of water via syringe. This slurry was stirred for 5 min. To this reaction mixture was added the aliphatic ester (0.003 mol). The ice bath was removed and the reaction mixture was stirred at room temperature for 3 h. The reaction was quenched by adding ice water until two clear layers formed. The aqueous layer was separated and stirred over acid-washed ion exchange resin (Amberlite IR-120) until a flame test for potassium ion was negative. The resin was removed by filtration and the filtrate was titrated with a standardized sodium hydroxide solution using phenolphthalein as indicator. The percent hydrolysis as determined by titration of the acid was as follows: acetic acid (97%), pivalic acid (94%). Routine titration of the acetic acid gave 92%. However, standardization of the procedure with sodium acetate showed that 5% of the acetic acid was taken up by the resin. The 97% yield reflects an adjustment for the method of analysis.

Synthesis of $CH_3{}^{18}OH$. Trimethyl phosphate (4.0 g, 0.0285 mol) and labeled water (3.67 g, 0.204 mol) containing 22.7 mol % oxygen-18 were sealed in a thick-walled glass tube.[11] This was heated in an oil bath at 105 °C for 26 h. After cooling to room temperature, the reactants were distilled at reduced pressure to yield 2.64 g of a water and methanol mixture. This mixture was distilled at atmospheric pressure to give 0.63 g of a mixture of methanol and water. The water was used as a chaser solvent in order to obtain the maximum yield of methanol. The distillation was stopped when the temperature of the distillate reached 90 °C.

Synthesis of Oxygen-18 Labeled Methyl Mesitoate. Freshly distilled mesitoyl chloride (9.44 g, 0.051 mol) was added dropwise to 0.63 g of the oxygen-18 labeled water–methanol mixture in 50 ml of dry ether which was cooled to 0 °C. After the addition was completed, the reaction mixture was stirred at room temperature for 24 h. Water was added to hydrolyze the excess acid chloride. The mesitoic acid was extracted from the ether layer with two 25-ml portions of saturated sodium bicarbonate solution and one 25-ml portion of a 10% sodium hydroxide solution. The ether layer was dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated to yield 2.47 g of labeled methyl mesitoate (49% based on trimethyl phosphate): IR (neat) 1730, 1270, 1090 cm^{-1}; mass spectrum *m/e* 180, 178, 148, 147, 146.

Acknowledgment. We are indebted to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for a grant which supported this investigation and to Mr. P. C. Price for the chemical ionization mass spectral measurements.

Registry No.—Benzoic acid, 65-85-0; 4-bromobenzoic acid, 586-76-5; 4-aminobenzoic acid, 150-13-0; *p*-anisic acid, 100-09-4; 4-(aminocarbonyl)benzoic acid, 6051-43-0; 1,4-benzenedicarboxylic acid, 100-21-0; mesoic acid, 480-63-7; benzeneacetic acid, 103-82-2; acetic acid, 64-19-7; pivalic acid, 75-98-9; $CH_3{}^{18}OH$, 5770-05-8; mesitoyl chloride, 938-18-1; ^{18}O labeled methyl mesitoate, 61076-10-6.

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(8) Chemical ionization mass spectrometry was carried out on a Du Pont 21-490 B mass spectrometer modified as described by I. C. Wang, H. S. Swofford, Jr., P. C. Price, D. P. Martinsen, and S. E. Buttrill, Jr., *Anal. Chem.*, **48**, 491 (1976).
(9) A referee has suggested that O^{2-} might be formed and add directly to the ester to form **9**. We think that this is unlikely, although we cannot unequivocally rule out this possibility.
(10) In many respects, our results parallel those of Roberts and Whiting,[7] who explored the use of hydroxide in dimethyl sulfoxide as a solvent. In relation to our earlier work,[2] it is possible that the conditions used by both Roberts and Whiting and us involve the same intermediates.
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Conformational Control. An Important Factor in the Stereoselective Reduction of Ketones by Bulky Hydride Reagents

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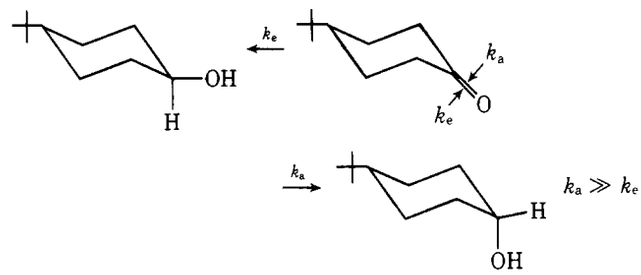
The recent interest accorded the development of highly hindered hydride reagents capable of stereoselective reduction of ketones to afford one diastereomer preferentially[1-5] prompts this discussion of an important factor which is frequently neglected but which subtly affects the product profile of such reductions.[6] This effect involves the conformational equilibria present in mobile ketones which is often at least partly responsible for decreasing the apparent stereoselectivity of hydride attacks.

The conformational effect is adequately illustrated by the reduction results from a series of alkyl substituted cyclohexanones by various di- and trialkyl borohydrides recently introduced[1-4] and recommended for their stereoselectivity of attack. Thus, the reagents approach predominantly from the equatorial side to afford largely the axial alcohol. As a case in point, 4-*tert*-butylcyclohexanone yields almost entirely *cis*-4-*tert*-butylcyclohexanol with various bulky hydrides as shown in Table II and illustrated in Scheme I. From the table,

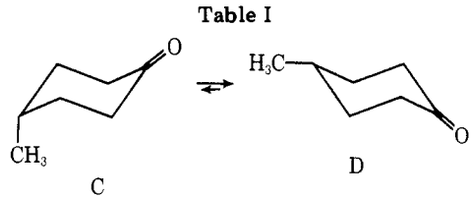
Scheme I



k_a must be substantially greater than k_e. In addition, the selectivity increases as the temperature is lowered as expected since a given difference in E_a between axial and equatorial attack is translated into a greater rate ratio as temperature decreases. The bulky trialkylborohydrides then, especially LTMBH and LTSBH, appear to offer an extremely high degree of discrimination toward equatorial attack which, for the *conformationally homogeneous* 4-*tert*-butylcyclohexanone, produces almost entirely one diastereomer (cis).

The expected situation is different for conformationally heterogeneous cyclohexanones. As presented in Scheme II, irrespective of the relative rate of ring inversion compared to

Table I



C D

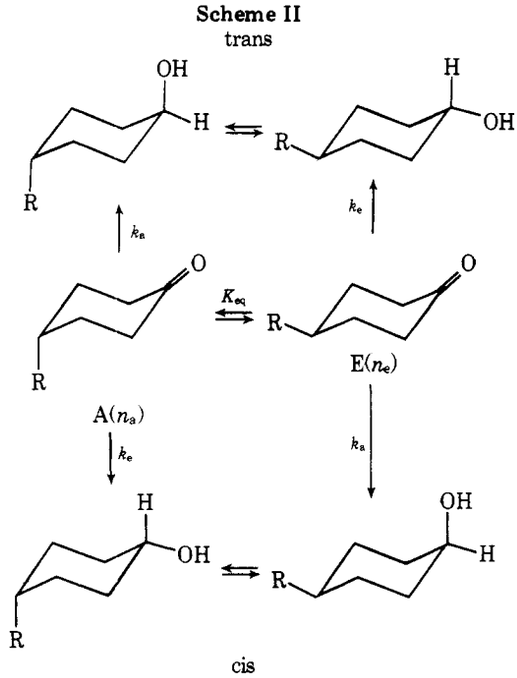
Temp, T°C	$K_{eq}{}^{10}$	% more stable equatorial isomer
100	9.87	90.8
25	17.57	94.7
0	22.86	95.8
−40	39.11	97.5
−78	79.91	98.8

Table II. Reduction of Substituted Cyclohexanones with Hydride Reagents

Cyclohexanone	Registry no.	Temp, °C	% equatorial alkyl computed[a]	% isomer from equatorial attack[b] (% expected axial-OH isomer)[c] Li-*sec*-Bu_3BH[d]	$LDMBH_2$[e]	LTMBH[f]	LTSBH[f]
4-*tert*-Butyl-	98-53-3	0	>99	93	94		
		−78	>99	96.5		99.4	99.4
3-Methyl-	591-24-2	0	95.8	85 (89.4)	99 (90.3)		
		−78	98.8	94.5 (95.5)		99 (98.3)	99.6 (98.3)
4-Methyl-	589-92-4	0	95.8	80.5[g] (89.4)	94 (90.3)		
		−40	97.5		96 (91.8)		
		−78	98.9	90 (95.5)		98 (98.3)	99 (98.3)
		−78	98.9				99 (98.3)
2-Methyl-	583-60-8	0	95.8	99.3 (89.4)	99 (90.3)	>99.5 (98.3)	99.7 (98.3)

[a] The computations were performed assuming $-\Delta G°_{25}$ for methyl is ca. 1.70 kcal/mol; for ethyl, 1.75 kcal/mol (ref 7). [b] In each case the diastereomer produced is the less stable isomer; cis for the 2- and 4-alkylcyclohexanols and *trans*-3-methylcyclohexanol. [c] Computed as % expected axial-OH isomer = % equatorial isomer in ketone × fraction of equatorial attack + % axial isomer in ketone × % axial attack, where the fractions of axial and equatorial attack with a given reagent at a particular temperature are derived from the fractions of axial and equatorial product, respectively, obtained with 4-*tert*-butylcyclohexanone. [d] Reference 1. [e] Reference 3. [f] Reference 4. [g] The potassium derivative afforded 88% cis; ref 2.

Scheme II



reduction rates, these reactions should be less stereoselective than homogeneous cases and dependent upon the relative equilibrium between A and E (Scheme II). Thus, it can be readily demonstrated that if % A and % E are the percentages of axial and equatorial hydroxyl products, respectively, produced by reduction of the conformationally homogeneous 4-*tert*-butyl case (Scheme I, where % A/% E = k_a/k_e) then the % cis product in the conformationally heterogeneous case (Scheme II) is n_A % E + n_E % A and % trans = n_E % E + n_A % A.[7] It should be noted that this latter percentage must be larger than for 4-*tert*-butylcyclohexanone since n_A, the mole fraction of conformer A, is nonnegligible and % E (which relates the amount of axial attack) is small.

However, as indicated in Table II, in certain instances the stereoselectivities for a number of conformationally heterogeneous cyclohexanones are nearly as great as for 4-*tert*-butylcyclohexanone! This result is surprising in view of the above discussion and, in fact, has been attributed to some special, unknown effect.[4] What may not be appreciated at first glance is that the observed stereoselectivity is attributable to the temperature dependence of the conformational equilibria present in these systems. As a case in point, 4-methylcyclohexanone exists as a temperature dependent equilibrium mixture of the axial and equatorial methyl forms C and D, respectively (Table I). Assuming a conformational energy (ΔG value) of about 1.70 kcal/mol for a methyl group,[9] this translates to equilibrium mixtures composed of ca. 91% of the equatorial conformer at 100 °C to ca. 99% equatorial at −78 °C. In other words, *a methyl group is almost as good a conformation biasing group at −78 °C as is a tert-butyl substituent!* Thus, the increases in the axial-hydroxyl isomers with decreasing temperatures is anticipated; in particular, the extraordinary percentages of axial alcohols obtained with LTMBH and LTSBH at −78 °C are no longer unexpected and are irrespective of any temperature dependence of the reagent selectivity.[11]

The 2-alkyl case is an exception since k_a and k_e are not likely to be the same as for the 4-*tert*-butyl analogue. In this situation, the proximity of the adjacent 2-alkyl group does influence the approach of bulky reagents and directs attack so as to afford almost entirely one diastereomer (cis) at all temperatures.[12]

Two points are noteworthy. The stereoselectivities displayed by the new, sterically congested alkylborohydride reagents reside in the high preference shown for equatorial approach and not to any directive action of remote 3- and 4-positioned alkyl groups. In addition, a subtle and newly appreciated principle arises from the discussion in that while the intrinsic stereoselectivity of a particular reaction in a cyclohexane system may be impaired by the conformational heterogeneity of the substrate, such impairment may be alleviated by conducting the reaction at low temperatures in order to minimize the heterogeneity and subsequently obtain the greatest amount of the product resulting from attack on the most favored conformation. In fact, this principle applies to all conformationally heterogeneous systems in which one conformation predominates for enthalpic reasons (as is usually the case); such predominance will always be enhanced at low temperatures. The converse of the above is also true; the amount of a product resulting from attack of a less favored conformation will be maximized by conducting the reaction at the highest convenient temperature since the conformational heterogeneity will increase with increasing temperature.

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Registry No.—*cis*-4-*tert*-Butylcyclohexanol, 937-05-3; *trans*-3-methylcyclohexanol, 7443-55-2; *cis*-4-methylcyclohexanol, 7731-28-4; *cis*-2-methylcyclohexanol, 7443-70-1; Li-*sec*-Bu_3BH, 38721-52-7; $LDMBH_2$, 51899-21-9; LTMBH, 60284-40-4; LTSBH, 61075-97-6.

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$$\frac{d\,\%_{cis}/dt}{d\,\%_{trans}/dt} = \frac{k_a[E] + k_e[A]}{k_a[A] + k_e[E]} = \frac{k_aK + k_e}{k_a + k_eK}$$

$$= \frac{k_a(n_E/n_A) + k_e}{k_a + k_e(n_E/n_A)} = \frac{n_Ek_a + n_Ak_e}{n_Ak_a + n_Ek_e} = \frac{n_E(k_a/k_e) + n_A}{n_E + n_A(k_a/k_e)}$$

$$= \frac{n_E(\%\ A/\%\ E) + n_A}{n_E + n_A(\%\ A/\%\ E)} = \frac{n_E\ \%\ A + n_A\ \%\ E}{n_E\ \%\ E + n_A\ \%\ A}$$

Integration over the entire course of reaction gives fraction (or %) cis product/fraction (or %) trans product = $(n_E\%\ A + n_A\%\ E)/(n_E\%\ E + n_A\%\ A)$ as indicated in the discussion. If the Curtin–Hammett principle does not apply (i.e., fast reactions, slow conformer interconversion) each conformer is converted independently to the two products as in Scheme I. Since the initial mole fractions of A and E are n_A and n_E, the result in the above discussion follows directly.
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(9) J. A. Hirsch, *Top. Stereochem.*, **1**, 199 (1967).
(10) Calculated from $-\Delta G = RT \ln K_{eq}$.
(11) Along these lines, the data in Table II further suggest that Hoozs' reagent, $LDMBH_2$[3], should also show superior selectivity at low (i.e., −78 °C) temperatures.
(12) The situation is complicated for the 3-alkylcyclohexanones at temperatures high enough so that the axial conformer makes a significant contribution. In this situation, the axial alkyl group may interfere with axial approach of the bulky reagents. In addition, equatorial attack may be slowed by the developing syn-axial OX/alkyl interaction. These possible complications disappear at low temperatures where only the equatorial alkyl conformer is significantly populated.

Communications

A Synthesis of the Ophiobolin Nucleus[1]

Summary: A ring contraction–ring expansion–annelation reaction sequence was followed for the synthesis of functionalized carbon skeleton of the ophiobolins.

Sir: The ophiobolins are the most abundant members of the relatively new class of C-25 terpenoids known as sesterterpenes.[2] Representatives of this class of natural products are ophiobolin A (**1**),[3] a metabolite of the plant pathogenic fungus *Cochliobolus miyabeanus,* and ceroplastol II (**2**),[4] a component of the desiccant wax produced by females of insect family *Ceroplastes albolineatus.*[5] The ring system of the ophiobolins is also found in a large family of diterpene aglycones known as fusicoccins.[6] The novel structure and biological activity[7] of the ophiobolins make them attractive targets for total synthesis. We would like to report the preparation of tetraester **3**, the first synthesis of the tricyclo[9.3.0.$0^{3,7}$]tetradecane ring system characteristic of the ophiobolins.[8] The synthesis described herein produces the trans BC ring juncture present in all ophiobolins. The location of substituents on the tricyclic nucleus makes **3** a potential intermediate in projected syntheses of several ophiobolins.

The known octahydronaphthalene **4**[9] was reduced with lithium in ammonia and the resulting enolate was trapped according to established procedures[10] to afford a high yield of enol ether **5**. The crude ether **5** was allowed to react with 1 equiv of *p*-bromobenzenesulfonyl azide in acetonitrile at 50 °C, followed by the addition of a small amount of water to effect hydrolysis of the intermediate imino ether.[11] The re-