$NaBH_4$ itself (the acyloxy intermediate). Then a secondary modifier that has two capabilities should be used. It must be able to covalently attach itself to the boron and also must be a polydentate ligand able to coordinate the sodium cation. Cation complexing is presumed to "lock" the chiral ensemble, and the resulting rigidity enhances the discrimination in the hydride-transfer process between the enantiotopic faces of the ketone.[8,9]

Experimental Section

General Procedure for Small-Scale Reductions (Runs 1–5 and 7–9 in Table I). To a stirred, nitrogen-blanketed suspension of $NaBH_4$ (0.38 g, 10 mmol) in THF (5 mL) was added a solution of the carboxylic acid (10 mmol) in THF (15 mL, followed by another 5-mL rinse). Almost at once 1 equiv of dihydrogen was evolved. Then a solution of DCHGF (usually 20 mmol in 15 mL of THF followed by a 10-mL rinse) was added all at once. There was another, but slower, evolution of dihydrogen: after 2–3 h, 1 equiv; after 5–8 h, 2 equiv. The ketone (10 mmol in 10 mL of THF) was added at various times relative to the DCHGF addition (see Table II), but for quantitative reduction in 48 h with 1 equiv of reagent it is best to add it after about 2–3 h. Waiting drastically lowers the yield but does not significantly affect the percent enantiomeric excess. The workup procedure is detailed in the following description of a larger scale propiophenone reduction.

Preparative-Scale Reduction of Propiophenone. To a 1-L oven-dried, three-necked flask equipped with a magnetic stirrer and a 250-mL addition funnel were added, under nitrogen, oven-dried $NaBH_4$ (3.78 g, 100 mmol) and THF (50 mL). To the resulting suspension was added racemic 2-phenylbutanoic acid (16.42 g, 100 mmol) in 150 mL of THF (plus a 50-mL THF rinse). A rapid gas evolution ensued. After the mixture was stirred for 15 min, a solution of DCHGF (68.08 g, 200 mmol) in 150 mL of THF (plus a 100-mL THF rinse) was added. The reaction mixture was then stirred for 2 h under nitrogen (gas evolution). Propiophenone (13.42 g, 100 mmol) was then added in 50 mL of THF (followed by a 50-mL THF rinse), and the reaction was stirred for 48 h. After about 20 h a white precipitate began to appear and then slowly thickened to a white gelatinous mass.

The reaction mixture was hydrolyzed with 250 mL of 1 M hydrochloric acid (considerable gas evolution). Two clear layers formed. The aqueous layer was extracted with ether (3 × 250 mL), and the combined organic layers were divided into two equal portions. Each was extracted with 5% NaOH solution (2 × 250 mL) and washed with water (2 × 250 mL). Then they were recombined, dried over Na_2SO_4 (48 h), filtered, and concentrated to give a white solid residue (86 g). The residue was triturated with cold pentane. Vacuum evaporation of the pentane gave a pale yellow oil (13.74 g). Vacuum distillation [61–62 °C (0.3 mm)] gave 9.20 g (68%) of ethylphenylcarbinol (no propiophenone detectable by GC): $[\alpha]_D$ +21.5° (c 9.375, ether); 39% ee (based on lit.[5] max $[\alpha]_D$ 55.54°); neat rotation $[\alpha]_D$ +11.5°; 39% ee (based on lit.[10,11] max $[\alpha]_D$ 29.16°).

DCHGF (59 g, 87%) was recovered from the pentane trituration residue.

Reduction of Propiophenone with an Excess of 3 (Run 6, Table I). A solution of (±)-2-phenylbutanoic acid (8.2 g, 50 mmol) in THF (75 mL plus a 25-mL wash) was added all at once to a stirred suspension of $NaBH_4$ (1.9 g, 50 mmol) in THF (25 mL). About 3 min later a solution of DCHGF (33.9 g, 100 mmol) in THF (75 mL plus a 50-mL wash) was added all at once. The resulting mixture was stirred for 2 h at room temperature (during which time it became a slightly cloudy solution). A solution of propiophenone (1.34 g, 10 mmol) in THF (25 mL plus a 25-mL wash) was added, and the reaction was stirred at room temperature for 48 h.

(8) Cation coordination may also promote the reaction of the hydroxyl group with the (acyloxy)borohydride intermediate, that is, assist in the process by binding the sugar derivative in a borohydride complex prior to reaction.

(9) We cannot exclude the possibility that there is some degree of asymmetric induction due to nonspecific, "noncovalent" interactions of the chiral sugar modifier and the reducing species present, for example, chiral media phenomena or cation coordination effects alone.[3]

The reaction was stirred for 10 min with 250 mL of 1 M HCl solution (gas evolution) and worked up as described above (preparative-scale reduction): crude yield 4.3 g; distilled yield 0.67 g [63–73 °C (0.25–0.30 mm)]; GC showed 100% carbinol, $[\alpha]^{23}_D$ +14.9°; 51% ee [based on $[\alpha]^{23}_D$ max 29.16° (l = 1, neat)].[10,11]

Acknowledgment. This research was supported by the Ventron Division of Thiokol. We thank Mr. Robert C. Wade for his encouragement and for enlightening discussions.

Registry No. 1,2:5,6-Di-*O*-isopropylidene-D-glucofuranose, 582-52-5; sodium borohydride, 16940-66-2; 1,2:5,6-di-*O*-cyclohexylidene-D-glucofuranose, 23397-76-4; isovaleric acid, 503-74-2; (±)-2-phenylbutanoic acid, 7782-29-8; (+)-pinanecarboxylic acid, 58096-27-8; (−)-pinanecarboxylic acid, 58096-29-0; 4-*tert*-butylcyclohexanone, 98-53-3; *cis*-4-*tert*-butylcyclohexanol, 937-05-3; *trans*-4-*tert*-butylcyclohexanol, 21862-63-5; 2-methylcyclohexanone, 583-60-8; *cis*-2-methylcyclohexanol, 7443-70-1; *trans*-2-methylcyclohexanol, 7443-52-9; acetophenone, 98-86-2; propiophenone, 93-55-0; (*R*)-(+)-ethylphenylcarbinol, 1565-74-8; chloroacetophenone, 532-27-4; 2-methyl-1-phenylpropan-1-one, 611-70-1; trifluoroacetophenone, 434-45-7; (*R*)-α-methylbenzenemethanol, 1517-69-7; (*R*)-α-(chloromethyl)benzenemethanol, 56751-12-3; (*R*)-2-methyl-1-phenylpropan-1-ol, 14898-86-3; (*R*)-α-(trifluoromethyl)benzenemethanol, 10531-50-7.

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(11) Even a small amount of propiophenone enhances the neat rotation of phenylethylcarbinol significantly. Therefore, if there is incomplete reduction the propiophenone cannot be considered an innocuous achiral diluent; it must either be removed before rotations are measured or its effect must be determined via a calibration curve.

Asymmetric Reduction of Prochiral Aromatic Ketones with Modified Reagents Prepared from Sodium Borohydride and Carboxylic Acids in the Presence of 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose

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Received August 13, 1979

Asymmetric reductions of prochiral ketones with the use of chirally modified metal hydrides continue to be studied actively.[1] By use of chiral hydride reagents prepared from lithium aluminium hydride (LAH), (*S*)-(−)-2,2'-dihydroxy-1,1'-binapthyl, and ethanol, enantiomeric excesses as high as 100% have been observed for the reduction of acetophenone.[2] Many studies, mostly based on the use of LAH derivatives modified by chiral alcohols,[3] amino alcohols,[4] and amines,[5] have been conducted, altering both

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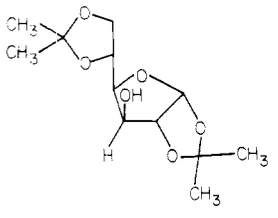
0022-3263/80/1945-4231$01.00/0

the reagents and the experimental conditions to obtain an optimum fit and to gain an insight into the mechanism of reduction.

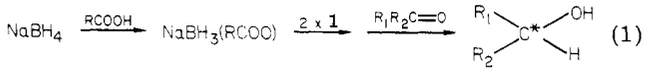
On the other hand, few studies on the use of sodium borohydride in the same type of asymmetric reduction have been reported. In the last few years, growing attention has been devoted to asymmetric synthesis under phase-transfer conditions.[6] In the presence of various optically active "onium" salts as phase-transfer catalysts, prochiral ketones indeed underwent asymmetric borohydride reduction to afford optically active carbinols. The highest optical yield (32%) found was obtained for phenyl *tert*-butyl ketone.[7] Very recently, in another study, interesting results have been obtained by Sugimoto et al. in the asymmetric reduction of aromatic ketones with sodium borohydride in the presence of bovine serum albumin in an alkaline solution, and substantial (20–78%) enantiomeric execesses have been obtained in the product alcohols.[8]

In contrast to these systems under aqueous conditions, we previously reported that ketones were asymmetrically reduced with sodium borohydride in the presence of hydroxymonosaccharide derivatives in nonaqueous solutions such as benzene and tetrahydrofuran.[9] The optical yields so obtained ranged from 2 to 28%, depending on the starting ketone, on the solvent, and particularly on the hydroxymonosaccharide derivative.

In the present paper, we report an asymmetric reduction of prochiral aromatic ketones with modified reagents prepared from sodium borohydride and carboxylic acids in the presence of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**)[10] in tetrahydrofuran solution.



The asymmetric reduction was studied by using the modified reagents, formed by initially treating sodium borohydride with 1 equiv of carboxylic acids (RCOOH) and in the presence of 2 mol of 1/mol of the reagents, unless otherwise stated (eq 1).



(1)

The action of a carboxylic acid on sodium borohydride may possibly lead to a sodium carboxyborohydride, as reported by Brown and Subba Rao[11] and by Gribble and Ferguson.[12]

Table I. Asymmetric Reduction of Propiophenone with Modified Reagents Prepared from Sodium Borohydride and Carboxylic Acids (RCOOH) in the Presence of 1 in Tetrahydrofuran at 25 °C[a]

run[f]	RCOOH	yield,[b] %	$[\alpha]^{20}_D$	optical yield, %[c]
1	none	100	+8.33	18
2	CH_3COOH	47	+18.4	39
3	CH_3CH_2COOH	82	+22.2	47
4	$CH_3(CH_2)_8COOH$	100	+20.6	44
5	$(CH_3)_2CHCOOH$	74	+25.0	53
6	$(CH_3)_3CCOOH$	100	+18.0	39
7	$(C_6H_5)_2CHCOOH$	100	+19.5	41
8	$C_2H_5CH(C_6H_5)COOH$	94	+25.1	53
9[d]	$(CH_3)_2CHCOOH$	21	+14.1	30
10[e]	$(CH_3)_2CHCOOH$	56	+29.5	63

[a] Conditions: reactions for 72 h; $NaBH_4$, 30 mmol; RCOOH, 30 mmol; **1**, 60 mmol; propiophenone, 30 mmol; total volume of the solvent, 50 mL. [b] Determined on the basis of relative peak areas of carbinol and unreacted propiophenone by GC. [c] Optical yield was calculated by optical rotation. A maximum value for 3-phenylpropanol of $[\alpha]^{21}_D$ −47.03° (acetone)[14] was obtained. [d] $NaBH_4$, 30 mmol; $(CH_3)_2CHCOOH$, 60 mmol; **1**, 60 mmol; propiophenone, 30 mmol; total volume of the solvent, 50 mL. [e] $NaBH_4$, 30 mmol; $(CH_3)_2CHCOOH$, 30 mmol; **1**, 120 mmol; propiophenone, 30 mmol; total volume of the solvent, 50 mL. [f] The absolute configuration was *R* in every case.

Propiophenone could be reduced by the modified reagent thus formed in the presence of 1 in a molar ratio of 1:1:2. The results with various reagents specified as carboxylic acids are given in Table I. As can be seen, all the modified reagents produce significant improvements in the asymmetric reduction. Thus, the reductions of propiophenone with the modified reagents in the presence of 1 result in considerably higher stereoselectivities (39–53%) than those obtained in the reduction with sodium borohydride (run 1). These high stereoselectivities indicate that the steric bulkiness and electronic nature of the modified reagent exert a marked effect on the course of the hydride-transfer step in the transition state. Of modified reagents used in this study, the ones specified as $(CH_3)_2CHCOOH$ or $C_2H_5CH(C_6H_5)COOH$ led to the highest stereoselectivities observed. In these ways up to 53% optical yields were obtained from the reduction of propiophenone to (*R*)-(+)-1-phenylpropanol (runs 5 and 8).

By changing the molar ratio of sodium borohydride/$(CH_3)_2CHCOOH$ from 1:1 to 1:2, the dihydride compound, represented by $NaBH_2[(CH_3)_2CHCOO]$, could become the dominant species, which would be less conducive to asymmetric induction than would be the corresponding trihydride[13] (runs 5 and 9). A decrease in the reduction yield was also realized.

The addition of four equimolar amounts of 1 to the reagent specified as $(CH_3)_2CHCOOH$ proves to be highly effective, giving 63% of an optical yield in the product carbinol (run 10). Furthermore, it should be emphasized that the present asymmetric reduction was carried out at 25 °C, not at temperatures as low as 0 to −120 °C.[2,4,5] Unfortunately, further investigation concerning the dependency of the amount of 1 on selectivity was hindered

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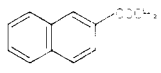
Table II. Asymmetric Reduction of Various Aromatic Ketones with Modified Reagent Prepared from Sodium Borohydride and $(CH_3)_2CHCOOH$ in the Presence of 1 in Tetrahydrofuran at 25 °C[a]

run[i]	ketones	yield,[b] %	$[\alpha]^{20}_D$	optical yield, %[c]
11	$C_6H_5COCH_3$	77	+33.6[d]	64
12	$C_6H_5COC_2H_5$	56	+29.5	63
13	$C_6H_5COC_3H_7$-*n*	66	+23.9[e]	55
14	$C_6H_5COC_3H_7$-*i*	80	+8.44[f]	18
15		100	+22.3[g]	53
16	*i*-$C_4H_9COCH_3$	70	−2.53[h]	12

[a] Conditions: reactions for 72 h; $NaBH_4$, 30 mmol; $(CH_3)_2CHCOOH$, 30 mmol; 1, 120 mmol; ketone, 30 mmol; total volume of the solvent, 50 mL. [b] Determined on the basis of relative peak areas of carbinol and unreacted ketone by GLC. [c] Optical yield was calculated by optical rotation. [d] Maximum value for $[\alpha]^{23}_D$ −52.5° (*c* 2.27, CH_2Cl_2).[15] [e] Maximum value for $[\alpha]^{20}_D$ − 43.6° (*c* 4.18, C_6H_6).[16] [f] Maximum value for $[\alpha]^{20}_D$ +47.7° (*c* 6.8, diethyl ether).[17] [g] Maximum value for $[\alpha]^{20}_D$ −41.9° (*c* 5.0, C_2H_5OH).[18] [h] Maximum value for $[\alpha]^{23-25}_D$ +21.1 (neat).[19] The optical rotations of carbinols were measured in the same solvents reported above. [i] The absolute configuration was *R* in all cases.

in tetrahydrofuran by the solubility limitation of 1 under the same conditions.

By use of the most effective reagent prepared from sodium borohydride and $(CH_3)_2CHCOOH$, a series of ketones were examined in the presence of 1 when the molar ratio of sodium borohydride/$(CH_3)_2CHCOOH$/1 was 1:1:4, and the reactions were found to proceed with varing degrees of success (Table II). Acetophenone, propiophenone, phenyl *n*-propyl ketone, and β-naphthyl methyl ketone appear to lead to the corresponding phenylcarbinols and a naphthylcarbinol in reasonably high optical yield (≥50%), whereas phenyl isopropyl ketone and isobutyl methyl ketone gave rather low percentages of asymmetric induction. For reasons still not understood at present, under all conditions used this system gave chiral phenylcarbinols possessing the *R* configuration.

The convenience of the experimental procedure and the ready availability of 1 by one-step condensation from D-glucose and acetone as well as great potential for more pronounced stereoselectivity for examining the modification of reagents (the combination of sodium borohydride/carboxylic acid/hydroxymonosaccharide derivative) make the present method attractive, despite the lack of consistently good asymmetric reduction on various ketones.

Experimental Section

Reagents. The ketones used were purified by being dried over CaH_2 and subsequently distilled under an atmosphere of nitrogen. Tetrahydrofuran was heated under reflux over sodium wire and distilled over $LiAlH_4$ under a nitrogen atmosphere. Carboxylic acids were distilled twice in a nitrogen atmosphere. Sodium borohydride was purified twice by recrystallization from 2,5,8-trioxanonane (diglyme). 1,2:5,6-Di-*O*-isopropylidene-α-glucofuranose was prepared according to a previous method.[10]

All the materials described were stored under a nitrogen atmosphere prior to use.

Instruments. Rotations were taken on a Zeiss Visual polarimeter with readings to ±0.02°. Gas chromatographic determinations were made on a Simazu GC-6A using a silicon SE-30 prepared column.

Procedures. All the experiments were carried out under a nitrogen atmosphere. The following is a detailed description of a typical experiment. A solution containing 2.64 g (30 mmol) of $(CH_3)_2CHCOOH$ in 10 mL of THF at 0 °C was added to 20 mL of a THF suspension containing sodium borohydride (30 mmol). A thick white precipitate appeared along with evolution of about 30 mmol of hydrogen. Three hours after the initial mixing, 31.2 g (120 mmol) of 1 in 20 mL of THF was added to the reagent formed. After the mixture was stirred for 1 h at 30 °C, to the resulting reagent was added propiophenone (4.02 g, 30 mmol) at 25 °C within 5 min of mixing, and the reduction mixture was stirred at 25 °C for 72 h. The reaction mixture was then hydrolyzed with excess 1 N HCl solution. The mixture was stirred an additional 1 h to hydrolyze compound 1 completely. Sodium hydroxide solution (50%) was added and the pH adjusted to 11. The ether extracts were washed with H_2O (three times), dried ($MgSO_4$), and concentrated to give a colorless oil. The crude product was purified by fractional distillation under reduced pressure. The purity was determined by GLC. Neither 1 nor any other compounds except unreacted ketone was detected by TLC, GLC, and GPC. Pure carbinol was isolated by preparative TLC. The optical yield was obtained from the known maximum rotation of the carbinol and the optical rotation of the sample isolated in the same solvent.

Registry No. 1, 28528-94-1; propiophenone, 93-55-0; sodium borohydride, 16940-66-2; acetic acid, 64-19-7; propanoic acid, 79-09-4; decanoic acid, 334-48-5; 2-methylpropanoic acid, 79-31-2; 2,2-dimethylpropanoic acid, 75-98-9; diphenylacetic acid, 117-34-0; α-ethylbenzeneacetic acid, 90-27-7; (*R*)-α-ethylbenzenemethanol, 1565-74-8; acetophenone, 98-86-2; butyrophenone, 495-40-9; isobutyrophenone, 611-70-1; 2-acetylnaphthalene, 93-08-3; 4-methyl-2-pentanone, 108-10-1; (*R*)-α-methylbenzenemethanol, 1517-69-7; (*R*)-α-propylbenzenemethanol, 22144-60-1; (*R*)-α-(1-methylethyl)-benzenemethanol, 14898-86-3; (*R*)-α-methyl-2-naphthalenemethanol, 52193-85-8; (*R*)-4-methyl-2-pentanol, 16404-54-9.

Stereoselective Synthesis of (±)-1-*O*-Methylloganin, 10-Hydroxyloganin, Secologanin, and Sweroside Aglucons from a Common 1-Hydroxy-4a,5,8,8a-tetrahydroisochromene Synthon[1]

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Received January 8, 1980

We have been investigating routes for the total synthesis of cyclopentanoid monterpenes ("iridoids"[3]) in which we are currently interested from a biogenetic and pharmacological viewpoint. One synthetic strategy has led, through a fruitful collaboration with researchers at Hoffmann-La Roche, to an efficient synthesis of (±)-1-*O*-methylsweroside (**2**) and (±)-1-*O*-methylsecologanin (**3**) aglucons from the (±)-1-hydroxy-4a,5,8,8a-tetrahydroisochromene synthon (**1**).[4] We now describe a modification of our original chemistry for the synthetic utilization of **1**,[4] which enables the synthesis of the following four racemic aglucon *O*-methyl ethers from **1**: 10-hydroxyloganin (**4**) and loganin (**5**), as well as **2** and **3**, formally. These new results nicely complement the synthesis of **2**–**5** carried out

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