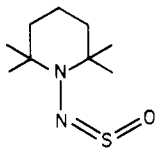
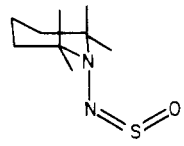


planar



perpendicular

TMP hydrazones and amidines display single NMR signals, even when the rotation is slow on the NMR time scale, because of the change of symmetry. On the other hand, we found that the ring carbons C-2,6 and C-3,5 of the TMP—N=S=O compound **4** become doublets, as in **2** and **3** (Figure 1). This means that the NSO moiety is still coplanar to the dynamic plane of the TMP ring (planar formula above), despite the large steric crowding. The conformational behavior of **4** is thus similar to that of the corresponding triazenes,[10] amides,[15] and *N*-nitroso amines[3,6,11] that remain planar and different from that of the corresponding hydrazones[3,6,11] and amidines[15] that become perpendicular.

It is also noteworthy to observe that the $\Delta G^{\ddagger}$ for NN rotation in **4** is equal to that of **3**, although there are, now, two methyls axial and two equatorial. The molecule, therefore, should experience not only the axial–axial repulsion but also the equatorial–substituent repulsion. To understand why the latter effect does not reduce the $\Delta G^{\ddagger}$ of **4** with respect to **3**, it might be argued that the TMP ring in **4** is a twisted chair, rather than a chair. In this way, in fact, both the axial–axial and equatorial–substituent repulsions can be, in part, relieved. This behavior parallels that observed in two similar situations[3,6,10] (i.e., TMP—N=N—Ph and TMP—N=NO).

In order to check whether this distorted conformation still allows distinction of the pseudoaxial from the pseudoequatorial methyls, we recorded the spectrum of **4** at the lowest attainable temperature. As shown in Figure 1, at −151 °C the four methyls yield four different signals. In fact, each pair of syn and anti methyls is now split further in two, because they are either in a pseudoaxial or in a pseudoequatorial situation.

The $\Delta G^{\ddagger}$ measured for the ring reversal process in **4** is 6.0 ± 0.2 kcal mol^{-1}, a value smaller than that of the unsubstituted 2,2,6,6-tetramethylpiperidine (i.e., 8.0 kcal mol^{-1}).[6] This might depend not only on the sp^2 contribution given to the ring nitrogen by the conjugation with NSO but also on the twisted arrangement that seems to lower further the barrier to ring reversal.

Experimental Section

The synthesis of derivative **2** has been previously reported:[20] the other compounds were obtained with the same method.[13,20] The hydrazines needed for the synthesis were prepared according to the literature.[3,6,11] The new compounds were identified by mass spectroscopy, and the expected molecular weights were obtained: **1**, *m/e* 132 (M$^+$); **3**, *m/e* 174 (M$^+$); **4**, *m/e* 202 (M$^+$).

The IR spectra also showed the typical[13] NSO bands: ν_{as} in the range 1170–1185 cm^{-1} (w) and ν_s in the range 1080–1090 cm^{-1} (vs). The ^{13}C NMR spectra gave the expected number and type of carbons: **1**, 55.0 (C-2,5), 23.3 ppm (C-3,4); **2**, 57.8 ppm (C-2,6); 26.0 (C-3,5), 23.7 ppm (C-4); **3**, 59.9 (C-2,6), 30.0 (C-3,5), 19.3 (Me 2,6), 13.0 ppm (C-4); **4**, 64.0 (C-2,6), 40.6 (C-3,5), 29.1 (Me-2,2,6,6), 16.9 ppm (C-4).

The elemental analysis of the three unknown products gave the following results. Found for **1**: C, 36.2; H, 6.2; N, 21.1 ($C_4H_8N_2SO$ requires: C, 36.3; H, 6.1; N, 21.2). Found for **3**: C, 48.4; H, 8.4; N, 16.0 ($C_7H_{14}N_2SO$ requires: C, 48.2; H, 8.1; N, 16.1). Found for **4**: C, 53.5; H, 9.2; N, 13.7 ($C_9H_{18}N_2SO$ requires: C, 53.4; H, 9.0; N, 13.8).

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The samples for running the low-temperature NMR spectra of compounds **2–4** were prepared by connecting a 10-mm tube, containing the compound, to a vacuum line; the gaseous solvents were then condensed in by means of liquid nitrogen. The tubes were subsequently sealed off and introduced into precooled probe of the spectrometer.

The temperature was monitored by a thermocouple inserted in a dummy tube before or after the spectral acquisition. The $\Delta G^{\ddagger}$ values were obtained for each compound at the various coalescence temperatures (see text) and the values averaged. In the case of **1** where the shift difference between carbons 2 and 5 is almost equal to that between carbons 3 and 4 there is a single coalescence temperature (−28 °C; see Table I). Therefore, to obtain additional data, we carried out a line-shape analysis at three different temperatures, and the averaged values were found to lie, as in the other cases, within ±0.1 kcal mol^{-1}. The spectra were recorded at 25.16 MHz (Varian XL-100) in the FT mode with a ^{19}F external lock.

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Registry No. **1**, 82665-38-1; **2**, 82665-39-2; **3**, 82665-40-5; **4**, 82665-41-6.

Stereochemistry of Reduction of Cyclic and Bicyclic Ketones by Lithium Diisobutyl-*tert*-butylaluminum Hydride

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Although in the past decade considerable efforts have been devoted to the development of the hindered alkali metal trialkylborohydrides which allow stereoselective reduction of cyclic and bicyclic ketones,[1,2] there are relatively few reports in the literature on the use of alkali metal trialkylaluminum hydrides.[3,4]

Studies directed toward stereoselective reduction with lithium trialkylaluminum hydrides were briefly described by Kovács.[4b] Contrary to the high stereoselectivity exhibited by the hindered trialkylborohydrides,[2] the reduction of 4-*tert*-butylcyclohexanone with lithium diisobutyl-*tert*-butylaluminum hydride in ether–hexane (1:1) affords a 49:51 mixture of cis and trans isomers. However, in the stereoselective reduction of cyclic ketone during the total synthesis of aphidicolin by Trost,[4c] lithium diisobutyl-*tert*-butylaluminum hydride exhibits the same degree of stereoselectivity achieved with lithium tri-*sec*-butylborohydride.[5]

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Table I. Reduction of Cyclic and Bicyclic Ketones with Li(*i*-Bu)$_2$(*t*-Bu)AlH at −78 °C for 3 h

ketone[a]	solvent[b]	% less stable isomer[c]	isolated yield, %
4-*tert*-butylcyclohexanone	A	38	95
	B	31	96
4-methylcyclohexanone	A	45	91
	B	23	97
3-methylcyclohexanone	A	49	97
	B	29	96
2-methylcyclohexanone	A	72	92
	B	70	96
2-*tert*-butylcyclohexanone	A	98	93
	B	97	99
3,3,5-trimethylcyclohexanone	A	99.0	99
	B	98.6	92
norcamphor	A	99.8	89
	B	99.5	97
camphor	A	94	70 (29)[d]
	A	94	97[e]
	B	98	99

[a] Ratio of hydride to ketone was 1.5. [b] A and B refer to toluene–hexane (4:1) and THF–hexane (4:1), respectively. [c] Analysis by GLC. [d] Absolute yield measured with an internal standard. The percent recovered ketone is given in parentheses. [e] Reaction was carried out at 0 °C for 1 h.

Due to the lack of systematic investigations on the reduction of cyclic ketones with this reagent and our interest directed toward the development of new reducing agents,[6] we undertook a detailed study of reductions of cyclic and bicyclic ketones with this reagent.

The reagent was prepared by treatment of equimolar amounts of diisobutylaluminum hydride in hexane with *tert*-butyllithium in pentane at −78 °C under nitrogen. The reduction was carried out with 1.5 equiv of the reagent at −78 °C in toluene–hexane (4:1) and tetrahydrofuran–hexane (4:1).[7] The reduction was normally complete within 3 h at −78 °C. The realative percentage of isomeric alcohols was determined by GLC analysis, and the yield was determined by isolation.

The stereochemical results of our reduction study are summarized in Table I. In the cases of 4-*tert*-butyl-, 4-methyl-, and 3-methylcyclohexanone which exert little steric effect, the predominant product formed was the thermodynamically more stable isomer in each case. The reduction of 2-methylcyclohexanone, the moderately hindered ketone, gave the less stable cis isomer preferentially, 72% cis in toluene–hexane. The increase in the steric requirements of the alkyl substituent in 2-alkylcyclohexanone from methyl to *tert*-butyl dramatically enhanced equatorial attack, producing the less stable cis isomer in 98% stereoselectivity in toluene–hexane. The stereoselectivity achieved with this reagent is superior to any of the lithium aluminum hydride type reagents currently available[8] and is comparable to lithium tri-*sec*-butylborohydride.[9] Even better stereoselectivity (99% trans) was observed in the reduction of 3,3,5-trimethylcyclohexanone, a hindered ketone.

This reagent reduced norcamphor, an unhindered bicyclic ketone, with remarkable stereoselectivity. Norcamphor was reduced to the endo alcohol at −78 °C in >99% stereoselectivity. Camphor, a highly hindered bicyclic ketone, was reduced to the exo alcohol at −78 °C in tetrahydrofuran–hexane in 98% stereoselectivity. Surprisingly, the reduction in toluene–hexane was not complete at −78 °C in 3 h, and GLC analysis revealed 70% conversion of camphor into borneol, with 94% being exo. However, it was possible to achieve complete conversion without a change in stereoselectivity at 0 °C in 1 h. The slow reduction of camphor in toluene–hexane is attributed to the lack of solubility of the reagent[10] and the large steric requirement of the reagent.

Although changes in solvent do not affect the stereochemical results of this reagent significantly, it appears that the hydride in toluene–hexane is prone to more equatorial attack than in tetrahydrofuran–hexane in cyclic ketones examined, except for camphor.[11]

The results presented here indicate that the use of this reagent provides a convenient method for conversion of hindered cyclic ketones and bicyclic ketones to the corresponding thermodynamically less stable alcohols. Moreover, in view of the easy preparation of the reagent, the easy workup, and high yield obtainable, we consider that this reagent complements other hydride reducing agents.

Experimental Section

General Methods. Toluene was purified by distillation from sodium under a nitrogen atmosphere. Tetrahydrofuran was purified by distillation from lithium aluminum hydride under a nitrogen atmosphere.

Most of the cyclic and bicyclic ketones utilized in this study were commercial products and were purified by distillation or sublimation. 2-*tert*-Butylcyclohexanone was prepared by the oxidation of 2-*tert*-butylcyclohexanol in methylene chloride by pyridinium chlorochromate.[12]

A standard solution of lithium diisobutyl-*tert*-butylaluminum hydride was prepared as follows. *tert*-Butyllithium in pentane (1.7 M, 11.7 mL, 20 mmol) was slowly added to diisobutylaluminum hydride in hexane (1.0 M, 20 mL, 20 mmol) at −78 °C under a nitrogen atmosphere, and the resulting mixture was diluted with either toluene (18 mL) or THF (18 mL) to yield lithium diisobutyl-*tert*-butylaluminum hydride (0.4 M) in either toluene–hexane or THF– hexane.

Proton nuclear magnetic resonance spectra were obtained on a Varian A-60 spectrometer. Gas chromatographic analyses of product mixtures were performed on a Varian 2800 gas chromatograph with an FID detector.

General Procedure for the Reduction of Cyclic and Bicyclic Ketones. In a dry 25-mL flask fitted with a rubber septum and a magnetic stirring bar was placed the ketone (1 mmol) in 8 mL of toluene or THF. To the resulting solution in a dry ice–acetone bath under a balloon-filled atmosphere of nitrogen was added dropwise a solution of lithium diisobutyl-*tert*-butylaluminum hydride (3.8 mL of 0.4 M solution, 1.5 mmol) in toluene–hexane or THF–hexane. After 3 h, the reaction mixture was treated with 0.5 mL of methanol and allowed to warm to room temperature. After the reaction mixture was further treated with 2 mL of 0.5 N HCl for 30 min, the organic layer was separated, the aqueous layer was extracted with ether (40 mL), and the combined organic layers were washed with brine and dried over anhydrous magnesium sulfate. The product was isolated on

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(9) Reduction of 2-*tert*-butylcyclohexanone with L-Selectride at −78 °C in THF gave cis isomer in >99% stereoselectivity.

(10) The reagent is insoluble in hexane and we have observed that in the reduction in toluene–hexane, the reagent gradually goes into solution as the reduction proceeds.

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solvent removal under vacuum and analyzed by NMR and GLC.

A 10-ft 10% THEED on 60/80-mesh Chromosorb W column was used to separate the products of reduction of 2-methylcyclohexanone (90 °C), 3-methylcyclohexanone (90 °C), and 4-methylcyclohexanone (80 °C). A 12-ft 10% Carbowax 20M on 60/80-mesh Chromosorb W column was used to separate the products in the cases of 2-*tert*-butylcyclohexanone (110 °C), 4-*tert*-butylcyclohexanone (130 °C), 3,3,5-trimethylcyclohexanone (135 °C), norcamphor (110 °C), and camphor (135 °C).

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Registry No. Li(*i*-Bu)$_2$(*t*-Bu)AlH, 62779-60-6; 4-*tert*-butylcyclohexanone, 98-53-3; 4-methylcyclohexanone, 589-92-4; 3-methylcyclohexanone, 591-24-2; 2-methylcyclohexanone, 583-60-8; 2-*tert*-butylcyclohexanone, 1728-46-7; 3,3,5-trimethylcyclohexanone, 873-94-9; norcamphor, 497-38-1; camphor, 76-22-2.

A Convenient Procedure for Upgrading Commercial (+)- and (-)-α-Pinene to Material of High Optical Purity

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α-Pinene, readily available in the (+) and (-) isomeric forms, is becoming of considerable importance for directed chiral synthesis. Hydroboration produces diisopinocampheylborane, which achieves asymmetric hydroboration of cis alkenes with high optical induction.[2] This reagent is readily transformed into monoisopinocampheylborane, suitable for the chiral hydroboration of trans and trisubstituted alkenes.[3] Hydroboration of α-pinene with 9-BBN produces *B*-pinanyl-9-BBN, a reagent that reduces deuterioaldehydes to primary alcohols, RCHDOH, with remarkably high enantiomeric purities.[4] This reagent also reduces acetylenic ketones to acetylenic alcohols with excellent results.[5] More recently it has been extended to many simple ketones.[6] A derivative of α-pinene, 2-hydroxypinan-3-one, is used for the asymmetric synthesis of α-amino acids.[7] Finally, α-pinene is readily converted to pinanediol,[8] and the latter compound has been used to form esters with boronic acids and converted to products with very high optical purities.[9]

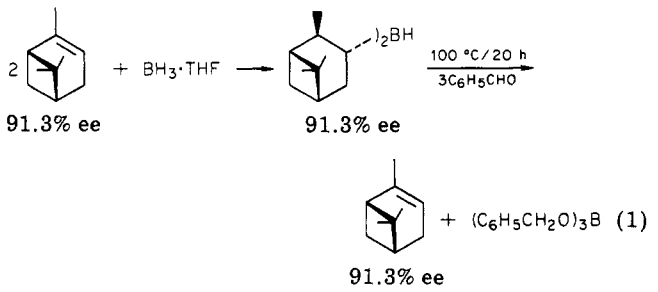
These promising applications make it desirable to have available α-pinene with high optical purity (if possible, a purity approaching 100%).

Regretably, the best available commercial (+)-α-pinene is 91.3% enantiomerically pure.[10] The commercially available (-)-α-pinene is comparatively expensive and is only 81.3% optically pure.[10] Fortunately, commercial (-)-β-pinene[10] of 92.1% ee is available and is readily isomerized by treatment with potassium 3-aminopropylamide[11] (KAPA) to (-)-α-pinene of 92% ee. We set ourselves the goal of finding a simple procedure that would upgrade such (+)- and (-)-α-pinene of ~92% to material approaching 100% ee.

A reasonable starting place for (-)-α-pinene appeared to be commercial (-)-β-pinene. The isomerization of (-)-β-pinene (92.1% ee) to (-)-α-pinene (92% ee) by KAPA was carried out on a 1-mol scale without any experimental difficulties. For (+)-α-pinene, the commerical material (91.3% ee) is satisfactory. Hydroboration of α-pinene with BH_3·THF[2c] or BH_3·SMe_2[2d] provides diisopinocampheylborane (Ipc_2BH). We had observed[2c] that the digestion of the product suspended in THF with 15% excess α-pinene causes the major isomer to become incorporated into the crystalline Ipc_2BH, with the minor isomer accumulating in the solution. Filtration of the solution removed the minor isomer and gave crystalline Ipc_2BH containing 99% of one isomer.

The problem was to find a convenient method to liberate α-pinene from Ipc_2BH. Elimination of up to two alkyl groups from trialkylboranes on treatment with aldehydes has been reported.[12] However, the elimination of the third alkyl group usually does not take place, even under very vigorous conditions.[12a] We have now discovered that, in the case of Ipc_2BH, even the last alkyl group on the boron can be eliminated on treatment with benzaldehyde under relatively mild conditions. The elimination of the alkyl group on boron depends on the structure of the alkyl group.[12] The 3-pinanyl group on boron appears especially favorable for such eliminations.[4-6]

Thus, treatment of Ipc_2BH with 3 mol of benzaldehyde, allowing the temperature to rise to 100 °C, displaces the α-pinene quantitatively, with the formation of tribenzyl borate (eq 1). The α-pinene is readily distilled away from



the tribenzyl borate. Small amounts of benzaldehyde in the product are readily removed by distilling the product from a small excess of lithium aluminum hydride. The product thus obtained is 100% chemically pure (GLC), with no trace of β-pinene, indicating that thermal isomerization[13] does not occur at the displacement temperature (100 °C). Similarly, no racemization has been noted under

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