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

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Asymmetric reduction of aromatic ketones with the reagents prepared from sodium borohydride and carboxylic acids in the presence of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose at 0 °C gives (*R*)-alcohols with enantiomeric excesses as high as 83%. The optimum conditions for producing maximum selectivity and maximum yield of reaction products from sodium borohydride and isobutyric acid have been examined.

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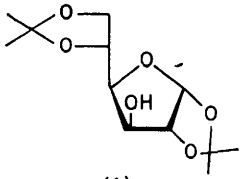
One of the most recently developed asymmetric syntheses is the enantioselective reduction of carbonyl compounds by chiral metal hydride complexes.[2] The most widely studied examples are those using lithium aluminium hydride chirally modified by optically active diols or amines, some of which give substantial stereoselectivities.[3a-g]

In contrast, little attention has been devoted to the use of sodium borohydride ($NaBH_4$) in this type of asymmetric reduction, although $NaBH_4$ is well known to be a mild and highly selective reducing agent.† We have previously found that prochiral ketones are asymmetrically reduced by $NaBH_4$ in the presence of hydroxymonosaccharide derivatives, although attempts at selectivity met with limited success.[5] It has recently been realized independently by both ourselves [1] and by Morrison *et al.*[6] that the stereoselectivities are greatly enhanced by addition of carboxylic acids to the above system so as to modify the $NaBH_4$.

In our preliminary communication [1] we described the testing of the modified reagents in the presence of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (1) for the



(1)

asymmetric reduction of ketones. The results show that reaction with an equimolar quantity of a carboxylic acid gives a reagent, presumably an acyloxyborohydride, which results in higher stereoselectivities than those achieved with $NaBH_4$ alone. The most effective systems were reagents prepared from $NaBH_4$ and isobutyric acid or 2-phenylbutyric acid in the presence of compound (1). These gave 1-phenylpropanols of the *R* configuration with up to 53% stereoselectivities in the reduction of propiophenone, while the extent of asymmetric reduction was only 18% with $NaBH_4$ in the presence of (1). We report here a detailed study of the reduction of aromatic ketones with these modified reagents in order to establish the optimum conditions for maximum stereoselectivity.

† Several studies have recently been reported on asymmetric reduction using $NaBH_4$ in aqueous solution in the presence of chiral phase-transfer catalysts (ref. 4*a*) or bovine serum albumin (ref. 4*b*).

Results and Discussion

Upon addition of 1 molar equivalent of isobutyric acid to the suspended $NaBH_4$ in tetrahydrofuran (THF), the theoretical amount of 1 mol of hydrogen was liberated within 1 h. Further addition of 2 mol of the monohydroxymonosaccharide (1) (R*OH) evolved 2.0 mol of hydrogen over 2 h, 1.0 equivalent of hydride remaining in the resulting reducing agent. No further uptake of hydrogen was observed even after 24 h; this was ascertained by analysis for residual hydrides in the reaction mixture. Consequently, the reaction of $NaBH_4$ with isobutyric acid (RCO_2H) and subsequent addition of (1) (R*OH) would be expected to proceed to an acyloxydialkoxyborohydride stage, according to equations (1) and (2). Unfortunately, the species present in this

$$NaBH_4 + RCO_2H \longrightarrow NaBH_3(OCOR) + H_2 \quad (1)$$

$$NaBH_3(OCOR) + 2\ R^*OH \longrightarrow NaBH(OCOR)(OR^*)_2 + 2H_2 \quad (2)$$

reaction mixture is not quite as simple as might appear from the equations, although the species in the equations might well be involved. A detailed study will be reported later.

Asymmetric reductions of propiophenone at 0 and 30 °C were carried out with suspensions of $NaBH_4$ in THF to which varying quantities of isobutyric acid and a fixed quantity (2 equiv.) of compound (1) were added. The results, summarized in Table 1, clearly show that the effect on stereoselectivity is greatly enhanced by adding isobutyric acid to the system and that the selectivity increases as the ratio of $NaBH_4$ to isobutyric acid in the reducing agent is increased both at 0 and at 30 °C. A decrease in the synthetic yield was observed, however, and further examination of the selectivity effect was prevented by incomplete reduction at ratios greater than 1.5.

It was evident that the optical yield appears, as usual, to increase by lowering the reaction temperature from

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TABLE 1

Effect of the ratio [Me_2CHCO_2H] : [$NaBH_4$] on the optical yield for the reduction of propiophenone in the presence of compound (1)

		1-Phenylpropan-1-ol	
T/°C	[Me_2CHCO_2H] / [$NaBH_4$]	Yield (%)	Optical yield [a]
30	0	40	18 (*R*)
	0.2	100	30 (*R*)
	0.4	100	31 (*R*)
	0.6	100	48 (*R*)
	0.8	100	47 (*R*)
	1.0	100	50 (*R*)
	1.2	100	60 (*R*)
	1.4	86	65 (*R*)
	1.5	57	67 (*R*)
0	1.0	84	75 (*R*)
	1.2	55	83 (*R*)
	1.4	36	85 (*R*)
−15	1.2	66	75 (*R*)

[a] Values for maximum rotation and configuration taken from ref. 14.

30 to 0 °C. However, further lowering of the temperature from 0 to −20 °C had little effect.

The effect of altering the amount of (1) relative to that of the reagent formed from $NaBH_4$ and isobutyric acid was examined. The use of 2 equivalents of (1) for the reagent formed from $NaBH_4$ (1 equiv.) and isobutyric acid (1.2 equiv.) in reduction at 0 °C provided a more satisfactory result than that obtained using 1 equivalent of (1). Sluggish reductions were found in cases where 3 and 4 equivalents of (1) were employed under otherwise similar conditions. Thus, the stoicheiometric quantities of $NaBH_4$, isobutyric acid, and (1) were found to be optimal at 1 : 1.2 : 2.0, respectively.

The reagent formed with (1) reduces propiophenone rapidly in quantitative yield at 30 °C over 2 h, while the reduction with $NaBH_4$ plus (1) is relatively slow and gives a yield of 40%. It should be pointed out, however, that the reaction with the reagent formed from $NaBH_4$ and isobutyric acid at a molar ratio of 1 : 1.2 did not proceed as expected. Reduction proceeded rapidly up to 50% conversion, with further reduction being very sluggish; 52% of the propiophenone had been reduced after 1 h and after 24 h the reduction had proceeded to only 83%. Furthermore, as shown in Table 2, a dependency of the chemical yield on the optical yield was observed with the reagent at the ratio 1 : 1.2, whereas selectivity was almost constant over a wide range of chemical yield with the reagent at the ratio 1 : 1.0 and with $NaBH_4$ alone. Accordingly, comparisons of optical yield with the reagent formed in a 1 : 1.2 ratio should be done at a constant chemical yield. Similar trends were observed with the reagents derived from other acids.

TABLE 2

Optical and chemical yields for the reduction of propiophenone with the reagent derived from $NaBH_4$ and isobutyric acid at molar ratios of 1 : 1.2 or 1 : 1.0 or with $NaBH_4$ in THF at 0 °C in the presence of compound (1)

	1-Phenylpropan-1-ol		
Reagent	Yield (%) [a]	Optical yield	Absolute configuration
$NaBH_4$ + Me_2CHCO_2H (1 : 1.2)	50	83	*R*
	55	83	*R*
	78	63	*R*
	83	66	*R*
$NaBH_4$ + Me_2CHCO_2H (1 : 1.0)	40	75	*R*
	84	72	*R*
$NaBH_4$	40	18	*R*
	100	18	*R*
	140	20	*R*
	200	18	*R*

[a] Ketone : reducing complex based on $NaBH_4$, 0.5 : 1.

The duration of the reaction of the reagent with (1) also noticeably affects both the chemical and the optical yields of the alcohols produced. After addition of (1) to suspensions of the reagent that reaction mixture initially turned almost clear and then became more and more turbid and gelatinous as time progressed. After 24 h, it could reduce propiophenone only very slowly and with little chiral efficiency. The reason for this effect is not clear at present since, as mentioned earlier, the reaction appeared to be complete after 2 h when no further uptake of hydrogen was observed, and, indeed, 1 equivalent of hydride still remained in the reducing agent even after 24 h. These results would suggest that the species present initially are somehow different from those present after 24 h; care was therefore needed to obtain reproducible results in the asymmetric reduction when this reagent was used with (1).

The effectiveness of the structure of the reagent on the stereoselectivity of the alcohol produced was also examined. A number of reagents modified by carboxylic acids, having increasing steric requirements, were investigated. The asymmetric reduction of propiophenone was carried out using these reagents which were prepared from $NaBH_4$ and various carboxylic acids at a molar ratio of 1 : 1.2 with subsequent addition of 2 mol of (1) in THF at 0 °C. They were similar to those employed in the studies of the reagent formed from $NaBH_4$ and isobutyric acid. The results are summarized in Table 3, together with details of the amounts of residual hydrides remaining in the resulting reagents after the reactions of $NaBH_4$ and acids at a 1 : 1.0 ratio, but not at the 1 : 1.2 ratio used for the asymmetric reduction.

All the reagents derived from simple monocarboxylic acids emerged as more effective asymmetric reducing agents than $NaBH_4$ alone, capable of reducing propiophenone to the chiral corresponding alcohol in high optical yield (40—83%). None of the acids listed in Table 3 was as effective as isobutyric acid and the influence of the steric bulkiness of the reagent appears to be insignificant during the course of the asymmetric reduction. In each of these cases the reagents with (1) gave the *R* enantiomer in excess regardless of their structures. The structural effect on the optical yield is not, however, rationalized in detail at present, since the precise quantity that gives maximum selectivity has been determined only in the case of isobutyric acid and the optimum quantity may vary for the other acids.

The reagents derived from hydroxycarboxylic acids such as 2-hydroxy-2-phenylacetic acid and (±)-malic acid did not reduce propiophenone in the presence of (1).

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One mol of 2-hydroxy-2-phenyl acetic acid rapidly consumed 2.0 equivalents of hydrides (determined as evolved hydrogen), presumably one by CO_2H and one by OH, and (±)-malic acid consumed 2.5 equivalents of hydrides, with only slow further uptake of hydride occurring. Further addition of 2 mol of (1) removes the residual hydrides on the reagents giving tetrasubstituted complexes which cannot react further.

TABLE 3

Asymmetric reduction of propiophenone with the reagents prepared from $NaBH_4$ and various carboxylic acids, methanol, and phenol in the presence of compound (1) in THF at 0 °C, and residual hydrides remaining in the reagents after preparation [a]

	1-Phenylpropan-1-ol		
Acid	Yield (%)	Optical yield	Residual hydride (equiv.)
None	40	18 (*R*)	4.00
$MeCO_2H$	40	56 (*R*)	3.00
$Me[CH_2]_2CO_2H$	40	55 (*R*)	
$Me[CH_2]_4CO_2H$	44	51 (*R*)	
$Me[CH_2]_8CO_2H$	41	44 (*R*)	
Me_2CHCO_2H	55	83 (*R*)	3.00
Et_2CHCO_2H	54	55 (*R*)	
$Et(Ph)CHCO_2H$	59	65 (*R*)	3.00
Ph_2CHCO_2H	46	66 (*R*)	
Me_3CO_2H	57	51 (*R*)	
CH_2=$CHCO_2H$	43	48 (*R*)	
Cyclo-$C_6H_{11}CO_2H$	58	40 (*R*)	
$PhCO_2H$	59	53 (*R*)	3.00
o-Cl-$C_6H_4CO_2H$	46	68 (*R*)	
$PhCH(OH)CO_2H$	>5		2.00
$HO_2CCH_2CH(OH)CO_2H$	>5		1.50
HO_2CCO_2H	>10		3.50
$HO_2CCH_2CO_2H$	>10		3.84
$HO_2C[CH_2]_4CO_2H$	>10		3.52
$HO_2CC_6H_4CO_2H$	>10		2.84
MeOH	91	5.2 (*R*)	3.00
PhOH	100	7.1 (*R*)	3.96 (3.00) [b]

[a] Ratio $NaBH_4$: RCO_2H : (1) is 1 : 1.2 : 2.0. [b] After 72 h.

That $NaBH_4$ reacts very slowly with some dicarboxylic acids is quite surprising. Thus, 3.50, 3.84, 3.52, and 2.84 equivalents of hydrides remained in the reducing agents derived from oxalic, malonic, adipic, and terephthalic acid, respectively, whereas the monocarboxylic acids reacted rapidly and quantitatively under the same conditions. The reducing abilities of the reagents were somewhat low, propiophenone being reduced in less than 10% conversion in each case.

Methanol reacted readily, evolving 1.0 mol of hydrogen. Unlike that of methanol, the reaction of phenol with $NaBH_4$ was comparatively sluggish, requiring 72 h for 1.0 mol of hydrogen to be evolved. This behaviour is quite surprising since the OH-group of phenol is much more acidic than that of methanol. To date the reason for this phenomenon has not been explained. The reagents from either methanol or phenol, contrary to the results using monocarboxylic acids as modifiers, gave lower degrees of asymmetric reduction than was obtained using $NaBH_4$, although enhanced reactivities on both reagents were observed: 91—100% *vs.* 40% for $NaBH_4$ and 40—60% for the reagents formed by $NaBH_4$ and monocarboxylic acids.

TABLE 4

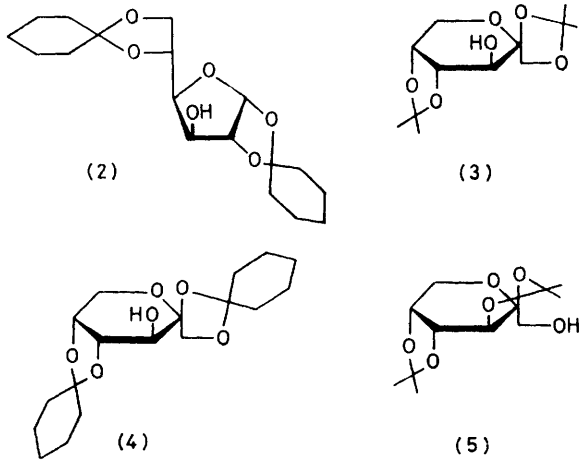
Asymmetric reduction of aromatic ketones with the reagent prepared from $NaBH_4$ and isobutyric acid in a molar ratio of 1 : 1.2 with compound (1) in THF at 0 °C

	Alcohols produced			
Ketone	Yield (%)	$[\alpha]_D^{25}$	Optical yield	Absolute configuration
Methyl phenyl ketone	62	+40.95 [b]	78 (2.7) [a]	*R*
		+35.10 [c]	77	*R*
Ethyl phenyl ketone	55	+39.03 [d]	83 (18)	*R*
		+24.74 [e]	85	*R*
		+44.32 [f]	80	*R*
		+27.66 [g]	85	*R*
Phenyl propyl ketone	53	+33.40 [h]	74 (14)	*R*
Isopropyl phenyl ketone	50	+27.19 [i]	57 (9.3)	*R*

[a] Values in parentheses were obtained by the asymmetric reductions with $NaBH_4$ plus compound (1) in THF. [b] In CH_2Cl_2 (U. Nagai, T. Shishido, R. Chiba, and H. Mitsuhashi, *Tetrahedron*, 1965, **21**, 1701). [c] In methanol (R. Huisgen and C. Ruchardt, *Liebigs Ann. Chem.*, 1956, **601**, 31). [d] In acetone (ref. 14*a*). [e] Neat (ref. 14*b*). [f] In ether (ref. 14*c*). [g] In ethanol (ref. 14*d*). [h] J. Kenyon and S. M. Partridge, *J. Chem. Soc.*, 1936, 128. [i] D. J.Cram and J. E. McCarty, *J. Am. Chem. Soc.*, 1957, **79**, 2866.

Table 4 shows the reduction of three additional phenyl alkyl ketones with the reagent derived from $NaBH_4$ and isobutyric acid in the ratio 1 : 1.2 to result in considerably higher optical yields than were obtained in the reduction using $NaBH_4$ without addition of isobutyric acid in the presence of (1). In each of these cases all the secondary alcohols had the *R* configuration. Increasing the size of the alkyl group from methyl to propyl made no significant difference, but isopropyl phenyl ketone gave a relatively lower optical yield.

To examine the structural effect of the hydroxymonosaccharides, four additional compounds (2)—(5) were



(2) (3) (4) (5)

employed in the asymmetric reduction of propiophenone. Treatment of the reagent formed from $NaBH_4$ and 1.2 equivalents of isobutyric acid with 2 mol of (2), (3), (4), or (5) evolved 2.0 mol of hydrogen. The results of the subsequent asymmetric reductions are

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TABLE 5

Asymmetric reduction of propiophenone with the reagent prepared from $NaBH_4$ and isobutyric acid in a 1 : 1.2 ratio with 2 equiv. of compounds (1), (2), (3), (4), or (5) in THF at 0 °C

	1-Phenylpropan-1-ol		
Hydroxymonosaccharide	Yield (%)	Optical yield	Absolute configuration
(1)	55	83 (18) [a]	*R* (*R*)
(2)	75	32 (21)	*R* (*R*)
(3)	42	11 (11)	*S* (*S*)
(4)	41	25 (5)	*S* (*S*)
(5)	48	8.7 (6)	*S* (*S*)

[a] Values in parentheses were obtained for the asymmetric reduction with $NaBH_4$ plus compounds (1), (2), (3), (4), or (5) in THF at 0 °C.

summarized in Table 5. Reactions of the reducing agents with (2), (3), (4), or (5) generally gave low optical yields. The products from runs using (3), (4), and (5) derived from D-fructose had negative rotation. It is significant to observe that when (2), (3), (4), or (5) are used in the asymmetric reduction, the effect of the acid in the reagent is not as pronounced as it is when the reagent with (1) is used.

Reaction Products from the Reaction of $NaBH_4$ *and Isobutyric Acid in the Presence of Compound* (1).—Rapid and quantitative evolution of hydrogen occurs after the addition of 1 mol of isobutyric acid to the suspension of $NaBH_4$ in THF as mentioned previously. Following addition, the reaction mixture was stirred for 1 h at 30 °C and the white microcrystalline solid was isolated by filtration under nitrogen. Analysis of the product showed a molar ratio of Na : hydride : Me_2CHCO_2H of 1 : 3.63 : 0.37. The yield was 71% based on sodium. Evaporation of the filtrate under vacuum yielded a similar white solid, analysis of which gave a Na : hydride : Me_2CHCO_2H ratio of 1 : 1.63 : 2.37, indicating the presence of acyloxyborohydride species in the solution. The filtrate contained 29% of the initial amount of sodium. Consequently, the reaction of $NaBH_4$ and isobutyric acid in a 1 : 1.0 ratio in THF yields a precipitate of $NaBH_{3.63}(OCOCHMe_2)_{0.37}$ as an empirical formula, leaving $NaBH_{1.63}(OCOCHMe)_{2.37}$ in the solution. The difference in the species present in the precipitate and in the solution is thus noteworthy, the result indicating that the reaction mixture must involve $NaBH_4$, and mono-, di-, and tri-substituted acyloxyborohydrides at the same time.

One can estimate from these analyses that the solid product may be mainly the mixture of 45 mol % of $NaBH_4$ and 26 mol % of $NABH_3(OCOCHMe_2)$, and the species existing in the solution may be a mixture of 18 mol % of $NaBH_2(OCOCHMe_2)_2$ and 11 mol % of $NaBH(OCOCHMe_2)_3$. The tetrasubstituted compound, $NaB(OCOCHMe_2)_4$, is not likely to exist in the reaction mixture since it has been noted [7] that it is formed very slowly even in the neat carboxylic acid. This must mean that the first reactions, $NaBH_4 + Me_2CHCO_2H$, is slow, with subsequent reactions, $NaBH_{4-n}(OCOCHMe_2)_n + Me_2CHCO_2H$, occurring much faster presumably because of the higher solubilities of the acyloxyborohydrides over that of $NaBH_4$ in THF. A result similar to this was obtained from the reaction of $NaBH_4$ and 2-phenylbutyric acid in the ratio 1 : 1.0 in THF. The reaction yielded a precipitate of unchanged $NaBH_4$, leaving $NaBH_3[OCOCH(Ph)Et]$, $NaBH_2[OCOCH(Ph)Et]_2$, and $NaBH[OCOCH(Ph)Et]_3$ in the solution. These results are summarised in Table 6.

Further reaction of the reagents thus formed with 2 mol of (1) (R*OH) evolved a further 2.0 mol of hydrogen, 1.0 equivalent of hydride remaining in the resulting reagents. The evolved hydrogen may arise from the reaction between the acyloxyborohydride species of the reagents and (1) as $NaBH_4$ has been demonstrated to be essentially inert to (1) in a separate experiment [equations (3) and (4)].

$$NaBH_4 + R^*OH \longrightarrow \text{No reaction}$$

$$NaBH_{4-n}(OCOR)_n + 2\ R^*OH \longrightarrow NaBH_{3-n}(OCOR)_n(OR^*) + NaBH_{2-n}(OCOR)_n(OR^*)_2 + 2\ H_2$$

The total number of equivalents of the acyloxyborohydrides produced in the reaction was 1.2 (Table 6) even though 2.0 mol of hydrogen are evolved. It is thus very likely that some disproportionation between $NaBH_4$ and the acyloxyborohydrides is occurring through an equilibrium. Indirect evidence for such an equilibrium is that a very exothermic reaction takes place upon addition of a suspension of $NaBH_4$ (0.7 mol) in THF to a slightly cloudy mixture of $NaBH_4$ (0.3 mol), isobutyric acid (1.0 mol), and (1) (2.0 mol) in THF, the reaction mixture immediately turning gelatinous. Each of these acyloxy-substituted species may then react with (1) evolving hydrogen. The full picture of the

TABLE 6

Reaction products from the reaction of $NaBH_4$ with either Me_2CHCO_2H or $Et(Ph)CHCO_2H$ in THF at 30 °C in THF for 1 h [a]

Reaction	Product	Mol%	Hydrides contained		Remarks
	$NaBH_4$	45	1.80 equiv.		insoluble
$NaBH_4 + Me_2CHCO_2H$	$NaBH_3(O_2CCHMe_2)$	26	0.78		insoluble
	$NaBH_2(O_2CCHMe_2)_2$	18	0.36	1.25	soluble
	$NaBH(O_2CCHMe_2)_3$	11	0.11		soluble
	$NaBH_4$	57	2.28		insoluble
$NaBH_4 + Et(Ph)CHCO_2H$	$NaBH_3[O_2CCH(Ph)Et]$	43	0.72		soluble
	$NaBH_2[O_2CCH(Ph)Et]_2$				soluble
	$NaBH[O_2CCH(Ph)Et]_3$				soluble

[a] Ratio $NaBH_4$: carboxylic acid was 1 : 1.0.

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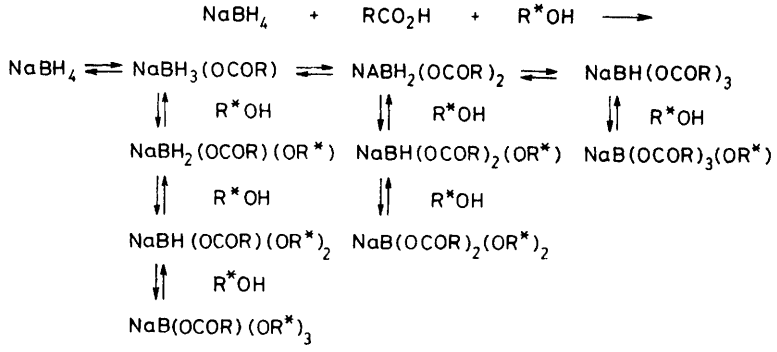
reaction species produced in the reaction of $NaBH_4$ with isobutyric acid (RCO_2H) in the presence of (1) (R*OH) is shown in the Scheme. Of the resulting species, those responsible for the asymmetric induction may be considered to be $NaBH_2(OCOR)(OR^*)$, $NaBH(OCOR)(OR^*)_2$, and $NaBH(OCOR)_2(OR^*)$, all of which are acyloxyalkoxyborohydrides chirally modified by (1). The sugar moieties, in addition to the carboxy-groups, attached covalently to the reducing agents would make a chiral environment with a high degree of very steric bulkiness around the hydrides which would be conducive



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to the asymmetric reduction. Additionally, as proposed for a similar system by Morrison,[6] the ethereal oxygens of the sugar groups might act as a polydentate ligand able to co-ordinate to the sodium cation. The co-ordination may allow a more rigid conformation for the hydride-transfer step thereby increasing the stereoselectivity of the process.

In conclusion, the modification of $NaBH_4$ by carboxylic acids in the presence of (1) provides more efficient chiral reducing agents than $NaBH_4$ alone, resulting in substantial optical yields as high as 83% in the reduction of propiophenone, although this system involves a wide variety of hydride species, only some of which may be effective for the asymmetric reduction.

EXPERIMENTAL

All reactions were carried out under nitrogen. Tetrahydrofuran was dried over sodium wire and distilled over lithium aluminium hydride immediately before use. Acetophenone, propiophenone, n-propyl phenyl ketone, and isopropyl phenyl ketone were dried and distilled over calcium hydride. Carboxylic acids and phenol were purified by distillation or recrystallization. Methanol was dried with magnesium and distilled. Sodium borohydride was purified twice by recrystallization from 2,5,8-trioxanonane. The purities of all reagents were checked by g.l.c. or n.m.r. spectroscopy. All the materials described were stored under nitrogen prior to use.

G.l.c. was performed on a Simazu GC-6A instrument (injection port, TCD detector, and heated collector temperature 250 °C; column temperature 210 °C) using a glass-coated analytical column (1.5 m × 3 mm) packed with PEG 20M on Chromosorb. The ratios of alcohols and unchanged ketones were determined by their peak areas. N.m.r. spectra were run on a Hitachi R-22 90-MHz spectrometer. Optical rotations were taken on a Zeiss visual polarimeter with readings to ±0.02° or on a JASCO DIP-SL automatic electronic polarimeter using a 1 cm thermostatted microcell. I.r. spectra were measured with a JASCO IR-G instrument for Nujol mulls. T.l.c. was run on silica gel 60F-254 pre-coated plates with 9 : 1 (v/v) benzene–ethyl acetate or 1,2-dichloroethane as the mobile phase. Na Analyses by flame photometry were performed on a Hitachi 170–30 instrument. Evolution of hydrogen was measured by Brown's method.[8]

1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose (1).—This compound was prepared as reported [9] and was recrystallized, (35%), m.p. 110—111 °C, $[\alpha]_D^{20}$ −18.5° (*c*, 10 in acetone) {lit.,[13] m.p. 110 °C, $[\alpha]_D^{20}$ −19° (*c*, 5 in acetone)}. 1,2:5,6-Di-*O*-cyclohexylidene-α-D-glucofuranose,[10] 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose,[11] 1,2:4,5-di-*O*-cyclohexylidene-β-D-fructopyranose,[12] and 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose [13] were prepared by reported procedures and were recrystallized.

General Procedure for Aymmetric Reduction of Propiophenone with the Reagent derived from $NaBH_4$ *and Isobutyric Acid in the Presence of Compound* (1) *in THF at* 0 °C.—A solution of isobutyric acid (12 mmol) in THF (5 ml) was added dropwise to a stirred suspension of $NaBH_4$ (10 mmol) in THF (5 ml) at 0 °C, over *ca.* 2 min. The resulting suspension was stirred at 30 °C for 1 h and then a solution of compound (1) (20 mmol) in THF (10 ml) was added. The mixture was stirred at 30 °C for 1 h and then cooled to 0 °C whereupon a solution of propiophenone (5 mmol) in THF (5 ml) was added dropwise over 3 min. The resulting mixture was stirred at 0 °C for 2 h, and then decomposed by the addition of 1M-HCl (10 ml). The hydrolysed mixture was filtered and the organic solvents were removed by evaporation under reduced pressure. The resulting aqueous layer was stirred for 1 h to decompose completely compound (1). The aqueous acid layer was slightly basified by 1M-NaOH at pH 7.5—8 and extracted with ether (3 × 10 ml) and the extract was washed with saturated NaCl solution (2 × 10 ml), dried ($MgSO_4$), and evaporated to give an oil. The ratio of alcohol to unchanged ketone was determined by g.l.c. The crude product was then chromatographed on silica gel. The pure alcohol was eluted with 1,2-dichloroethane and distilled (bulb-to-bulb) to give 1-phenylpropan-1-ol (625 mg, 46% of isolated material) which was characterized by i.r. and n.m.r. spectroscopy and was homogeneous on g.l.c. and t.l.c. The optical rotations of the neat alcohol and for solutions in acetone, ether, and ethanol were measured. The optical yield was calculated

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by the observed optical rotation and the known maximum rotation of 1-phenylpropan-1-ol.[14] The optical rotations and optical yields were $[\alpha]_D^{25}$ (neat) +24.74° (85%) $[\alpha]_D^{25}$ (*c*, 5.48 in ethanol) +27.66 (85%) $[\alpha]_D^{25}$ (*c*, 7.50 in ether) +44.32 (80%) $[\alpha]_D^{25}$ (*c*, 6.50 in acetone) +39.03 (83%). Thus, each of these optical yields calculated are in reasonable agreement with each other. Acetone was used for measurements of optical rotation unless otherwise stated. The optical rotations were found to be independent of the concentration of unchanged ketones present for the solutions in ether, acetone, benzene, methanol, and 1,2-dichloroethane; this is different for the case of 1-phenylethanol in cyclopentane as previously reported.[15]

A number of other asymmetric reductions using different reagents such as ketones, reagents derived from other acids, sugar derivatives, *etc.*, were performed under conditions similar to those described above. The results are summarized in Tables 1—5.

Reaction of $NaBH_4$ *with Isobutyric Acid in THF.*—A solution of isobutyric acid (100 mmol) in THF (100 ml) was added dropwise to a stirred suspension of $NaBH_4$ (100 mmol) in THF (150 ml) at 0 °C over *ca.* 10 min. The resulting slurry was stirred at 30 °C for 1 h. The solid was separated by filtration under nitrogen and dried at room temperature *in vacuo*. Analysis of the solid showed a Na : hydride : Me_2CHCO_2H ratio of 1 : 3.63 : 0.37 (obtained by flame photometry, measurement of hydrogen evolution and g.l.c.). The amount of solid recovered was 71% based on the initial sodium concentration. The filtrate contained 29% based on sodium. The solid, after evaporation of the solvent, had a Na : hydride : Me_2CHCO_2H molar ratio of 1 : 1.63 : 2.37.

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