authors and should not be interpreted as necessarily representing the official policies, either expressed or implied, of the U.S. Government. We also thank David J. Kiemle for determining the high-field NMR spectra and the Sterling-Winthrop Research Institute for the support of undergraduates who prepared synthetic intermediates.

**Registry No.** 1, 77439-76-0; 2, 80904-75-2; 3, 125973-97-9; 4, 125973-98-0; 5, 125973-99-1; 6, 125974-00-7; 7, 125974-01-8; 8, 122551-89-7; 9, 125974-02-9; 10, 125974-03-0; 11, 125974-04-1; 12, 125974-05-2; 13, 125974-06-3; 13a, 125995-42-8; 13b, 96450-70-3; 14, 125974-07-4; 14a, 125974-09-6; 14b, 125974-11-0; 15, 125974-08-5; 16, 125995-61-1; 17, 41473-35-2; 18, 766-40-5; 19, 62674-12-8; 24, 81189-55-1; 5-chloro-4-methyl-2(5*H*)-furanone, 56014-76-7; 5-acetoxy-3,4-dichloro-2(5*H*)-furanone, 63031-44-7; 3-(chloromethyl)-3,5,5-trichloromethyl-2(5*H*)-furanone, 125974-10-9.

**Supplementary Material Available:** Reconstructed CI/GCMS chromatogram of MX (RIC), CI/GCMS of MX, GCMS of MX, 2D $^{13}C$-$^{1}H$ correlated spectrum of MX, INADEQUATE spectrum of 18 (5 pages). Ordering information is given on any current masthead page.

# (+)- and (−)-[2-(1,3-Dithianyl)]myrtanylborane. Solid and Stable Monoalkylboranes for Asymmetric Hydroboration[1]

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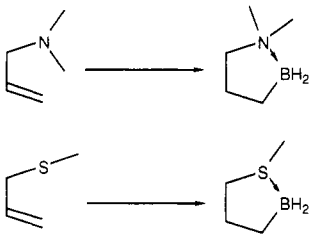
Both (+)- and (−)-myrtenyldithiane derivatives were independently prepared from commercially available chiral precursors and were easily, and in one step, converted by means of borane complexes into solid and stable chiral monoalkylboranes: (+)- and (−)-[2-(1,3-dithianyl)]myrtanylborane ($MDBH_2$). These new chiral reagents, when tested on representative classes of olefins, present a reactivity profile similar to $IpcBH_2$: they achieve the asymmetric hydroboration of trisubstituted double bonds with high asymmetric induction. Reduction of asymmetric prochiral ketones with $MDBH_2$ achieves high diastereoselectivity but low enantioselectivity. The likely intramolecular stabilization of $MDBH_2$ not only accounts for the easy access to monoalkylboranes but also for its remarkable physical properties, whereas its efficiency in asymmetric hydroboration is at the same level as that of similar reagents.

## Introduction

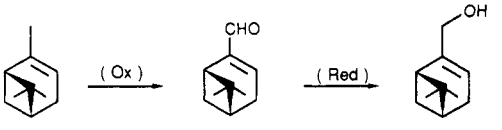
Since the discovery of asymmetric hydroboration by Brown and Zweifel, in 1961,[4] numerous nonenzymatic asymmetric syntheses by means of organoborane reagents have been reported.[5a] Today there exists a large choice of useful chiral organoboranes for asymmetric synthesis from olefins such as, for example, $Ipc_2BH$, $IpcBH_2$, $Lgf_2BH$, LimBH,[3] and, more recently, dicaranylboranes.[6-11] However, stable and uncomplexed monosubstituted chiral borane derivatives are rather uncommon: (+)- and (−)-monoisopinocampheylboranes ((+)-$IpcBH_2$, and (−)-$IpcBH_2$, **1** and **2**), were, for a long time, the only synthetically available representatives of chiral monoalkylboranes[7,12,13a,b] in a complexed form (Figure 1). Recently, (−)-mono(2-ethylapoisopinocampheyl)borane ($EapBH_2$) has been described[13c] in a complexed form. The scarcity of chiral monoalkylboranes is largely due to the fact that hydroboration of olefins rapidly passes through the monoalkylborane step to the dialkyl- or trialkylborane one. Consequently, synthesis of a reagent like $IpcBH_2$ cannot result from a one-step addition of "$BH_3$" to the chiral olefinic precursor.[12]

In some instances intramolecular stabilization is known to stop the reaction at the monohydroboration stage: for example, hydroboration of allylic amines and sulfides proceeds only to the monoalkylborane compounds (Scheme I).[15,16] Therefore, in an attempt to favor such intramolecular stabilization when reacting a borane complex with a chiral olefin, we have considered chiral heterocyclic structures (Figure 2) easily accessible from commercially available compounds.[14] Interestingly, all these olefins when reacted with $BH_3$–L (L = Lewis base) gave monoalkyl-

**Scheme I**




**Scheme II. (+)-Myrtenol (4) from (+)-α-Pinene (3)**

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† CNRS UPR 8402-Inserm U 249.
‡ Société Expansia.

(1) Part of this work was presented at the 7th IUPAC Conference on Organic Synthesis in Nancy, France, July 4–7, 1988.
(2) Thanks are due to Société Expansia, Aramon, France, for a doctoral grant to R. Kiesgen de Richter, analytical support, and technical assistance.
(3) $Ipc_2BH$, diisopinocampheylborane; $IpcBH_2$, monoisopinocampheylborane; $Lgf_2BH$, dilongifolylborane; LimBH, limonylborane.
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(7) Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 5514.
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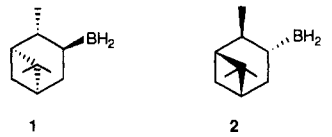
0022-3263/90/1955-2855$02.50/0 



1 2

**Figure 1.** Structures of (+)- and (−)-monoisopinocampheylboranes ((+)- and (−)-IpcBH$_2$, 1 and 2).

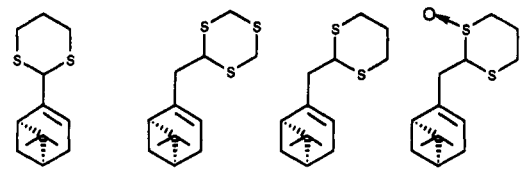
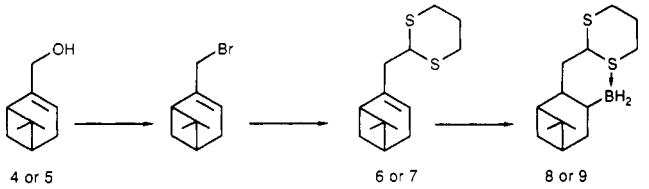


**Figure 2.**

**Scheme III. (+)- or (−)-Myrtenol (4 or 5) Yielding (+)- or (−)-MD (6 or 7) and Finally (+)- or (−)-MDBH$_2$ (8 or 9)**



4 or 5 6 or 7 8 or 9

boranes. Amongst them [2-(1,3-dithianyl)]myrtanylborane (MDBH$_2$) was obtained in the solid state and was a stable compound although uncomplexed. These very important properties prompted us to further study MDBH$_2$ as a potentially valuable chiral reagent in asymmetric hydroboration for laboratory as well as for industrial applications.

We now wish to report the synthesis and the characteristics of both enantiomers of MDBH$_2$ and comparative preliminary examples of the asymmetric hydroboration of representative classes of prochiral olefins. Reduction of prochiral ketones with these new reagents will also be considered although known monoalkylboranes do not appear to be reagents of choice in this case.

## Results and Discussion

**Synthesis of (+)- and (−)-MDBH$_2$ (8 and 9).** Myrtenol is the common precursor for the preparation of both enantiomers (Scheme III). But while (−)-myrtenol (5) as a common natural compound is commercially available in large amounts, its enantiomer, (+)-myrtenol (4), is not readily available. We have obtained it from the abundant monoterpene (+)-α-pinene (3) by modifications of the processes described by Julia[17] or Sharpless[18] (Scheme II).

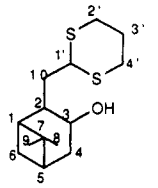


**Figure 3.** Structure of alcohol 10 resulting from enantiospecific replacement of BH$_2$ by an OH group.

**Table I. $^{13}$C NMR Chemical Shifts for 7 and 10 in CDCl$_3$ (δ, Reference TMS)**

| C | δ | C | δ |
|---|---|---|---|
| | 7 | | |
| 1 | 45.6 | 8 | (21.1)[a] |
| 2 | 143.4 | 9 | (26.3)[a] |
| 3 | 120.1 | 10 | 43.0 |
| 4 | 31.3 | 1′ | 45.3 |
| 5 | 40.7 | 2′ | 30.4 |
| 6 | 31.8 | 3′ | 25.9 |
| 7 | 38.0 | 4′ | 30.4 |
| | 10 | | |
| 1 | 50.1 | 8 | (23.5)[a] |
| 2 | ((46.3))[a] | 9 | (27.1)[a] |
| 3 | 69.3 | 10 | (((38.0)))[a] |
| 4 | (((37.6)))[a] | 1′ | ((46.2))[a] |
| 5 | 41.2 | 2′ | 30.2 |
| 6 | 33.0 | 3′ | 25.7 |
| 7 | 41.4 | 4′ | 30.2 |

[a] Chemical shifts inside corresponding parentheses may be exchanged.

Thus, (+)-myrtenal was obtained in 65% yield from (+)-α-pinene (3) after oxidation by *tert*-butyl hydroperoxide in the presence of a catalytic amount of SeO$_2$. Reduction of (+)-myrtenal was achieved by sodium borohydride in ethanol to yield (+)-myrtenol (4) in 50% overall yield. The choice of NaBH$_4$ in ethanol as a reducing agent was interesting because the reaction proceeds smoothly at room temperature without noticeable 1,4-reduction. Moreover, the final workup is easier than with other hydrides.

Myrtenyldithianes were obtained in two steps from the alcohols (Scheme III). First, (+)- or (−)-myrtenol (4 or 5) underwent mild bromination[19] at 0 °C by (Ph)$_3$PBr$_2$ in good yield (90%). Triphenylphosphine dibromide was preferred to other brominating agents such as PBr$_3$ because it avoids the allylic transposition that is likely as a side reaction. Secondly, (+)- and (−)-myrtenyl bromides were coupled with 2-lithio-1,3-dithiane, at −40 °C, according to the Seebach–Corey process[20] in 69% yield. Apparently this two-step synthesis proceeds without racemization: the compounds obtained from both (+)- and (−)-myrtenol have very similar physical properties and opposite [α]$_D$.

Hydroboration of (+)- and (−)-2-myrtenyl-1,3-dithiane (6 and 7 MD) resulted from the reaction, at 0 °C, of 1 equiv of BH$_3$–THF (or any suitable other borane complex) and stopped at the monohydroboration step (Scheme III), confirming the hypothesis that intramolecular stabilization could occur in such structures.

(+)- and (−)-MDBH$_2$ (8 and 9) were isolated in the form of white powders by solvent evaporation in vacuum fol-

(11) For reviews, see: (a) Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *Tetrahedron* **1981**, *37*, 3547. (b) Brown, H. C.; Singaram, B. *Acc. Chem. Res.* **1988**, *21*, 287. (c) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*; Wiley-Interscience: New York, 1975.

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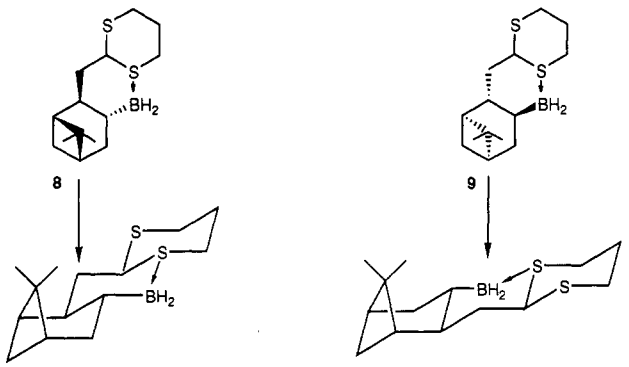

**Figure 4.** Structures of (+)-(1*R*,2*S*,3*R*,5*R*)-$MDBH_2$ (**8**) and (-)-(1*S*,2*R*,3*S*,5*S*)-$MDBH_2$ (**9**).

lowed by crystallization in heptane to eliminate starting materials and to achieve enantiomeric purity.

**Absolute Configuration.** Zweifel and Brown[21] have clearly demonstrated that the anti-Markovnikov cis addition of "$BH_3$" occurs at the side opposite to the *gem*-dimethyl bridge and, therefore, they were able to deduce the absolute configuration of (-)-$Ipc_2BH$ (and later of (-)-$IpcBH_2$) from the absolute configuration of the precursor (+)-α-pinene. For our own part, we have performed an alkaline oxidation ($NaOH/H_2O_2$) of (+)- and (-)-$MDBH_2$ to form the corresponding (+)- and (-)-dithianyl derivatives of isopinocampheol, respectively. As this oxidation is well known to proceed with complete retention of configuration,[21] we have examined these alcohols **10** (Figure 3) as model structures for $MDBH_2$ by $^{13}C$ NMR spectroscopy (Table I). The $C_4$ carbon is the most sensitive to the spatial arrangement of the $CH_2$ and OH substituents. Indeed, assuming a trans diequatorial relationship between substituents and a chair conformation for the pinanyl moiety, the theoretical $C_4$ chemical shift was computed by the Beierbeck and Saunders method[22,23] based on gauche interactions between atoms. From the reference structure *trans*-2-methylcyclohexanol,[24] a value of 37.3 ppm was found, corresponding very well to the experimental one (37.6 or 38.0 ppm, Table I). Other spatial arrangements for the two substituents (cis relationship and/or a boat conformation for the $C_2$, $C_3$, $C_4$ moiety) result in a shielding effect for $C_4$ of at least 4 ppm caused by γ 1,3-diaxial shielding interactions and/or loss of β deshielding interactions. This confirms previous proofs in related series[21,25] for a trans diequatorial relationship in 2,3 substitutions. Furthermore, in Dreiding models of $MDBH_2$ such a spatial arrangement can account for an intramolecular stabilization between sulfur and boron atoms by formation of a pseudo-six-membered ring. Consequently, the monoalkylborane formed from (+)-(1*R*,5*R*)-α-pinene is (+)-(1*R*,2*S*,3*R*,5*R*)-$MDBH_2$ (**8**) and the one formed from (-)-(1*R*,5*S*)-myrtenol is (-)-(1*S*,2*R*,3*S*,5*S*)-$MDBH_2$ (**9**). For clarity they are represented (Figure 4) in the chair conformation for the pinanyl moiety (as well as for the pseudo-six-membered ring) as done by others in similar cases.[26] However, it is well known that pinanyl structures are generally more or less flattened as a consequence of the bridged system. This seems to be the case in pinanylboranes derivatives as revealed by X-ray structure determinations.[27-29] Most probably, a similar flattening exists in structures **8** and **9**.

**Table II. Physical and Analytical Properties of (+)- and (-)-$MDBH_2$ (8 and 9)**

| | 8 | 9 |
|---|---|---|
| mp, °C | 110–115 | 110–112 |
| $[\alpha]^{20}_D$ (*c* 5, toluene), deg | +44 ± 1 | -43 ± 1 |
| active $H^-$ (methanolysis), % | 100 ± 5 | 100 ± 5 |
| boron analysis, % | 98–100 | 98–100 |
| $^{11}B$ NMR, ppm | -8.5 | -8.5 |
| B-$H_2$ (IR),[a] $cm^{-1}$ | 2360 | 2360 |
| stability (4 °C, nitrogen) | >1 year | >1 year |

[a] Bellamy, J. L. *The Infrared Spectra of Complexes Molecules*, 3rd ed.; Chapman & Hall: London, 1975; Vol. 1, p 122.

**Enantiomeric Purity of (+)- and (-)-$MDBH_2$ (8 and 9).** The enantiomeric purity of $MDBH_2$ was indirectly determined by checking the enantiomeric purity of the corresponding alcohols **10** obtained as above. The (+)- and (-)-dithianyl derivatives of isopinocampheol and their racemate, prepared by mixing equal amounts of each alcohol and derivatized by means of (4*R*,5*R*)-(+)-2-chloro-4,5-dimethyl-1,3,2-dioxaphospholane 2-oxide,[30] were examined by $^{31}P$ NMR spectroscopy. A single signal was observed in the spectrum of each of the derivatized enantiomers, corresponding respectively to one of the two signals observed for the derivatized racemate (11.30 and 11.55 ppm referred to phosphoric acid). Thus, alcohols **10** appear to be enantiomerically pure compounds and, consequently, we may assume the enantiomeric purity of **8** and **9** to be very near 100%.

**Physical Properties.** The essential physical and analytical characteristics of the new monoalkylboranes are presented in Table II. $MDBH_2$ are relatively high melting solids with good stability under nitrogen in a refrigerator (more than 1 year). They appear to be free from other boron derivatives and not very sensitive to moisture: after a 15-min exposure to atmospheric air no $B(OH)_2$ signal (near 30 ppm[31a]) could be detected in $^{11}B$ NMR spectroscopy. Surprisingly, the observed chemical shift (-8.5 ppm, reference $BF_3$-$O(C_2H_5)_2$ for $^{11}B$ in structures **8** and **9** is considerably more shielded than expected. Normally, the signal should have been deshielded to appear in the low field region of the spectrum. However, when boron is covalently linked to a sulfur atom, it suffers drastic shielding and appears between -10 and -20 ppm.[31b] Consequently, the chemical shift observed here seems to support the hypothesis of a strong interaction between boron and sulfur atoms resulting in an intramolecular stabilization.

**Asymmetric Hydroboration with (+)- and (-)-$MDBH_2$.** The asymmetric induction achievable by means of $MDBH_2$ was tested on selected prochiral olefins and the results were compared, when possible, with those published for the monoalkylborane (-)-$IpcBH_2$. Preliminary results presented in Table III clearly demonstrate that $MDBH_2$ and $IpcBH_2$ possess similar profiles as asymmetric hydroborating reagents. The decreasing order of the asymmetric induction is as follows: trisubstituted double bonds (cyclic or not), disubstituted double bonds, and *gem*-di-

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**Table III. Comparative Asymmetric Inductions Achievable with (+)- or (-)-$MDBH_2$ (8 or 9) and (-)-$IpcBH_2$ from Prochiral Olefins**

| | | (-)-$IpcBH_2$ | | $MDBH_2$ | | | |
|---|---|---|---|---|---|---|---|
| olefin used | alcohol obtained[a] | % ee | config | 8 or 9 | % ee[f] config | yield, % | solvent used |
| *cis*-2-butene | 2-butanol | 24 | *S*[b] | 9 | 35[g] *R* | 82 | THF |
| 2-methyl-2-butene | 3-methyl-2-butanol | 53 | *S*[d] | 9 | 34[h] *R* | 71 | THF |
| | | | | 8 | 36 *S* | 64 | diglyme |
| | | | | 9 | 40 *R* | 75 | diglyme |
| 1-methylcyclohexene | *t*-2-methylcyclohexanol[c] | 72 | 1*S*,2*S*[d] | 8 | 71[i] 1*S*,2*S* | 76 | THF |
| | | | | 9 | 70 1*R*,2*R* | 87 | THF |
| 2,3-dimethyl-1-butene | 2,3-dimethyl-1-butanol | *a* | | 8 | 6[j] *S* | 56 | THF |
| 1-methylcyclopentene | *t*-2-methylcyclopentanol[c] | 55 | 1*S*,2*S*[d] | 8 | 36[k] 1*S*,2*S* | 86 | THF |

[a] No data available for $IpcBH_2$; alcohol (*S*) was obtained in 1.5% ee by Masamune, S.; Kim, B. M.; Petersen, P. S.; Sato, T.; Vennstra, S. J. *J. Am. Chem. Soc.* **1985**, *107*, 4549. [b] Mandal, A. K.; Yoon, N. M. *J. Organomet. Chem.* **1978**, *156*, 183. [c] *t* = trans. [d] Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 5514. [e] Purification by preparative GC on Carbowax 400. [f] % ee computed from maximal rotations in literature. [g] Based on $[\alpha]_D = -13.5°$ (neat): Leroux, P. I.; Lucas, H. J. *J. Am. Chem. Soc.* **1951**, *73*, 41. [h] Based on $[\alpha]_D = +5.34°$ (*c* 5, EtOH): Pickard, R. H.; Kenyon, J. *J. Chem. Soc.* **1913**, *103*, 1957. [i] Based on $[\alpha]_D = +42.9°$ (*c* 1, MeOH): Bäckström, R.; Sjöbers, B. *Arkiv. Kemi* **1967**, *26*, 549. [j] Based on $[\alpha]_D = -2.95°$ (*c* 60.5, $CHCl_3$): Tsuda, K.; Kishida, Y.; Hayatsu, R. *J. Am. Chem. Soc.* **1960**, *82*, 3396. [k] Based on $[\alpha]_D = +43.9°$ (*c* 1, MeOH): Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 532.

**Table IV. Comparative Diastereoselectivity Achievable with $MDBH_2$ from Ketones**

| | | | | % alcohol | |
|---|---|---|---|---|---|
| ketone used | alcohols obtained | borane[a] | solvent | cis | trans |
| 4-*tert*-butylcyclohexanone | 4-*tert*-butylcyclohexanols | $B_2H_6$ | diglyme | 8 | 92 |
| | | $B_2H_6$ | THF | 18 | 82 |
| | | $Ipc_2BH$ | diglyme | 37 | 63 |
| | | 8 or 9 | THF | 18 | 82 |
| | | 8 or 9 | diglyme | 5 | 95 |
| 2-methylcyclohexanone | 2-methylcyclohexanols | $B_2H_6$ | THF | 26 | 74 |
| | | $Ipc_2BH$ | THF | 66 | 34 |
| | | $Ipc_2BH$ | diglyme | 94 | 6 |
| | | 8 or 9 | THF | 51 | 49 |
| | | 8 or 9 | diglyme | 99 | 1 |

[a] Comparative results are from Brown, H. C.; Varma, V. *J. Org. Chem.* **1974**, *39*, 1631 and Hajos, A. *Complex Hydrides*; Elsevier: Amsterdam, 1979; Chapter 12.

substituted double bonds. The resulting asymmetric induction is sometimes excellent in the first case but is very poor in the latter.

**Reduction of Ketones with $MDBH_2$.** The new reagents were also tested for reduction of ketonic compounds. The results we obtained on model cyclic ketones were excellent in terms of diastereoselectivity (Table IV). In this respect, $MDBH_2$ appears equivalent to or sometimes better than the best known borane reagents. However, in enantioselective reduction of prochiral ketones, the results were as disappointing as with other monoalkylboranes: for example, we obtained only 7% ee in reduction of acetophenone. This result compares with the 9% obtained by others[11] with the same substrate and similar reagents.

## Conclusions

(+)- or (-)-$MDBH_2$ are monoalkylboranes resulting from the reaction between borane complexes and (+)- or (-)-2-myrtenyl-1,3-dithiane, respectively. Intramolecular stabilization between boron and sulfur atoms may well account for their straightforward preparation and for very interesting properties: they are solid and stable uncomplexed compounds. However, in our preliminary assays, the intramolecular stabilization appears not to interfere with enantioselectivity in asymmetric hydroboration of prochiral alkenes nor in reduction of prochiral ketones: they achieve asymmetric hydroboration of trisubstituted double bonds with high asymmetric induction, whereas the reduction of ketones is achieved with very poor asymmetric induction. Finally, their profile as chiral reagents is close to that of the well-known monoalkylborane $IpcBH_2$. Because they are the first chiral monoalkylboranes that can be prepared and easily stored in both enantiomeric forms before use, work is in progress to enlarge the scope of applications. Moreover, $MDBH_2$ is easy to handle and because the precursors are readily available in relatively large amounts, both large-scale synthesis and industrial applications are currently being considered.

## Experimental Section

**Materials.** Tetrahydrofuran, boron trifluoride etherate, and (+)-α-pinene (Aldrich) were purified by standard procedures.[5a,11c] The rotation of the (+)-α-pinene used was $[\alpha]^{22}_D = +47.1°$ (neat) and that of (-)-myrtenol (Aldrich) was $[\alpha]^{22}_D = -47.5$ (neat). 1,3-Dithiane, triphenylphosphine, bromine, *n*-butyllithium (15 or 20% in hexane), and sodium borohydride are from commercial sources. Alkenes also from commercial sources were at least 98% pure in gas chromatography (GC). Commercial ketones were purified by distillation and kept under nitrogen before use. All reactions were carried out under nitrogen in glassware dried at 150 °C and cooled under nitrogen. Melting points are uncorrected and were obtained in capillary tubes on a Tottoli apparatus. The optical rotations were measured by using a digital micropolarimeter Jobin Yvon or a Perkin-Elmer spectropolarimeter. $^1H$ NMR spectra were recorded on a Bruker WP60 spectrometer and $^{31}P$ and $^{13}C$ NMR spectra on a pulsed WP80 DS Bruker spectrometer using, respectively, phosphoric acid or TMS as internal reference. $^{11}B$ NMR spectra were recorded on a Varian FT 100 spectrometer, using boron trifluoride etherate as external reference. IR spectra were recorded on a Perkin-Elmer 377 spectrometer. Gas chromatographic analyses were effected on an Intersmat IGC 16 apparatus or on a Girdel 30 apparatus; analyses were also effected on a Hewlett-Packard GC/MS apparatus equipped with a 25-m OV1 column. All chiral alcohols obtained were purified on a preparative GC Varian 1520 apparatus equipped with a 6-ft Carbowax 400 column.

**Preparation of (+)-Myrtenal.**[17,18] A 70% solution of *tert*-butyl hydroperoxide (480 mL, 3.5 mol) was extracted with dichloromethane (600 mL). After decantation and separation of a water layer amounting to 120 mL at least, the organic layer was stirred at room temperature with selenium dioxide (4 g, 36 mmol) until dissolution. Then (+)-α-pinene (**3**) (136 g, 1 mol) was added in a 3-h period, the temperature being kept under 30 °C. After the addition was complete, the mixture was stirred at 35 °C for 48 h. The final mixture was washed with a 10% aqueous solution of potassium hydroxide (500 mL) and then with water in order to reach a pH = 7. If necessary, an excess of hydroperoxide can be destroyed by dimethyl sulfide in acetic acid.[18] The organic layer was dried over $Na_2SO_4$ and the solvent removed under reduced pressure (15 mm) to yield an oil (240 g) containing (+)-myrtenal (65% by GC analysis) used in the following step without further purification.

**Preparation of (+)-Myrtenol (4).** The preceding oily crude aldehyde was dissolved in absolute ethanol (700 mL) and sodium

borohydride (17 g, 0.45 mol) was cautiously added in portions to the stirred alcoholic solution maintained at 20 °C. After a 12-h stirring period at room temperature, the excess of hydride was carefully destroyed by dropwise addition of a 5% aqueous solution of hydrochloric acid until no more hydrogen evolution could be observed and the pH reached a value of about 4 or 5. After evaporation of the solvent under reduced pressure, the remaining mixture was extracted with diethyl ether and washed with brine until pH = 7. The combined organic layer, after drying over $Na_2SO_4$, was concentrated under reduced pressure to give an oily residue (160 g). The residue was distilled under vacuum (1.5 Torr) to give a fraction boiling at 70–72 °C containing 76 g (50%) of (+)-myrtenol (4), $[\alpha]^{20}_D$ +46.8° (neat) (lit.[17] $[\alpha]^{20}_D$ +47.5°).

**Synthesis of (+)- and (-)-$MDBH_2$ (8 and 9).** In the following synthesis we shall describe only one example, i.e., preparation of (-) enantiomer **9** from (-)-myrtenol. For the corresponding (+) enantiomer 8 the synthesis from (+)-myrtenol and results were identical except for the opposite optical rotation (Table II).

**Preparation of (-)-Myrtenyl Bromide.**[19] Triphenylphosphine (525 g, 2 mol) was dissolved in dichloromethane (1 L) under a nitrogen atmosphere and cooled at 0 °C in an ice bath. Bromine (103 mL, 2 mol) was added dropwise during about 1 h (the addition was stopped when two consecutive drops imparted a persisting orange color to the solution). Then, (-)-myrtenol (**5**) (300 g, 1.96 mol) was added at 0 °C over a 2-h period and the solution was stirred for 12 h at room temperature. After cautious neutralization with 15% aqueous sodium carbonate (1 mol), the organic layer was separated and dried with $MgSO_4$, and the solvent was removed under reduced pressure to yield a pale yellow solid residue. This residue was washed with *n*-heptane (3 × 500 mL) in order to extract the myrtenyl bromide from the solid triphenylphosphine oxide. Evaporation of the *n*-heptane under reduced pressure gave an oily residue (410 g), which yielded, after distillation under vacuum (45–47 °C, 0.05 mmHg), pure (-)-myrtenyl bromide (381 g, 90%), $[\alpha]^{22}_D$ -25.3° (*c* 3, $CHCl_3$) (lit.[17] $[\alpha]^{22}_D$ +20.8° (*c* 3.46, $CHCl_3$) for the (+) isomer).

**Preparation of (-)-MD (7).**[20] A 15% solution of *n*-butyllithium in *n*-hexane (505 mL) was added to a solution of 1,3-dithiane (86 g, 0.716 mol) in THF (500 mL) at -40 °C, under a nitrogen atmosphere. After the addition was completed, the solution was stirred at -20 °C for 3 additional hours; then myrtenyl bromide (152 g, 0.716 mol) was added over a 1-h period, at -40 °C. The mixture was slowly (2 h) heated to -10 °C and hydrolyzed by an aqueous solution of ammonium chloride. The organic phase was decanted, extracted with diethyl ether, dried on $Na_2SO_4$, and evaporated under reduced pressure to yield a yellow oily residue. After distillation (125 °C, 0.4 mmHg) the pure compound **7** was obtained as a pale yellow oil (125.5 g, 69%), $[\alpha]^{22}_D$ -11.2° (*c* 3, $CHCl_3$). Anal. Calcd for $C_{14}H_{22}S_2$: C, 66.08; H, 8.71; S, 25.20. Found: C, 66.03; H, 8.55; S, 25.30. See $^{13}C$ NMR in Table I.

**Preparation of (-)-$MDBH_2$ (9).** A molar (0.5 mol) BH3–THF solution was cooled and stirred at -10 °C, and a solution of (-)-MD (**7**) (125 g, 0.492 mol) in THF (100 mL) was added dropwise over a 1.5-h period. The temperature was allowed to rise slowly to room temperature and stirring was continued for 12 h; then the solvent was removed under reduced pressure. The solid residue obtained was suspended in *n*-hexane and the precipitate was collected by filtration under nitrogen, dried, and stored under nitrogen to give (-)-$MDBH_2$ (**9**) (119 g, 90%). Physical and analytical properties of **9** and its enantiomer **8** are presented in Table II.

**General Procedure for Asymmetric Hydroboration with (+)- and (-)-$MDBH_2$ (8 and 9).** As the procedures were the same whatever the unsaturated compound and the $MDBH_2$ used, we shall describe only two representative examples in two types of solvent. The conditions and results (hydroborating agent and solvent used, yield, configuration, enantiomeric excess) in each experiment are presented in Table III. All reactions with borane reagents were carried out under nitrogen, in nitrogen-filled dry flasks, equipped with a septum inlet, a magnetic stirring bar, and a reflux condenser connected to a mercury bubbler.

**Asymmetric Hydroboration of 1-Methylcyclohexene in THF.** A 0.7 M solution of (+)-$MDBH_2$ (**8**) (16 g, 59.75 mmol) in THF was stirred at -20 °C in a 250-mL dry flask. 1-Methylcyclohexene (5.73 g, 59.75 mmol) was slowly added. The temperature was allowed to reach room temperature slowly and stirring was continued for 22 h. Then the organoborane was hydrolyzed by methanol (2 mL) and oxidized by the successive addition of a 3 N sodium hydroxide solution (20 mL, 60 mmol) and a 30% (weight) hydrogen peroxide solution (20 mL, 196 mmol). The mixture was then heated at 40 °C for 1.5 h. After cooling to room temperature, the aqueous phase was saturated by $K_2CO_3$, and extracted three times with diethyl ether. The combined organic phases were dried over $Na_2SO_4$ and evaporated under reduced pressure. The oily residue was fractionally distilled (70–71 °C, 16 mmHg) to yield *trans*-2-methylcyclohexanol (5.2 g, 76%, GC purity 96–97%). An aliquot (1 g) of the alcohol was further purified by preparative gas chromatography on a Carbowax 400 column at 110 °C to achieve a GC purity of 99.9%, $[\alpha]^{22}_D$ +30.6° (*c* 1 in MeOH), 71% ee (lit. fnt *i*, Table III, $[\alpha]^{22}_D$ +43.1°).

**Asymmetric Hydroboration of 2-Methyl-2-butene in Diglyme.** In the same way as that described above, 2-methyl-2-butene (10.2 g, 145 mmol) was slowly added (30 mn) to a 0.1 M solution in diglyme of **9** (48.5 mmol in 50 mL) at -20 °C. The temperature and stirring were maintained for a 24-h period. Then the organoborane was hydrolyzed with methanol (2 mL) and oxidized at 0 °C by the successive addition of a 3 N sodium hydroxide solution (15 mL, 45 mmol) and a 30% (weight) hydrogen peroxide solution (15 mL, 147 mmol). The mixture was then heated at 40 °C for 1.5 h. The raw aqueous/organic phase was fractionally distilled (98–102 °C) to yield a two-phase fraction (water + alcohol). After the saturation of the water phase with NaCl, the organic layer was separated to yield crude 3-methyl-2-butanol (6.8 g, GC purity 75%). The alcohol was further purified by preparative gas chromatography on a Carbowax 400 column at 100 °C to achieve a GC purity of 99.9% (total yield calculated on $MDBH_2$ 75%), $[\alpha]^{22}_D$ -2.13° (*c* 6, EtOH), 40% ee (lit. fnt *h*, Table III, $[\alpha]^{22}_D$ 5.34° (*c* 5, in EtOH)).

**General Procedure for Reduction of Ketones with $MDBH_2$.** As the procedures were the same for all the ketones used, we shall describe only two representative examples in two types of solvent. The conditions and results (solvent used, yield, configuration) of each experiment done are presented in Table IV. For acetophenone, a prochiral ketone, the procedure will also be detailed. All reactions with borane reagents were carried out in the same way and using the same equipment as described above for hydroboration of olefins.

**Reduction of 2-Methylcyclohexanone in THF.** A 0.7 M solution of $MDBH_2$ (**8** or **9**) (4 g, 14.9 mmol) in THF was stirred at -10 °C in a 100-mL dry flask. 2-Methylcyclohexanone (1.7 g, 15.1 mmol) was slowly introduced by mean of a hypodermic syringe. After the addition was completed, the solution was allowed to warm slowly to room temperature and was stirred for 3 h. Then, the medium was hydrolyzed by the addition of a 3 N NaOH solution (10 mL). The resulting mixture was stirred for 1 h at room temperature and the aqueous phase was saturated with $K_2CO_3$, decanted, and extracted three times with diethyl ether. The organic phases collected were dried over $Na_2SO_4$ and concentrated under reduced pressure to give oily crude alcohols (6.2 g). A GC analysis on an OV1 column revealed a 100% conversion to alcoholic compounds and a cis/trans proportion of 51/49, respectively (average of three different assays).

**Reduction of 4-*tert*-Butylcyclohexanone in Diglyme.** A 0.7 M solution of $MDBH_2$ (**8** or **9**) (4 g, 14.9 mmol) in diglyme was stirred at -10 °C in a 100-mL dry flask. 4-*tert*-Butylcyclohexanone (2.3 g, 15 mmol) dissolved in a minimum of diglyme was slowly added by means of a hypodermic syringe. After the addition was completed, the solution was allowed to warm slowly to 0 °C and was stirred for 2 h. Then, the mixture was hydrolyzed by the addition of a 3 N NaOH solution (10 mL). The resulting mixture was stirred for 1 h at room temperature and the aqueous phase was saturated with $K_2CO_3$, decanted, and extracted three times with diethyl ether. The combined organic phases collected were dried over $Na_2SO_4$ and concentrated under reduced pressure to give oily crude alcohols (6.9 g). A GC analysis of this crude oil, on an OV1 column, revealed a 100% conversion to alcoholic compounds and a cis/trans proportion of 5/95, respectively (average of three different assays).

**Reduction of Acetophenone.** A solution of (-)-$MDBH_2$ (**9**) (8.5 g, 31.7 mmol) in THF (40 mL) was stirred and cooled at -20 °C; then acetophenone (3.8 g, 31.7 mmol) and $BF_3$–$Et_2O$ (4 mL, 32 mmol) in THF (40 mL) were slowly added. Cooling and stirring were continued for 90 h; then the solution was heated slowly to

0 °C and a 3 N NaOH solution (21 mL) was added. The aqueous phase was saturated with $K_2CO_3$, decanted, and extracted three times with diethyl ether. The combined organic phases collected were dried over $Na_2SO_4$ and concentrated under reduced pressure. The oily residue obtained was fractionally distilled (44–47 °C, 0.1 mmHg) to yield α-methylbenzyl alcohol (2.8 g, 72%). Preparative HPLC purification achieved a GC purity of 99%, $[\alpha]^{22}_D$ +2.96° (neat), 7% ee.[11]

**Registry No.** 3, 7785-70-8; 4, 6712-78-3; 5, 19894-97-4; 7, 84619-19-2; 8, 84525-73-5; 9, 125827-38-5; (+)-myrtenal, 23727-16-4; (−)-myrtenyl bromide, 55527-89-4; 1,3-dithiane, 505-23-7; 1-methylcyclohexene, 591-49-1; (1*S*,2*S*)-*trans*-2-methylcyclohexanol, 15963-37-8; (1*R*,2*R*)-*trans*-2-methylcyclohexanol, 19043-03-9; 2-methyl-2-butene, 513-35-9; (*R*)-3-methyl-2-butanol, 1572-93-6; (*S*)-3-methyl-2-butanol, 1517-66-4; 2-methylcyclohexanone, 583-60-8; *cis*-2-methylcyclohexanol, 7443-70-1; *trans*-2-methylcyclohexanol, 7443-52-9; 4-*tert*-butylcyclohexanone, 98-53-3; *cis*-4-*tert*-butylcyclohexanol, 937-05-3; *trans*-4-*tert*-butylcyclohexanol, 21862-63-5; acetophenone, 98-86-2; (+)-α-methylbenzyl alcohol, 1517-69-7; *cis*-2-butene, 590-18-1; (*R*)-2-butanol, 14898-79-4; 2,3-dimethyl-1-butene, 563-78-0; (*S*)-2,3-dimethyl-1-butanol, 15071-36-0; 1-methylcyclopentene, 693-89-0; (1*S*,2*S*)-*trans*-2-methylcyclopentanol, 39947-48-3.

# The in Situ Activation of Thioglycosides with Bromine: An Improved Glycosylation Method†

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A one-step conversion of thioglycosides into 1,2-*trans*- or 1,2-*cis*-*O*-glycosides was accomplished, in situ, by treatment with bromine in the presence of a glycosyl acceptor and a promoter such as silver triflate or mercuric cyanide. This mild "one-pot" procedure gives *O*-glycosides in excellent yields with high stereochemical control, even with unreactive and hindered glycosyl acceptors. The reaction conditions are compatible with various protecting groups such as acetates, benzoates, benzyl ethers, *N*-phthalimido groups, and benzylidene acetals.

## Introduction

Thioglycosides are stable and versatile derivatives that allow flexible strategies for the synthesis of complex oligosaccharides.[1] As glycosyl donors thioglycosides can be activated for glycosylations by conversion into glycosyl halides, usually under mild conditions that are compatible with sensitive protecting groups such as acetals. The glycosyl halides may then be employed in glycoside synthesis using "halophilic" reagents such as silver or mercury salts or tetraethylammonium bromide.[1] In some cases the preparation of glycosyl halides from thioglycosides, and their subsequent utilization in glycosylations, has been difficult due to low yields and side reactions.[1,2]

Alternatively, the *direct* glycosylation of alcohols with thioglycosides can be accomplished using various thiophilic reagents as promoters.[1] Promotion by methyl triflate[1,3] or dimethyl(methylthio)sulfonium triflate[1,4] (DMTST) is well documented and gives excellent results, but methyl triflate is a potential carcinogen and is also highly toxic, whereas DMTST is prepared using carcinogenic methylating agents. Benzeneselenyl triflate,[5] which should also be treated as toxic, suffers from a lack of stereoselectivity when used with glycosyl donors that have nonparticipating groups at O-2. Nitrosyl tetrafluoroborate,[6] a powerful activating agent, has been reported[7] to give irreproducible yields, especially in glycosylations of unreactive alcohols. More attractive methods for direct glycosylations with thioglycosides include promotion by methylsulfenyl triflate[7] (prepared in situ from methylsulfenyl bromide and silver triflate) and transformation of the thioglycosides into bromides using a copper(II) bromide/tetrabutylammonium bromide complex followed by in situ glycosylation using suitable promoters.[8]

As part of a study[9] to map the combining sites of antibodies against the *Brucella* A polysaccharide antigen using synthetic oligosaccharides,[10] the glycosylation of the alcohol **3** with the thioglycoside **1**[10] was envisaged as a route to the target trisaccharide **4** (Scheme I). Activation of the thioglycoside **1** with methylsulfenyl triflate (prepared in situ) was considered an attractive alternative to the hazardous methyl triflate[3] previously used[10] in similar syntheses. When the glycosylation of **3** was attempted using silver triflate and crude methylsulfenyl bromide (prepared as described[7] by reaction of dimethyl disulfide and bromine in 1,2-dichloroethane for 4 h) as promoters, the *bromide* **2** was isolated unexpectedly in 27–37% yields, in addition to the expected trisaccharide **4** (34–47%). Though an excess of silver triflate (1.5 equiv relative to **1**) was used[7] no further change in the product distribution was observed after ~30 min, as determined by TLC.[11] The formation of the bromide **2** was not detected in the

† NRCC Publication No. 31282.

(1) Fügedi, P.; Garegg, P. J.; Lönn, H.; Norberg, T. *Glycoconjugate J.* **1987**, *4*, 97 and cited references.

(2) In one case preparation of a glycosyl bromide by treatment of a thioglycoside with bromine resulted in the formation of the corresponding *benzyl* glycoside as a byproduct in the subsequent glycosylation. The benzyl glycoside was presumed to derive from a reaction between the glycosyl bromide, moisture, and benzyl bromide (formed from toluene used for concentration of the glycosyl bromide). In another case, cleavage of a *p*-methoxybenzyl ether (Classon, B.; Garegg, P. J.; Samuelsson, B. *Acta Chem. Scand.* **1984**, *B38*, 419) upon treatment of a thioglycoside with bromine was assumed to account for the diversity of products obtained. Kihlberg, J.; Eichler, E.; Bundle, D. R., unpublished results.

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(5) Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1988**, *29*, 1061.

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(8) Sato, S.; Mori, M.; Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1986**, *155*, c6.

(9) Bundle, D. R. *Pure Appl. Chem.* **1989**, *61*, 1171.

(10) Peters, T.; Bundle, D. R. *Can. J. Chem.* **1989**, *67*, 491.

(11) This was probably due to deactivation of the silver triflate by sulfides, such as methyl ethyl disulfide, which are formed in the reaction. In fact, the silver triflate promoted reaction of **3** and the glycosyl bromide **2** was complete in less than 5 min (66% of **4** was isolated), whereas the addition of dimethyl disulfide (1 equiv relative to **2**) yielded a mixture of **4** (52%) and unreacted **2** (15%) at equilibrium (reached after ~30 min, TLC).

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