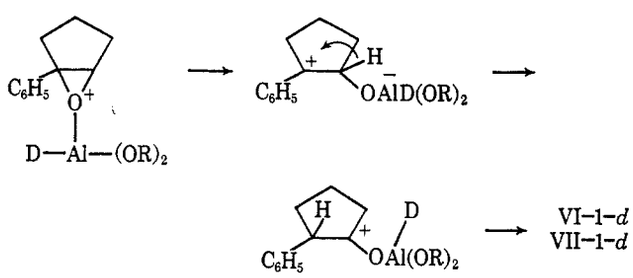


phenylcyclopentanols (VI and VII) resulting from a number of AlD_3 reductions of V and 2-phenylcyclopentanone (IX).

The four major reduction products are formed by three pathways, which have different importance depending on conditions. With excess AlD_3 (runs 1 and 6) bimolecular reduction of the epoxide–alane complex is the predominant course. On the other hand,



inverse addition of insufficient alane results in substantial 1,2-hydride shift prior to reduction of the benzylic cation (runs 4, 5, and 7). Presumably the less reactive $Al(OR)D_2$ and $Al(OR)_2D$ species are involved here. The third pathway for reduction is Ashby's intramolecular mechanism,[4] which leads to VII-2-*d*.



It may be expected that the *cis*/*trans* ratio in reduction of 2-phenylcyclopentanone by alane should parallel the steric course of reduction of V leading to *α-deuterated* alcohols, under similar conditions, since the same type of intermediate may be involved. The last two entries in Table I show that there is qualitative agreement on this point.

It is noteworthy that formation of *trans*-2-phenylcyclopentanol-2-*d*, predicted by Ashby's intramolecular reduction mechanism,[4] is a minor product over the entire range of conditions studied. This may be a consequence peculiar to the cyclopentene oxide system, since this bicyclic structure possesses substantial strain energy (bond angle and torsional strain) and is more apt to undergo Lewis acid catalyzed ring opening[10] than styrene oxide, which gives mainly α-phenylethanol under comparable conditions[6] or even 1-phenylcyclohexene oxide, which is a secondary–tertiary epoxide like V.

Reductions of V with AlD_3 in THF (runs 6 and 7), prepared by Brown's method, gave results similar to "mixed hydride" in ether which contained lithium chloride (runs 1–5). It appeared that lithium sulfate had not completely precipitated from the THF solution of alane in these cases. However, in one experiment a clear alane THF solution virtually free of lithium sulfate was obtained and this gave *exclusively cis*-2-phenylcyclopentanol from V, using excess alane (>2 moles/mole of V). Thus, lithium salts play an important role in alane reductions, perhaps more than solvent changes.

Undoubtedly, the three types of reductions of unsymmetrical epoxides possible with alane will have different importance as the substrate structure is changed. At this time, however, it is clear that predictable differences in product(s), stereochemistry, and deuterium labeling can be achieved from a single substrate by varying reactant ratios and experimental conditions. We do not plan to extend our investigations to other systems.

Experimental Section[11]

Materials.—Lithium aluminum hydride and deuteride were obtained from Alpha Inorganics Division of Aldrich Chemical Co. 1-Phenylcyclopentene, 1-phenylcyclopentanol, and *trans*-2-phenylcyclopentanol were prepared as described by Tallent.[7]

1-Phenylcyclopentene oxide (V) was prepared (69%) by epoxidation of 1-phenylcyclopentene with monoperphthalic acid[12] in ether at 0° for 36 hr. The reaction mixture was washed with aqueous sodium hydroxide solution, dried over sodium sulfate, and finally distilled under reduced pressure (after solvent removal), bp 123–125° (4 mm). Characteristic infrared bands appeared at 6.9, 7.1, 9.4, 10.84, 11.0, 11.43, 11.9, 13.25, and 14.4 μ.

Anal. Calcd for $C_{11}H_{12}O$: C, 82.45; H, 7.56. Found: C, 82.24; H, 7.38.

A sample of V was found to rearrange readily to 2-phenylcyclopentanone[13] (IX) in 40% sulfuric acid at *ca.* −10°.

Typical Reduction Procedures. A. Normal Addition of V to Alane in Ether.—To a solution of 0.71 g (5.3 mmoles) of anhydrous aluminum chloride in 50 ml of ether was added 0.60 g (15.8 mmoles) of $LiAlH_4$ at 0°. After stirring for 45 min at room temperature, a solution of 1.68 g (10.5 mmoles) of 1-phenylcyclopentene oxide (V) in 50 ml of ether was added during 45 min and the solution then allowed to reflux for 2 hr. The reaction mixture was hydrolyzed with 50 ml of 10% hydrochloric acid, washed with distilled water then saturated aqueous sodium bicarbonate, and dried over magnesium sulfate. After filtration and concentration of the ether solution, vpc analysis was used to determine the relative amounts of VI, VII, and VIII present; a 4-ft Tide column operating at ~160° was used with a helium flow rate of ~180 cc/min. The order of elution of the three phenylcyclopentanols was VIII, then VI, then VII. The *cis*- and *trans*-2-phenylcyclopentanols, usually the only alcohols present, could be separated clearly by alumina chromatography,

(10) This apparently is a major difficulty in preparing 1-phenylcyclopentene oxide; great care is necessary to avoid forming 2-phenylcyclopentanone.

(11) Melting points and boiling points are uncorrected. Infrared spectra were measured on a Beckman IR-5A spectrometer, using Nujol mulls for solids or neat liquids. Nuclear magnetic resonance spectra were recorded with a Varian A-60 spectrometer, using carbon tetrachloride as solvent and tetramethylsilane as internal standard. Vapor phase chromatography analyses were on F & M Model 300 and 700 instruments.

(12) G. B. Payne, *J. Org. Chem.*, **24**, 1354 (1959).

(13) W. Baker and P. G. Jones, *ibid.*, **16**, 787 (1951).

eluting first with 30–60° petroleum ether, then petroleum ether progressively richer in diethyl ether (up to 60:40). Using this technique, *cis*-2-phenylcyclopentanol (VI) was first eluted and subsequently further purified by distillation, bp 113–115° (2 mm).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.42; H, 8.71. Found: C, 81.45; H, 8.42.

trans-2-Phenylcyclopentanol[7] was also purified and both alcohols assayed for deuterium (when AlD_3 was used) by nmr spectroscopy[5] (see discussion).

B. Inverse Addition of Ethereal Alane[8] to 1-Phenylcyclopentene Oxide (V).—To a solution of 0.212 g (1.59 mmoles) of aluminum chloride in 50 ml of anhydrous ether at 0° was added 0.2 g (4.76 mmoles) of $LiAlD_4$. This solution was stirred at room temperature for 0.5 hr, whereupon it was added dropwise to a solution of 3.06 g (19.1 mmoles) of 1-phenylcyclopentene oxide (V) in 50 ml of anhydrous ether. The reaction mixture was brought to reflux for 1 hr followed by hydrolysis with 5% aqueous hydrochloric acid solution. The ether layer was separated and washed with a saturated solution of aqueous bicarbonate, then water, followed by drying over magnesium sulfate.

The ether was distilled and the residue was subjected to alumina chromatography and vpc analysis as above.

C. Reaction of 1-Phenylcyclopentene Oxide (V) with AlH_3/THF Reagent.[6]—To 50 ml of anhydrous THF was added 1.14 g (30 mmoles) of $LiAlH_4$ at 0°. To this solution was added 1.47 g (0.80 cc) of 100% H_2SO_4 slowly *via* a syringe, while the solution was stirred vigorously. Hydrogen evolution was indicated by means of a gas bubbler. The solution was stirred at room temperature for 1 hr, followed by standing overnight in an atmosphere of nitrogen to permit the lithium sulfate precipitate to settle.

The THF solution was removed carefully (cloudy, owing to some Li_2SO_4 that had not settled) by a syringe and injected into a dry, three-neck, 200-ml, round-bottom flask fitted with a syringe cap, reflux condenser to which a gas bubbler was connected, and an inlet tube. To the AlH_3/THF solution was added 0.5 g (3 mmoles) of 1-phenylcyclopentene oxide (V) in 10 ml of THF in *ca.* 10 sec. This reaction mixture was stirred under a nitrogen atmosphere for 1 hr at room temperature whereupon it was hydrolyzed with methanol followed by work-up with Rochelle's salt (sodium potassium tartrate) solution to break up the trimethoxyaluminum complex. The THF solution was then separated and dried over magnesium sulfate. Solvent evaporation afforded 0.4 g of crude product; alumina chromatography and vpc analyses were then carried out as above.

It should be noted that this method of preparing alane in THF gave results with styrene oxide identical with those obtained by Brown and Yoon:[8] 74% α-phenylethanol and 26% β-phenylethanol.

Registry No.—Alane, 7784-21-6; V, 10294-00-5; VI, 2362-73-4; IX, 1198-34-1; AlD_3, 10294-03-8.

The Generation of Angular Methyl Groups in Fused-Ring Systems[1]

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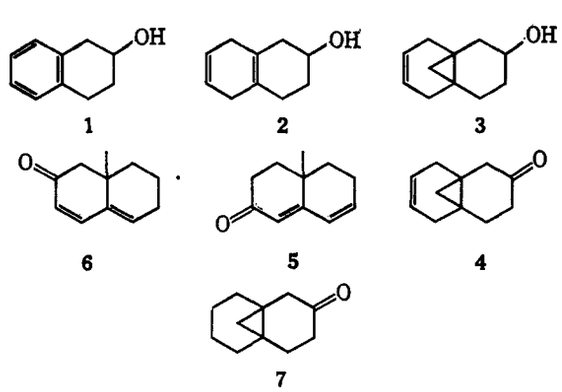
A stereospecific method for introducing an angular methyl group, which uses the known stereospecificity of the Simmons–Smith cyclopropanation with subsequent opening of the cyclopropane to form a methyl group is discussed. Base-catalyzed ring opening of tricyclo[4.4.1.$0^{1,6}$]undec-8-en-3-one (4) leads to self-condensation. Acid-catalyzed ring opening of ketone 4 gives both possible ring-opened ketones in a ratio depending upon the acid used.

One of the major problems that one faces in the total synthesis of the terpenes and steroids is the stereospecific introduction of angular methyl groups. The key to success in most work to date is the elaboration of a methylcyclohexanone *via* the Robinson annelation[2] or various modifications[3] of the basic theme. Although this general approach has enjoyed success as a route to fused cyclic systems possessing an angular methyl group, as pointed out by Marshall and Fanta, it is also often plagued by low yields and impure products.[4] Some versatility is also lost in that one must always engage in annelating a new ring, rather than being able to introduce a methyl group to a suitably fused, preformed array.

It has been previously observed that cyclopropane rings could be opened smoothly to give angular methyl groups.[5] These observations plus the recently accumulated knowledge that in the Simmons–Smith reaction[6] certain polar groups may direct formation of the cyclopropyl ring *cis* to themselves[7] suggests that a synthetic sequence could be designed involving a stereospecifically formed cyclopropane ring and its subsequent selective opening to produce an angular methyl group. We chose to investigate, as a model, the conversion of 1 to 5. While this investigation was in progress, a similar scheme was shown to be of value in the conversion of estradiol to 10α-testosterone.[8]



(1) Support of this work by a grant (AM-10474-01) from the U. S. Public Health Service is gratefully acknowledged.

(2) E. C. duFeu, F. J. McQuillan, and R. Robinson, *J. Chem. Soc.*, 53 (1937).

(3) (a) L. Valluz, J. Valls, and G. Nomine, *Angew. Chem.*, **77**, 185 (1965); (b) G. Stork, *Pure Appl. Chem.*, **9**, 131 (1964).

(4) J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, **29**, 2501 (1964).

(5) (a) J. J. Bonet, H. Wehrli, and K. Schaffner, *Helv. Chim. Acta*, **45**, 2615 (1962); (b) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Am. Chem. Soc.*, **87**, 275 (1965); (c) A. J. Birch, J. M. Brown, and G. S. R. Subba Rao, *J. Chem. Soc.*, 3309 (1964); (d) S. Rahkit and M. Gut, *J. Am. Chem. Soc.*, **86**, 1432 (1964).

(6) H. E. Simmons and R. D. Smith, *ibid.*, **81**, 4256 (1959).

(7) (a) S. Winstein and J. Sonnenberg, *ibid.*, **83**, 3235 (1961); (b) W. G. Dauben and G. H. Berezin, *ibid.*, **85**, 468 (1963); (c) J. J. Sims, *ibid.*, **87**, 3511 (1965); (d) T. Hanafusa, L. Birladeanu, and S. Winstein, *ibid.*, 3510 (1965).

(8) R. Ginsig and A. D. Cross, *ibid.*, 4629 (1965).