sequences with argon. The reactor was heated to 180 °C in 30 min in a mantle heater and thermostated at this temperature for 5 h with stirring. The reaction was terminated by rapid cooling, and the reactor was discharged. Evolved hydrogen was measured by means of a buret, and the identity of the gaseous produce was checked by GLC (active carbon). The reaction mixture was diluted with ether (100 mL), and excess aminoarene was removed by washing the ethereal solution with 100 mL aqueous 5% HCl. The ether layer was separated and dried with anhydrous magnesium sulfate. Distillation of the evaporated solution gave 1-methylindole in 46% yield.

Analytical Procedure. All boiling points and melting points were uncorrected. The identification of products was made by ^{1}H NMR, ^{13}C NMR, and IR spectra and elemental analysis. The ^{1}H and ^{13}C NMR spectra were recorded at 100 and 25.05 MHz, respectively, with a JEOL JNM FX-100 spectrometer. Samples were dissolved in $CDCl_3$ or Me_2SO-d_6, and the chemical shifts are expressed relative to Me_4Si as an internal standard. The IR spectra were measured on a Nicolet Model 5MX Fourier transfer infrared spectrometer. Elemental analyses were performed at Microanalytical Center of Kyoto University. The GLC analyses of products were made by Shimadzu GC-8APF with a column (3 mm × 3 m) packed with Poly-I 110 (5%) on Chromosorb W AW DMCS, 60–80 mesh. The GC analysis of gaseous product was made by Shimadzu GC-8AT with a column (3 mm × 3 m) packed with active carbon, 60–80 mesh. In some cases, the yields were determined by the internal standard method according to the calibration curve obtained in separate experiments for each product.

Acknowledgment. The present work was supported in part by Grant-in-Aid for Scientific Research No. 60119001 from the Ministry of Education, Science, and Culture.

Supplementary Material Available: Experimental procedure, NMR data, IR data, and analyses of 5-methyl- and 7-methylquinoline (eq 2), 2-methyl- and 4-methylquinoline (eq 3), quinoline, 8-methylquinoline, 6-methylquinoline, 8-chloroquinoline, 6-chloroquinoline, 6-methoxyquinoline, 7,8-benzoquinoline, 1,4-diphenylpiperazine (eq 5), 1,4-dibenzylpiperazine (eq 7), 2,3,4-trimethyl- and 2,3,6-trimethylindole (eq 8), 1,2-dimethyl- and 1,3-dimethylindole (eq 9), 2-phenylindole (eq 10), 1-methylindole, 1-ethylindole, 1-propylindole, 1-butylindole, 1-ethyl-5-methylindole, 2,3-dimethylindole, 1,2,3-trimethylindole, 2,3,7-trimethylindole, 2,3,5-trimethylindole, 7-chloro-2,3-dimethylindole, 5-chloro-2,3-dimethylindole, 5-methoxy, 2,3-dimethylindole, 1,2,3,4-tetrahydrocarbazole, 9-methyl-1,2,3,4-tetrahydrocarbazole, 9-ethyl-1,2,3,4-tetrahydrocarbazole, 8-methyl-1,2,3,4-tetrahydrocarbazole, 6-methyl-1,2,3,4-tetrahydrocarbazole, 8-chloro-1,2,3,4-tetrahydrocarbazole, 6-chloro-1,2,3,4-tetrahydrocarbazole, and 6-methoxy-1,2,3,4-tetrahydrocarbazole (8 pages). Ordering information is given on any current masthead page.

Regiocontrolled Opening of Cyclic Ethers Using Dimethylboron Bromide

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The cleavage of various cyclic ethers (3- to 7-membered rings) was achieved under very mild conditions using dimethylboron bromide to afford the corresponding bromo alcohols. In particular, 2-substituted tetrahydrofurans were regioselectively cleaved by a predominantly S_N2-type mechanism favoring the formation of primary vs. secondary bromides. Dimethylboron bromide also cleaved chemoselectively substituted tetrahydrofurans in the presence of functional groups such as acyclic ethers, silyl ethers, esters, amides, ketones, etc.

We have reported previously on the synthetic utility of organoboron bromide reagents such as dimethylboron bromide (Me_2BBr) in the transformation of functional groups. Examples include the regeneration (i) of parent alcohols from alkyl, benzyl, MEM, MOM, and MTM ethers,[1,2] (ii) of aldehydes and ketones from their corresponding acetals and ketals,[2] (iii) of diols from their acetonides,[2] and (iv) of sulfides from sulfoxides.[3] α-Bromo ethers obtained under aprotic conditions from acetals treated with Me_2BBr have also served as useful intermediates for the synthesis of thioglycosides,[4] cyanomethyl ethers,[4] and hemithioacetals.[4]

We have also recently described the synthesis of optically active 1,3-diols and commented on their usefulness as precursors in the synthesis of natural products.[5] Our approach to the syntheses of these 1,3-diols was based on the stereocontrolled preparation of optically active 4-hydroxytetrahydrofuran derivatives followed by a regiocontrolled opening of the newly formed heterocycle by dimethylboron bromide.

Our interest in Me_2BBr arose from its tendency to cleave a C–O bond in a S_N2 fashion,[1] in contrast to other reagents such as BBr_3. This was illustrated by the treatment of 2-methyltetrahydrofuran with Me_2BBr, which led predominantly to 5-bromo-2-pentanol.[1]

We are reporting, herein, on an expanded study of the opening of cyclic ethers with Me_2BBr. The scope and limitations of this reagent in these reactions are discussed.

Results and Discussion

I. Cleavage of Symmetrical Cyclic Ethers. We have found that dimethylboron bromide reacts with simple cyclic ethers of various ring sizes to give the corresponding bromo alcohols in excellent yield, as summarized in Table I.

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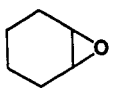
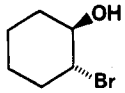
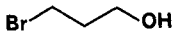
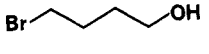
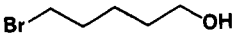
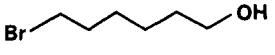
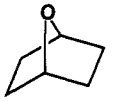
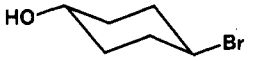
(1) Guindon, Y.; Yoakim, C.; Morton, H. E. *Tetrahedron Lett.* **1983**, *24*, 2969.
(2) (a) Guindon, Y.; Morton, H. E.; Yoakim, C. *Tetrahedron Lett.* **1983**, *24*, 3969. (b) Guindon, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 3912.
(3) Guindon, Y.; Atkinson, J. G.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 4538.
(4) Morton, H. E.; Guindon, Y. *J. Org. Chem.* **1985**, *50*, 5379.
(5) (a) Lactone portion of compactin: Guindon, Y.; Yoakim, C.; Bernstein, M. A.; Morton, H. E. *Tetrahedron Lett.* **1985**, *26*, 1185. (b) (1*R*,3*R*,5*S*)-*endo*-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane: Guindon, Y.; St-Denis, Y.; Daigneault, S.; Morton, H. E. *Tetrahedron Lett.* **1986**, *27*, 1237.

0022-3263/87/1952-1680$01.50/0

Table I. Cleavage of Symmetrical Cyclic Ethers[a]

entry	substrate	product[b]	T, °C	reactn time, h	yield,[c] %
1	 1	 2	−78	0.25	90
2	 3	 4	0	2	78
3	 5	 6	0	2	100
4	 7	 8	25	18	93
5	 9	 10	0	2	75
6	 11	 12[d]	0	4	85

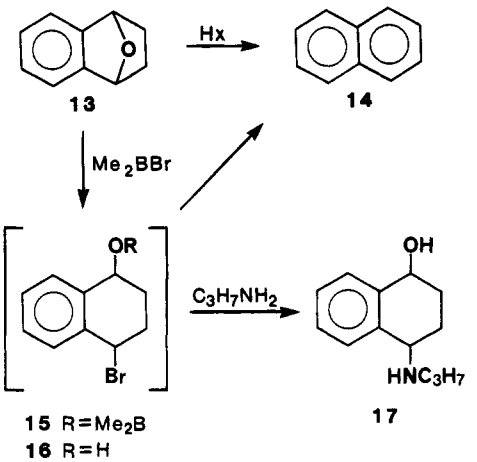
[a] All reactions were carried out at a concentration of 0.2 M using 2.2 equiv of Me_2BBr and 0.2 equiv of Et_3N in CH_2Cl_2. [b] All products were identified by comparison with authentic material. [c] Isolated yield. [d] The 3,5-dinitrobenzoate derivative of **12** was prepared and compared with an authentic material, mp 163–164 °C (lit. mp 164–165 °C).

Thus, upon treatment with Me_2BBr, cyclohexene oxide **1** (entry 1) is cleaved at −78 °C to afford the corresponding *trans*-halohydrin **2**, in excellent yield (90%). Oxetane (**3**), tetrahydrofuran (**5**), and oxepane (**9**) representative of 4-, 5-, and 7-membered ring cyclic ethers (entries 2, 3, and 5) are cleaved at 0 °C within 2 h to give the corresponding bromo alcohols in excellent yield. Tetrahydropyran (**7**), in contrast, required 18 h at room temperature to yield 5-bromo-1-pentanol in 93% yield (entry 4).[6]

It is interesting to note that treatment of the bicyclic ether 7-oxabicyclo[2.2.1]heptane (**11**) with Me_2BBr for 4 h at 0 °C led to the *trans*-4-bromocyclohexanol (**12**). In contrast, aqueous HBr treatment of **11** was reported to afford a cis and trans mixture of **12** after 6 days at 50 °C.[7]

The use of Me_2BBr in aprotic conditions also permits advantage to be taken of otherwise unstable intermediates for synthetic purposes. It was reported, for instance, that 1,4-epoxy-1,2,3,4-tetrahydronaphthalene (**13**) is converted under protic acidic conditions to naphthalene (**14**)[9] (Scheme I). In contrast, treatment of **13** with Me_2BBr would be expected to lead to the boronate ether **15**, which could be used as a substrate for other reactions such as nucleophilic displacement. Hence, treatment of **13** with Me_2BBr followed by addition of propylamine to the reaction mixture led to the formation of the 1,4-disubstituted tetrahydronaphthalene **17** in 69% yield.[8] Moreover, quenching the solution of the boronate **15** with aqueous sodium bicarbonate solution has allowed isolation and characterization by H^1 NMR of the unstable bromo alcohol **16**. This compound on standing was converted into naphthalene (**14**).

Scheme I



II. Cleavage of Unsymmetrical Epoxides. Dimethylboron bromide reacts at −78 °C with primary, secondary, tertiary, and benzylic epoxides to give the corresponding bromohydrins in excellent yield.[10] The results are summarized in Table II. As illustrated in entries 1, 2, and 4 (Table II) the products obtained arose

(6) (a) Tetrahydropyran was reported to be stable upon treatment with refluxing Me_3SiBr for 7 days.[6b] (b) Kricheldorf, H. R.; Morber, G.; Regel, W. *Synthesis* **1981**, 383.

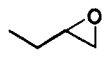
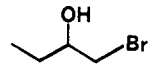
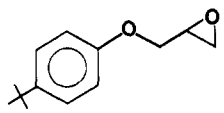
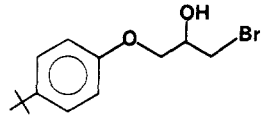
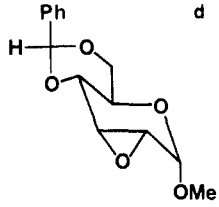
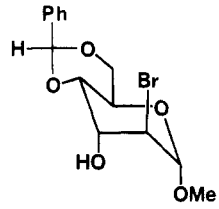
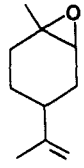
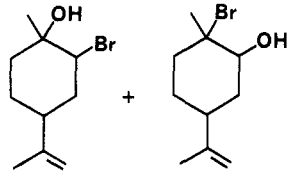
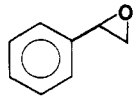
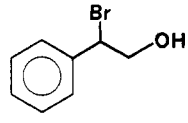
(7) Noyce, D. S.; Bastian, B. N.; Lau, P. T. S.; Monson, R. S.; Weinstein, B. *J. Org. Chem.* **1969**, *34*, 1247.

(8) For another example see: Adams, J.; Belley, M. *J. Org. Chem.* **1986**, *51*, 3878.

(9) Wittig, G.; Pohmer, L. *Chem. Ber.* **1956**, *89*, 1334.

(10) (a) Concurrently with the completion of this work, $(Me_2N)_2BBr$ was reported to transform epoxides to bromohydrins: Bell, T. W.; Ciaccio, J. A. *Tetrahedron Lett.* **1986**, *27*, 827. (b) Silicon halides have also been used for the preparation of halohydrins. See for example ref 6 and: Andrews, G. C.; Crawford, T. C.; Contillo, L. G. *Tetrahedron Lett.* **1981**, *22*, 3803 and references cited therein.

Table II. Opening of Unsymmetrical Epoxides[a]

entry	substrate	product[b]	yield,[c] %
1	 **18**	 **19**	70
2	 **20**	 **21**	98
3	 **22** d	 **23**	93
4	 **24**	 **25** + **26** **(25/26 4:1)**[e]	89
5	 **27**	 **28**	96

[a] All reactions were carried out at −78 °C for 15 min at a concentration of 0.1 M using 2.2 equiv of dimethylboron bromide and 0.2 equiv of Et_3N in CH_2Cl_2. [b] Known products were identified by comparison with authentic material. New products exhibited spectral properties consistent with assigned structures and gave satisfactory combustion analysis. [c] Isolated yield. [d] Reaction was carried out at a concentration of 0.05 M in a mixture of CH_2Cl_2/THF (1/1) for 45 min. [e] The ratio of products was determined by ^1H NMR analysis.

from the attack of the bromide on the less hindered side of the epoxide. These results are in accord with the propensity of Me_2BBr to cleave a C–O bond through an S_N2-type mechanism.

The regioselectivity observed in the opening of the epoxide **22** is explained by the attack of the bromide on C-2, this position permitting the favored trans-diaxial opening of the epoxide. It is also important to note that this reaction was carried out with tetrahydrofuran as cosolvent to diminish the reactivity of dimethylboron bromide, thus allowing selective cleavage of the epoxide functionality in the presence of the cyclic acetal as well as the benzylidene group which would have been cleaved at −78 °C in methylene chloride.

However, in the case of a benzylic epoxide (entry 5) dimethylboron bromide reacts by following an apparent S_N1-type mechanism, the bromide adding at the benzylic position.

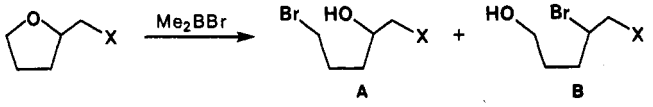
III. Cleavage of Unsymmetrical Tetrahydrofurans. There has been very little work done on the cleavage of substituted tetrahydrofurans. Thus, 2-methyltetrahydrofuran has been opened with $MgBr_2/Ac_2O$,[11] $RCOCl/Pd^{II}/R'_3SnX$,[12] $RCOCl/Pt^{II}$,[13] and BBr_3[14] to give in all cases specifically or predominantly the secondary chlorides or bromides. However, during the preparation of this paper, this opening was also reported to yield selectively the primary halides with $(C_4H_9)_4N^+Br^-$ or I^-/BF_3 etherate.[15] This last work was also limited to the opening of 2-methyltetrahydrofuran.

The regiocontrolled opening of unsymmetrical tetrahydrofuran derivatives bearing at least one substituent at position 2 of the heterocycle has been investigated in some detail in the present work. A number of tetrahydrofurans were selected in order to establish the relative importance of factors that could have an impact on the regiocontrol of the opening: (a) steric factors; (b) intramolecular coordination of the Lewis acid to neighboring functionalities (neighboring orientation effect).

We have shown previously that 2-methyltetrahydrofuran (entry 1, Table III) is opened at 0 °C by Me_2BBr to give a 3.5/1 ratio of primary vs. secondary bromides,[1] respectively. Knowing the sensitivity of Me_2BBr to steric factors in the context of the cleavage of acetals,[2b] we have also investigated these effects on the opening of the tetrahydrofuran ring. This study was performed on furfuryl alcohol derivatives bearing substituents of varying sizes, and the results are given in Table III. A better regiocontrolled opening of the tetrahydrofuran ring, from the less hindered side, was seen with increasing bulkiness of

(11) Goldsmith, D. J.; Kennedy, E.; Campbell, R. G. *J. Org. Chem.* **1975**, *40*, 3571.
(12) Pri-Bar, I.; Stille, J. K. *J. Org. Chem.* **1982**, *47*, 1215.
(13) Fitch, J. W.; Payne, W. G.; Westmoreland, D. *J. Org. Chem.* **1983**, *48*, 751.
(14) Kulkarni, S. V.; Patil, V. D. *Heterocycles* **1982**, *18*, 163.
(15) Yadav, V. K.; Fallis, A. G. *J. Org. Chem.* **1986**, *51*, 3372.

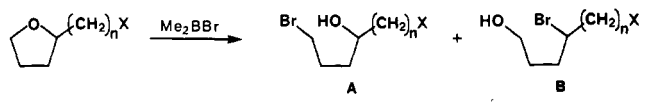
Table III. Opening of 2-Substituted Tetrahydrofurans[a]



entry	substrate (X), compd	products A	products B	ratio A/B[b]	yield,[c] %
1	H, **29**	**30**	**31**	3.5/1	83
2	OMe, **32**	**33**	**34**	4/1	87
3	OEt, **35**	**36**	**37**	9/1	94
4	*O*-*i*-Pr **38**	**39**	**40**	20/1	95
5	*O*-*t*-BDPSi,[d] **41**	**42**[e]	**43**	>25/1	88
6	$(CH_2)_2$-*O*-*t*-BDPSi, **44**	**45**	**46**	5/1	90

[a] All reactions were carried out at 0 °C at a concentration of 0.2 M using 2.2 equiv of Me_2BBr and 0.2 equiv of Et_3N in CH_2Cl_2. [b] The ratio was determined by ^1H NMR analysis of the reaction mixture. When only one isomer was detected, the ratio >25/1 was used. [c] Isolated yield of the isomeric mixture. [d] *O*-*t*-BDPSi = (*tert*-butyldiphenylsilyl)oxy. [e] The product was characterized as its acetate by ^1H NMR.

Table IV. Opening of 2-Substituted Tetrahydrofurans[a]



entry	substrate (X), compd (*n*)	products A	products B	ratio A/B[b]	yield,[c] %
1	OMe, **32** (1)	**33**	**34**	4/1	87
2	OMe, **47** (2)	**48**	**49**	>25/1	84
3	OMe, **50** (3)	**51**[d]	**52**[d]	4/1	70
4	CO_2Et, **53** (0)	**54**	**55**	>25/1	82
5	CO_2Et, **56** (1)	**57**	**58**	>25/1	85
6	CO_2Et, **59** (2)	**60**	**61**	9/1	92
7	CO_2Et, **62** (3)	**63**	**64**	4/1	90

[a] All reactions were carried out at 0 °C for 2 h at a concentration of 0.2 M, using 2.2 equiv of Me_2BBr and 0.2 equiv of Et_3N in CH_2Cl_2. [b] The ratio was determined by ^1H NMR analysis of the reaction mixture. [c] Isolated yield of the isomeric mixture. [d] The product was characterized as its acetate by ^1H NMR.

the group attached to the methylene group at C-2 of the tetrahydrofuran structure.

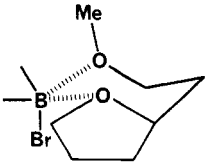
As illustrated in entries 2–5, Table III, the ratio of primary over secondary bromides increased from 4/1 for the methoxy to >25/1 for (*tert*-butyldiphenylsilyl)oxy group. Conversely, the relative preponderance of the primary bromide decreased as the distance between the bulky group and the reactive site increased (a ratio of >25/1 for **41** as opposed to 5/1 for **44**). The chemoselectivity obtained is also noteworthy. Indeed, the acyclic ethers [e.g., methoxy in **32**, entry 2 (Table III), and in **47** and **50**, entries 2 and 3 (Table IV)] were not cleaved under these reaction conditions. This difference of reactivity may be explained by the greater basicity[16] of the intracyclic oxygen in the tetrahydrofuran structure over the one involved in a methoxy functionality. This also suggests that the product-determining step in these openings is the activation of the oxygen as opposed to the nucleophilic attack of the bromide in the context of a presumed ionic mechanism. Once the more basic ring oxygen has complexed with dimethylboron bromide, cleavage then takes place by an S_N2-type attack of bromide at the less hindered site.

Semiempirical molecular orbital calculations (CNDO) were performed to determine the net atomic charges at the atoms and, hence, their relative basicities. We concern ourselves with oxygen atoms only because this is relevant to Lewis acid attack under nonsolvating conditions. Molecular conformations were minimized by molecular mechanics (MM2) procedures prior to submission for CDNO molecular orbital calculations. The oxygen of tetrahydrofuran was calculated as having a net atomic charge of 0.2559–, whereas methyl *n*-propyl ether has 0.2426–. A simple *C*-furanoside, 2-(methoxymethyl)tetrahydrofuran (**32**), afforded a value of 0.2676– for the ring oxygen and 0.2399– for the exocyclic oxygen. These calculations substantiate chemical evidence for the ring oxygen being more basic in these systems.

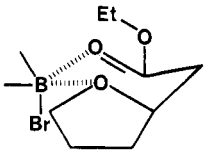
The influence of neighboring functionalities that could coordinate with Me_2BBr was then examined. This study was performed on a series of tetrahydrofurans substituted in position 2 with an alkyl chain bearing either a terminal alkoxy or a carbethoxy group. The results are summarized in Table IV. Improved regiocontrol was observed (see entries 2 and 5) in the opening of the tetrahydrofurans, which allowed the formation of a putative 6-membered ring complex, involving the Lewis acid with the ring oxygen and the methoxy, as in **47a** or the carbethoxy as in **56a**. The length of the chain bearing the methoxy or carbethoxy functionality significantly altered the regiocontrol of the opening as illustrated in entries 1 and 3 (for methoxy) and 6 and 7 (for carbethoxy).

Thus, the extent of the regiocontrol in the opening of tetrahydrofurans can be affected by both steric factors and the electronic properties of an adjacent functionality (neighboring orienting functionality).

The regiospecific opening observed for the 2-carbethoxytetrahydrofuran **53** (entry 4) resulted from the destabilization of a potential carbocation α to the carboxylate rather than the two factors cited above. It is also of considerable synthetic interest that in the cleavage of **56** (entry 5) no β-elimination of the hydroxyl group was detected.



47a



56a

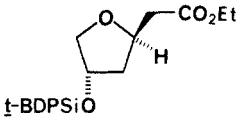
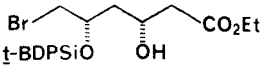
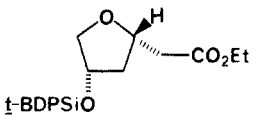
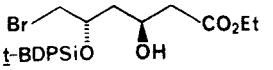
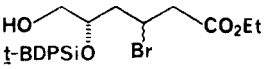
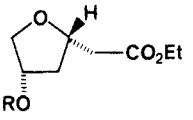
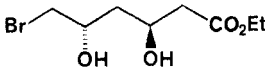
These "directing" factors are sometimes opposed with regard to their influence on the opening of the cycle. A representative example of this scenario is illustrated in Table V in entries 1 and 2, whereas two 2,4-disubstituted tetrahydrofurans possessing a trans (**65**) or cis (**67**) relationship[17] between their substituants showed a significant difference of reactivity and regioselectivity when treated with Me_2BBr. On the one hand, the β-*C*-glycoside **65** (trans) reacted with Me_2BBr at 0 °C within 2 h to give in an excellent yield the primary bromide **66**[18] as the only product of the reaction. The presence of a carbethoxy functionality in a position that permits the desired orienting effect, combined with the intrinsic property of Me_2BBr to react in an S_N2 fashion, led to the observed regiospecific opening of the ring.

(16) Some pK_a measurements have been reported for acyclic and cyclic ethers: diethyl ether, –3.59; dimethyl ether, –3.83; tetrahydrofuran, –2.08; 2-methyltetrahydrofuran, –2.65. See: Arnett, E. M.; Wu, C. Y. *J. Am. Chem. Soc.* **1962**, *84*, 1684.

(17) The assignment of relative stereochemistry was based on NMR-based analysis; see: Bernstein, M. A.; Morton, H. E.; Guindon, Y. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1155.

(18) The chemical and stereochemical integrity of the bromide **66** was confirmed by transforming it to a known analogue of a natural product; see ref 5a.

Table V. Opening of Disubstituted Tetrahydrofurans[a]

entry	substrate	temp, °C (time, h)[b]	products	yield,[c] %
1	 **65**	0 (2)	 **66**	82
2	 **67**	25 (18)	 **68**	33
			 **69**	12
3	 **70** R=H **71** R=Me_2B	0 (3)	 **72**	90

[a] The reactions were carried out at a concentration of 0.2 M using 2.2 equiv of Me_2BBr and 0.2 equiv of Et_3N in CH_2Cl_2. In entry 3, 4.0 equiv of Me_2BBr and 1.1 equiv of Et_3N were used. [b] Reaction time corresponds to the disappearance of the starting material. [c] Isolated yields.

In contrast, the results obtained in the opening of the α-*C*-glycoside **67** (entry 2) were very different, the reaction had to be performed at room temperature for 18 h, and a significant amount (25%) of the product obtained was the secondary bromide **69**. Presumably, the orienting effect of the carbethoxy functionality on the α-face of the molecule **67** was counterbalanced by the presence of a bulky substituent in a cis relationship, the (*tert*-butyldiphenylsilyl)oxy group possibly disrupting the formation of cyclic coordinated intermediate structure as proposed in **56a**. This explanation would be supported if a decrease of the substituent size at C-4 of the tetrahydrofuran would favor the primary bromide.

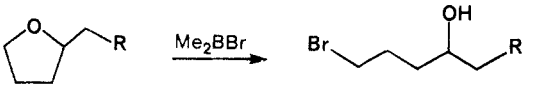
This hypothesis was confirmed by the opening of the secondary alcohol **70** with Me_2BBr (3.0 equiv) in the presence of Et_3N (1.1 equiv), which led to the primary bromide **72** in a ratio greater than 25/1. In the course of this reaction, the secondary alcohol **70** would have been transformed to the boronate **71**. This boronate, being a sterically less demanding group then the *tert*-butyldiphenylsilyl ether, did not interfere with the progression of the reaction and allowed the expression of the orienting effect of the carbethoxy functionality.

IV. Chemoselectivity. The chemoselectivity observed in the present work is of synthetic interest. As already discussed, the epoxide was opened in the presence of cyclic acetal and benzylidene groups (Table II, entry 3) and tetrahydrofurans were cleaved in the presence of other functionalities such as silyl ethers (Table III, entry 5; Table IV, entries 1 and 2), acyclic ethers (see Table IV, entries 2–4), and esters[19] (Table V).

Moreover, other functionalities could be present within the molecule without being altered by the reaction condition, and a few examples are presented in Table VI. Unsymmetrical tetrahydrofurans bearing acetates (entry 1), tosylates (entry 2), acetamides (entry 3), and a ketone (entry 4) were cleaved by dimethylboron bromide with complete regioselectivity (>25/1) with no concurrent modification of the other functionalities present.

(19) In some cases, methyl esters may be cleaved by Me_2BBr at room temperature. Ethyl esters are stable to Me_2BBr under the conditions studied.

Table VI. Chemoselectivity in Opening 2-Substituted Tetrahydrofurans[a]



entry	substrate (R), compd	product[b]	yield,[c] %
1	OAc, **73**	**74**	83
2	OTs, **75**	**76**	93
3	NHCOPh,[d] **77**	**78**	87
4	COMe, **79**	**80**	80

[a] All reactions were carried out at 0 °C for 2 h at a concentration of 0.2 M using 2.2 equiv of Me_2BBr and 0.2 equiv of Et_3N in CH_2Cl_2. [b] Only the primary bromide derivatives were observed by ^1H NMR analysis. [c] Isolated yield. [d] Reaction time was 3 h.

Conclusion

In summary, dimethylboron bromide is a very mild and efficient reagent for the cleavage of cyclic ethers. In particular, tetrahydrofurans substituted at the 2-position react in a predictable fashion by a predominently S_N2-type mechanism, giving rise to primary bromides. In this series, the nature of the substituents has a quantitative influence on the outcome of the reaction via steric factors and/or the presence of other complexing functionalities.

Moreover, the chemoselectivity of dimethylboron bromide should be of considerable utility since a wide range of functional groups elsewhere in the molecule are unaffected.

Experimental Section

General Procedures. Melting points are uncorrected. Infrared (IR) spectra were taken on a Perkin-Elmer Model 681 spectrophotometer. Proton nuclear magnetic resonance (^1H NMR) spectra were obtained by using a Varian EM 90 or a Bruker AM 250. In all instances, tetramethylsilane was used as a reference. Mass spectrometric measurements were performed by Morgan Schaffer, Montreal, Quebec, using a Hitachi Perkin-Elmer RMU-6D mass spectrometer. Elemental analyses were performed by Guelph Chemical Laboratories Ltd., Guelph, Ontario, or

Galbraith Laboratories Inc., Knoxville, TN. Flash chromatography was accomplished with use of 230–400-mesh silica gel (E. Merck) according to the procedure developed by Still et al.[20] Preparative TLC was performed with silica gel GF (Analtech). The purity of known compounds was ascertained by TLC using commercial silica gel plates (Analtech, Uniplate-Silica Gel GF) and spectral means (IR, ^1H NMR).

All reactions were carried out under an inert atmosphere of argon. Glassware and syringes were dried in an oven (120 °C) prior to use. Chlorinated solvents as well as triethylamine were distilled from CaH_2 and stored over 4A molecular sieves. THF was used as purchased (Aldrich Chemical Co., Gold Label).

Dimethylboron bromide was purchased from the Alfa Division of Ventron Corp. or prepared from tetrabutyltin and boron tribromide.[2b] Care should be taken in manipulating neat dimethylboron bromide: it is *pyrophoric* when exposed to moist air. Solutions of these reagents were prepared in dry CH_2Cl_2 (1.5–2.0 M) and could be stored at −15 °C for several months without noticeable decomposition. Starting materials were obtained from Aldrich Chemical Co. or prepared under standard conditions.

Representative Procedure for the Cleavage of Symmetrical Cyclic Ethers 1, 3, 5, 7, 9, and 11. Cleavage of Cyclohexene Oxide (1). To a cold (−78 °C), stirred solution of the epoxide 1 (98 mg, 1 mmol) in 4 mL of dry methylene chloride were added successively triethylamine (0.025 mL, 0.2 mmol) and a solution of dimethylboron bromide (1.56 M, 1.3 mL) in methylene chloride. After 15 min at −78 °C the reaction mixture was cannulated into a vigorously stirred solution of saturated aqueous sodium bicarbonate (10 mL). The organic layer was decanted and the aqueous layer extracted with methylene chloride (10 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and evaporated to dryness. The oily residue was coevaporated with methanol to hydrolyze traces of boronate of final product observed in the crude material, affording trans 2-bromocyclohexanol in 90% yield: IR 3400 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 1.0–2.5 (m, 8 H, $(CH_2)_4$), 2.6 (s, 1 H, OH, D_2O exchangeable), 3.4–3.75 (m, 1 H, *CH*OH), 3.75–4.1 (dq, 1 H, CHBr); mass spectrum, *m/e* 180 (Br = 81, M^+).

Cleavage of symmetrical cyclic ethers **3**, **5**, **7**, **9**, and **11** was similarly performed. Reaction times, temperatures, and yields are reported in Table I.

Cleavage of 1,4-Epoxy-1,2,3,4-tetrahydronaphthalene (13). To a cold (0 °C) stirred solution of **13** (200 mg, 1.5 mmol) in 6 mL of dry methylene chloride was added triethylamine (0.022 mL) followed by dropwise addition of a solution of dimethylboron bromide (1.56 M, 1.05 mL) in methylene chloride. The resulting solution was stirred for 15 min at 0 °C and quenched as described below for the formation of the bromo alcohol **16** or the amino alcohol **17**.

(A) Bromo Alcohol 16. The reaction mixture was poured over a stirred solution of sodium bicarbonate and extracted with ether. The organic layer was washed with brine (2×), dried over sodium sulfate, filtered, and evaporated to dryness. There was obtained as an oil 318 mg (93%) of the bromo alcohol **16**: ^1H NMR ($CDCl_3$) δ 1.04–2.60 (m, 4 H, $(CH_2)_2$), 3.74 (s, 1 H, OH), 4.85 (br s, 1 H, CHBr), 5.60 (m, 1 H, *CH*OH), 7.27–7.59 (m, 4 H, Ar).

(B) Amino Alcohol 17. Propylamine (0.49 mL, 6 mmol) was added to the reaction mixture and the ice bath removed. The solution was stirred at 25 °C for 5 h. The reaction mixture was then poured over 1 N HCl, the aqueous layer was washed with ether, than basified with 2 N NaOH, and extracted with ether, and the organic layer was washed with brine (2×). After drying over sodium sulfate, the ether was evaporated to dryness, giving 213 mg (69%) of the amino alcohol **17** as an oil: IR (neat) 3350 cm^{-1} (OH, NH); ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, CH_3), 1.46 (m, 2 H, CH_2CH_3), 1.76–2.70 (m, 6 H, $(CH_2)_2$, CH_2NH), 3.40 (s, 2 H, NH, OH), 3.87 (m, 1 H, CHN), 4.66 (m, 1 H, *CH*OH), 7.80 (m, 4 H, Ar). Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.96; H, 9.78; N, 6.79.

Representative Procedure for the Cleavage of Unsymmetrical Epoxides 18, 20, 24, and 27. Cleavage of (+)-Limonene Oxide (24). To a cold (−78 °C), stirred solution of a (+)-limonene oxide (**24**) mixture of cis and trans (152 mg, 1 mmol) in 9 mL of dry methylene chloride were added successively triethylamine (0.025 mL, 0.2 mmol) and a solution of dimethylboron bromide (1.56 M, 1.3 mL) in methylene chloride. After 15 min at −78 °C the reaction mixture was cannulated into a vigorously stirred solution of saturated aqueous sodium bicarbonate (10 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and evaporated to dryness. The resulting oily residue was shown to be a mixture of the final products **25** and **26** in a 4/1 ratio by ^1H NMR analysis. The two components were separated by preparative TLC, eluting with ethyl acetate/hexane (1/9). There was obtained, as the less polar compound, 30 mg (13%) of the bromo alcohol **26** as an oil of which the expected cis/trans isomers were distinguishable by ^1H NMR [($CDCl_3$) δ 1.73 (s, 3 H, CH_3), 1.75 (s, 3 H, $CH_2{=}CCH_3$), 1.3–2.43 (m, 7 H), 2.45 (d, 1 H, OH, D_2O exchangeable), 4.00 and 4.05 (2 dd, 1 H, *CH*OH, appears as 2 doublets on D_2O exchange), 4.72 (2 s, 2 H, $C{=}CH_2$)] and 160 mg (69%) of the more polar bromo alcohol **25** as an oil of which the cis/trans isomers were also distinguishable by ^1H NMR [($CDCl_3$) δ 1.43 and 1.84 (2 s, 3 H, CH_3), 1.74 (s, 3 H, $CH_2{=}CCH_3$), 1.5–2.6 (m, 8 H), 4.07 and 4.20 (2 br s, 1 H, CHBr), 4.76 (br s, 2 H, $C{=}CH_2$)]. Anal. Calcd for $C_{10}H_{17}BrO$: C, 51.51; H, 7.35; Br, 34.27. Found: C, 51.93; H, 7.47; Br, 34.07.

Cleavage of unsymmetrical epoxides **18**, **20**, and **27** was similarly performed, and yields are reported in Table II.

Cleavage of Epoxide 22. To a cold (−78 °C), stirred solution of epoxide **22**[21] (132 mg, 0.5 mmol) in a mixture of dry methylene chloride/tetrahydrofuran (1/1) (9 mL) was added successively triethylamine (0.015 mL, 0.12 mmol) and a solution of dimethylboron bromide (1.56 M, 0.65 mL) in methylene chloride. After 45 min at −78 °C the reaction mixture was cannulated into a vigorously stirred solution of saturated aqueous sodium bicarbonate (10 mL). The organic layer was decanted and the aqueous layer extracted with methylene chloride (10 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and evaporated to dryness. The semisolid residue was triturated with minimum amount of ether (3 mL) and filtered, affording 15 mg (11%) of recovered starting material. The filtrate was evaporated to dryness and the residue triturated with hexane and filtered to afford 142 mg (93% based on starting material consumed) of the bromo alcohol **23**: mp 110–113 °C; IR (KBr) 3485 cm^{-1} (OH); ^1H NMR (Me_2SO-d_6) δ 3.36 (s, 3 H, OCH_3), 3.76 (m, 1 H, HC*H*), 4.1–4.3 (m, 5 H, H_2, H_3, H_4, H_5, *H*CH), 4.88 (s, 1 H, H_1), 5.6 (d, 1 H, OH), 5.74 (s, 1 H, ArC*H*), 7.3–7.5 (m, 5 H, Ar); mass spectrum, *m/e* 346 (Br = 81, M^+).

An analytical sample was purified on preparative TLC, eluting with ethyl acetate/hexane (1/3); mp 116–117 °C. Anal. Calcd for $C_{14}H_{17}BrO_5$: C, 48.71; H, 4.97; Br, 23.15. Found: C, 48.51; H, 4.85; Br, 22.85.

Representative Procedure for the Cleavage of 2-Substituted Tetrahydrofurans 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62, 73, 75, and 79 and of Disubstituted Tetrahydrofuran 65. Cleavage of 2-(Methoxymethyl)tetrahydrofuran (32). To a cold (0 °C) stirred solution of the 2-(methoxymethyl)tetrahydrofuran (**32**; 350 mg, 3 mmol) in dry methylene chloride (12 mL) and triethylamine (0.06 mL) was added dropwise a solution of dimethylboron bromide (1.56 M, 3.84 mL, 6 mmol) in methylene chloride. The solution was stirred for 2 h at 0 °C. The reaction mixture was poured over a stirred saturated solution of sodium bicarbonate and extracted with ether. The organic layer was washed with brine (2×), dried over sodium sulfate, filtered, and evaporated to dryness. The resulting oily residue was shown to be a mixture of the final products **33** and **34** in a 4/1 ratio by ^1H NMR analysis. The two compounds were separated by flash chromatography using 15% ethyl acetate/hexane. Bromo alcohol **33**: oil; 401 mg (65%); IR (neat) 3400 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 1.30–2.20 (m, 4 H, $(CH_2)_2$), 2.34 (s, 1 H, OH), 3.26 (dd, 2 H, HC*H*OCH$_3$), 3.40 (s, 3 H, OCH_3), 3.48 (m, 2 H, *H*CHOMe, CH_2Br), 3.84 (m, 1 H, *CH*OH). Anal. Calcd for C, 36.57, H, 6.65. Found: C, 36.53; H, 6.52. More polar bromo alcohol **34**: oil; 97 mg (16%); IR (neat) 3400 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 1.44 (s, 1 H, OH), 1.64–2.14 (m, 4 H, $(CH_2)_2$), 3.40 (s, 3 H, OCH_3), 3.64 (t, 2 H, CH_2OH), 3.73 (m, 2 H, CH_2OCH_3), 4.14 (m, 1 H, CHBr). Anal.

(20) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(21) Wiggins, L. F. *Methods in Carbohydrate Chemistry*; Whistlre, R. L., Wolfrom, M. L., Eds.; Academic: New York, 1963; Vol. II, p 188.

Calcd for $C_6H_{13}BrO_2$: C, 36.57; H, 6.65. Found: C, 36.21; H, 6.48.

Cleavage of the 2-substituted tetrahydrofurans **29**, **35**, **38**, **41**, and **44** was similarly performed, and yields are reported in Table III. Similarly, yields of the opening of the 2-substituted tetrahydrofurans **47**, **50**, **53**, **56**, **59**, and **62** are reported in Table IV whereas for the disubstituted tetrahydrofuran **65** the yield is reported in Table V. For the cleavage of the other monosubstituted tetrahydrofurans **73**, **75**, and **79** yields are reported in Table VI.

Cleavage of Disubstituted Tetrahydrofuran 67. To a cold (0 °C) solution of the disubstituted tetrahydrofuran **67**[5] (100 mg, 0.24 mmol) in 1.6 mL of dry methylene chloride and triethylamine (0.003 mL, 0.025 mmol) was added dropwise a solution of dimethylboron bromide (1.56 M, 0.41 mL). The ice bath was removed and the solution stirred at room temperature for 18 h. The reaction mixture was poured over a stirred solution of saturated sodium bicarbonate and extracted with ether. The organic layer was washed with brine (2×), dried with sodium sulfate, filtered, and evaporated to dryness. The two compounds were separated by flash chromatography using 10% ethyl acetate/hexane, affording 38 mg (33%) of the bromo alcohol **68** as an oil [^{1}H NMR ($CDCl_3$) δ 1.08 (s, 9 H, *t*-Bu), 1.28 (t, 3 H, CH_3), 1.77 (m, 2 H, CH_2), 2.40 (d, 2 H, CH_2COOEt), 2.79 (d, 1 H, OH, D_2O exchangeable), 3.20 (dd, 2 H, CH_2Br), 3.36 (dd, 1 H, CH_2Br), 4.16 (q, 2 H, OCH_2CH_3), 4.10–4.40 (m, 2 H, CHOH, CHOSi), 7.38–7.74 (m, 10 H, Ar)] and 15 mg (13%) of the more polar bromo alcohol **69** as an oil of which the diastereoisomers are distinguishable by ^{1}H NMR [($CDCl_3$) δ 1.10 (s, 9 H, *t*-Bu), 1.27 (t, 3 H, CH_3), 1.86 (br t, 1 H, OH, D_2O exchangeable), 1.90–2.00 (m, 2 H, CH_2), 2.71 and 2.86 (2 m, 2 H, CH_2COOEt), 3.44–3.58 (m, 2 H, CH_2OH, which appears as 2 ddd on D_2O exchange), 4.02 (m, 1 H, CH), 4.17 (q, 2 H, OCH_2CH_3), 4.24 and 4.58 (m, 1 H, CH), 7.36–7.80 (m, 10 H, Ar)].

Cleavage of Disubstituted Tetrahydrofuran 70. To a cold (0 °C) solution of the disubstituted tetrahydrofuran **70** (71 mg, 0.41 mmol) in dry methylene chloride (1.6 mL) and triethylamine (0.066 mL, 0.48 mmol) was added, dropwise, a solution of dimethylboron bromide (1.56 M, 0.79 mL) in methylene chloride. After being stirred 3 h at 0 °C, the reaction mixture was poured over a stirred solution of saturated sodium bicarbonate and extracted with ether. The organic layer was washed with brine (2×), dried with Na_2SO_4, filtered, and evaporated to dryness, giving 94 mg (90%) of the crude bromo alcohol **71**: IR (neat), 3420 (OH), 1725 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3 H, CH_3), 1.74 (t, 2 H, CH_2), 2.51 (d, 2 H, CH_2COOEt), 3.48 (d, 2 H, CH_2Br), 3.08–3.70 (m, 2 H, 20 H), 4.17 (q, 2 H, OCH_2CH_3), 3.95–4.51 (m, 2 H, 2 CHOH).

Cleavage of 2-(Benzamidomethyl)tetrahydrofuran (77). To a cold (0 °C) stirred solution of 2-(benzamidomethyl)tetrahydrofuran (**77**) (205 mg, 1 mmol) in dry methylene chloride (4 mL) and triethylamine (0.16 mL, 1.15 mmol) was added dropwise a solution of dimethylboron bromide (1.56 M, 1.92 mL) in methylene chloride. The ice bath was then removed and the solution stirred 18 h at 25 °C. The solution was poured over a stirred solution of sodium bicarbonate and extracted with ether. The organic layer was washed with brine (2×), dried over sodium sulfate, filtered, and evaporated to dryness. The white solid residue was triturated in ether, filtered, and air-dried, giving 250 mg (87%) of the pure bromo alcohol **78**: mp 77–79 °C; IR (KBr) 3340 (OH, NH), 1640 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.57–1.79 (m, 2 H, CH_2), 1.92–2.18 (m, 2 H, CH_2), 3.00 (d, 1 H, OH), 3.38–3.46 (m, 1 H, CHNH), 3.49 (t, 2 H, CH_2Br), 3.64–3.74 (m, 1 H, CHNH), 3.83–3.95 (m, 1 H, CHOH), 6.66 (s, 1 H, NH), 7.42–7.82 (m, 5 H, Ar). Anal. Calcd for $C_{12}H_{16}BrNO_2$: C, 50.36; H, 5.64; Br, 27.92; N, 4.89. Found: C, 50.10; H, 5.69; Br, 28.07; N, 4.84.

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Supplementary Material Available: Spectral data of final products obtained by cleavage of unsymmetrical tetrahydrofuran derivatives (5 pages). Ordering information is given on any current masthead page.

Quassinoid Synthesis. 2. Preparation of a Tetracyclic Intermediate Having the Bruceantin Tetrahydrofuran Ring

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A synthetic approach to the quassinoid compound bruceantin is described. Tricyclic acid **5**, prepared from 2-(methoxycarbonyl)cyclohexanone in one step by the method of Fuchs, is converted into ketal lactone **6** and thence into diol **7**. The primary hydroxyl may be selectively protected to give any of several derivatives, including the tetrahydropyranyl derivative **10**. Allylic oxidation of this substance provides enone **13**, which is dehydrated by treatment with 4-(dimethylamino)pyridine in refluxing acetic anhydride to obtain **16**. Lithium/ammonia reduction of **16** yields saturated ketone **23**, which is carboxylated by the Stiles procedure to obtain the enolic β-keto ester **26**. This material is dehydrogenated to **28** by a novel procedure wherein the enol is heated with thionyl chloride and collidine in refluxing carbon tetrachloride. It is proposed that the dehydrogenation occurs by sulfenylation on carbon, followed by pyrolytic elimination of the resulting sulfenyl chloride (Scheme III). The elements of the eventual tetrahydropyranone ring are introduced at this stage by reaction of **28** with silyl ketene acetal **29** at high pressure. The product, enol silane **31**, is deprotected by treatment with pyridinium *p*-toluenesulfonate in warm ethanol to obtain **39**. Bromocyclization of this material upon treatment with *N*-bromosuccinimide in tetrahydrofuran affords bromo ether **40**, which rearranges to tetrahydrofuran **41** upon being heated at reflux in *N*,*N*-dimethylformamide solution. Deprotection of the latter material provides the β-keto ester **42**, a viable intermediate for a bruceantin synthesis.

The quassinoids, a group of related diterpenoids found in plants of the family *Simaroubacea*, possess a wide spectrum of biological activity.[1] One quassinoid that has elicited considerable medicinal[1] and synthetic[2] interest is

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