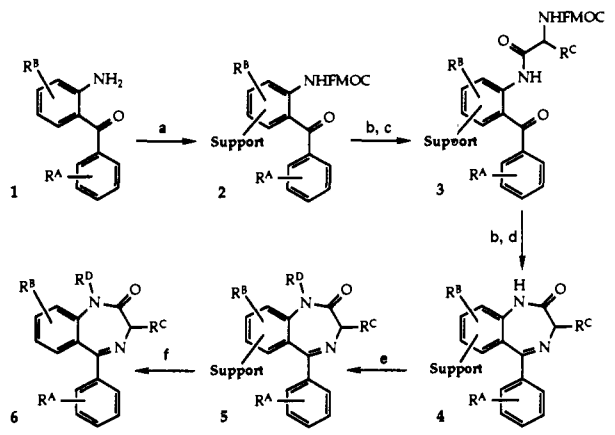
Scheme I[a]



[a] (a) See supplementary material; (b) 20% piperidine in DMF; (c) *N*-FMOC-amino acid fluoride, 4-methyl-2,6-di-*tert*-butylpyridine; (d) 5% acetic acid in DMF, 60 °C; (e) lithiated 5-(phenylmethyl)-2-oxazolidinone in THF, -78 °C, followed by alkylating agent and DMF; (f) TFA/H_2O/Me_2S (95:5:10).

Table I. 1,4-Benzodiazepine Derivatives **6** (Scheme I)

entry	derivative R^A	R^B	R^C	R^D	yield (%)[a]
6a	4'-OH	5-Cl	CH_3	H	95
6b	4'-OH	5-Cl	CH_3	CH_3	100
6c	4'-OH	5-Cl	CH_3	CH_2CH_3	97
6d	4'-OH	5-Cl	CH_3	CH_2CHCH_2	90
6e	4'-OH	5-Cl	$CH(CH_3)_2$	CH_2CH_3	85
6f	4'-OH	5-Cl	CH_2CO_2H	CH_2CH_3	95
6g	4'-OH	5-Cl	$(CH_2)_4NH_2$	CH_2CH_3	95
6h	4'-OH	5-Cl	$CH_2Ph(4\text{-}OH)$	CH_2CH_3	98
6i		4-CO_2H,5-Cl	CH_2Ph	CH_3	100
6j		4-CO_2H,5-Cl	CH_3	CH_2Ph	93

[a] Yields are based on support-bound starting material **2**.

The FMOC protecting group in **3** is then removed by treatment with piperidine in DMF. Exposure of the resulting free amine to 5% acetic acid in DMF provides the cyclic product **4**. Complete cyclization is observed in the synthesis of 1,4-benzodiazepine derivatives with various steric and electronic properties (Table I), again demonstrating that general conditions have been identified for the solid-phase synthesis of diverse benzodiazepine derivatives.

Alkylation of the anilide of **4** then provides the fully derivatized 1,4-benzodiazepine **5** (Scheme I). Ideally, an excess of the base would be employed to achieve complete deprotonation and alkylation of the anilide, but employment of excess of commonly used bases such as LDA or NaH would result in deprotonation and subsequent alkylation of acidic functionality present elsewhere in the molecule. To maximize synthesis generality we therefore chose to employ lithiated 5-(phenylmethyl)-2-oxazolidinone[8] as the base since it is basic enough to completely deprotonate the anilide of **4**, but not basic enough to deprotonate amide, carbamate, or ester functionalities. Upon deprotonation of **4**, the appropriate alkylating agent is added followed by addition of anhydrous DMF to accelerate the alkylation reaction. By employing these conditions 1,4-benzodiazepine derivatives containing esters and carbamates have been alkylated in high yields on solid support with no overalkylation observed (compounds **6f** and **6g** in Table I where side chains were protected as a *tert*-butyl ester and a *tert*-butyl carbamate, respectively). Complete alkylation is observed for both activated alkylating agents such as methyl iodide and benzyl bromide and unactivated alkylating agents such as ethyl iodide.

The benzodiazepine product **5** is cleaved from the support with concomitant removal of acid-labile protecting groups by exposure to 85:5:10 trifluoroacetic acid/water/dimethyl sulfide. Employing this reaction sequence we have synthesized multiple structurally diverse benzodiazepine derivatives **6** in very high overall yields (Table I). In addition, racemization does not occur during the reaction sequence as determined by chiral HPLC analysis of the benzodiazepine derivatives **6a** and **6c** prepared from both (*R*)- and (*S*)-*N*-FMOC-alanine (Table I).[9] With the employment of this general and expedient solid-phase synthesis methodology, the construction and screening of a large combinatorial library of benzodiazepine derivatives are currently in progress and will be reported shortly. The solid-phase synthesis of other classes of therapeutically important organic compounds is also under investigation and will be reported in due course.

Supplementary Material Available: Listings of experimental procedures for attaching the aminobenzophenone derivatives to the solid support and for the solid-phase synthesis of the benzodiazepine derivatives, including analytical data for all of the 1,4-benzodiazepine derivatives and intermediates (8 pages). Ordering information is given on any current masthead page.

(8) The pK_a of 5-(phenylmethyl)-2-oxazolidinone is 20.5 in DMSO as determined by Bordwell. Evans, D. A.; et al. *J. Am. Chem. Soc.* **1990**, *112*, 4011-4030. Lithiated 5-(phenylmethyl)-2-oxazolidinone is employed rather than unsubstituted 2-oxazolidinone due to its greater solubility in tetrahydrofuran.

(9) Pirkle, W. H.; Tsipouras, A. *J. Chromatogr.* **1984**, *291*, 291-298.

Direct Evidence for an Oxocarbenium Ion Intermediate in the Asymmetric Cleavage of Chiral Acetals

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The Lewis acid mediated cleavage of chiral acetals has been the subject of numerous investigations over the past several years and is a useful tool for the asymmetric synthesis of carbon–carbon bonds.[1] With allylsilanes[2] and allylstannanes[3] as nucleophiles, this reaction can provide chiral ethers with diastereoselectivities ranging from 5:1 to >500:1. The origin of this selectivity has been studied, mostly by studying the behavior of model acetals,[4] but these studies are inconclusive because the behavior of the model compounds is known to vary with minor variations in the structure of the acetals.[5] We wish to report the results of a more direct approach to studying the reactivity of chiral acetals which utilizes the stereospecifically deuterated acetal **1**[6] (Table I) to determine

(1) Johnson, W. S.; Harbert, C. A.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1968**, *90*, 5279. Johnson, W. S.; Harbert, C. A.; Ratcliffe, B. E.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1976**, *98*, 6188. McNamara, J. M.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7371. Sekizaki, H.; Jung, M.; McNamara, J. M.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7372. For a recent review of the chemistry of chiral acetals, see: Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477.

(2) Johnson, W. S.; Crackett, P. H.; Elliot, J. D.; Jagodzinski, J. J.; Lindel, S. D.; Natarajan, S. *Tetrahedron Lett.* **1984**, *25*, 3951.

(3) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6485.

(4) For previous mechanistic studies of this type of acetal opening, see: (a) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088. (b) Choi, V. M. F.; Elliot, J. D.; Johnson, W. S. *Tetrahedron Lett.* **1984**, *25*, 591. (c) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *J. Organomet. Chem.* **1985**, *285*, 83. (d) Maruoka, K.; Yamamoto, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 668. (e) Yamamoto, Y.; Nishi, S.; Yamada, J. *J. Am. Chem. Soc.* **1986**, *108*, 7116. (f) Silverman, R.; Edington, C.; Elliot, J. D.; Johnson, W. S. *J. Org. Chem.* **1987**, *52*, 180. (g) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4259. (h) Schreiber, S. L.; Wang, Z. *Tetrahedron Lett.* **1988**, *29*, 4085. (i) Denmark, S. E.; Willson, T. M.; Almstead, N. G. *J. Am. Chem. Soc.* **1989**, *111*, 9258. (j) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107. (k) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089. (l) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6458. (m) Sammakia, T.; Smith, R. *J. Org. Chem.* **1992**, *57*, 2997.

(5) See refs 4j-m.

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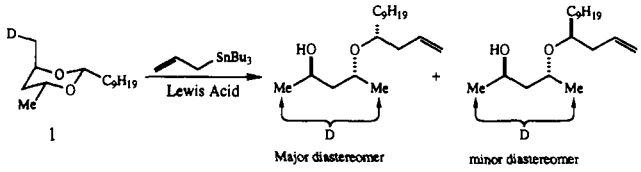
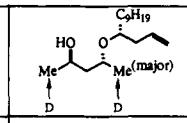
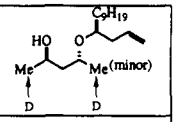
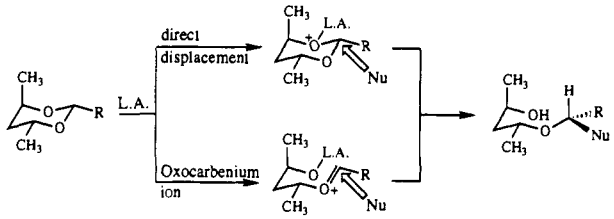
Table I[a]



Lewis acid (conditions)	Major : Minor		
1. $TiCl_4$ (a)	5 : 1	1.5 : 1	1.2 : 1
2. $TiCl_4$ (b)	16 : 1	1.7 : 1	1.5 : 1
3. $TiCl_4$ (c)	44 : 1	1.4 : 1	1.2 : 1
4. $TiCl_3(Oi\text{-}Pr)$ (b)	24 : 1	4.7 : 1	2 : 1
5. $TiCl_2(Oi\text{-}Pr)_2$ (b)	≥200 : 1	4.5 : 1	(insufficient material)

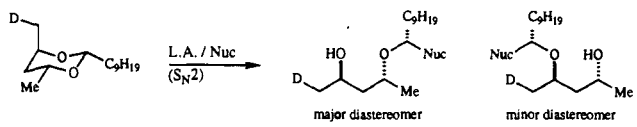
[a] Conditions: (a) 10 equiv of Lewis acid, rapid addition, CH_2Cl_2, −78 °C; (b) 10 equiv of Lewis acid, 2-h addition, CH_2Cl_2, −78 °C; (c) 0.3 equiv of Lewis acid, 3-h addition, CH_2Cl_2, −78 °C, 21% conversion.

Scheme I

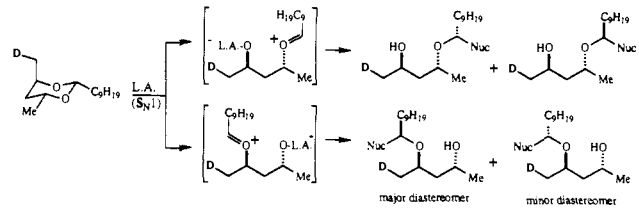


the origin of the stereoselectivity as well as the overall mechanism of reactions with allylstannanes.

There are two extreme mechanisms which can be drawn for the addition of nucleophiles to acetals, ranging from direct nucleophilic displacement of a Lewis acid–ether complex to prior formation of a cationic intermediate that subsequently undergoes attack by a nucleophile (Scheme I). Our deuterium-labeled acetal is capable of distinguishing between these two mechanisms by indirectly labeling the oxygens and thereby determining which of the C–O bonds is cleaved during the reaction. If the reaction proceeds by a direct displacement mechanism, then the major product must be derived from complexation to the oxygen proximal to the axial methyl group (bearing deuterium) followed by cleavage of that C–O bond, while the minor product would be derived from complexation to the oxygen proximal to the equatorial methyl group (which does not bear deuterium) followed by cleavage of that C–O bond. The major product would then bear a deuterium atom on the methyl group next to the hydroxyl, while the minor product would bear a deuterium atom on the methyl group next to the ethereal oxygen, with no crossover. On the other hand,



if the reaction proceeds by way of an equilibrating oxocarbenium ion mechanism, then complexation and cleavage of either C–O bond would provide a common intermediate which would then undergo stereoselective attack to provide the products. The position of the deuterium label in the product would still depend on which of the two C–O bonds was cleaved, but according to this mechanism either of the two bond cleavages can provide the major and minor products. The deuterium label would therefore appear in both of the methyl groups and in a common ratio in both diastereomeric products. Thus, by determining whether the position of the deuterium depends on the stereochemistry of the products and is stereospecific, we can determine whether the reaction proceeds by way of a direct displacement mechanism or an oxocarbenium ion mechanism. This will also reveal whether the diastereoselection is due to selective complexation to one acetal oxygen or due to a diastereoselective addition to an oxocarbenium ion intermediate.



Results using allyltributylstannane and various ratios of $TiCl_4/Ti(O\text{-}i\text{-}Pr)_4$ are shown in Table I.[7] It can be seen that the position of the deuterium is nearly the same for both diastereomers and that the reaction does not provide stereospecific incorporation of deuterium under any of the conditions examined.[8] Thus, regardless of which oxygen is initially attacked by the Lewis acid, the major diastereomer is produced. *This rules out the direct displacement mechanism and shows that the diastereoselectivity is not due to selective complexation to one of the two acetal oxygens, suggesting that the reaction proceeds predominantly by way of an oxocarbenium ion mechanism.* It is interesting to note that the oxygen which undergoes preferential complexation[9] is fortuitously the same oxygen which would require activation in order to provide the major diastereomer if the reaction were proceeding by way of an S_N2 mechanism. Also, the sterically larger and less Lewis acidic titanium complexes display greater selectivity toward the two diastereotopic oxygens which undergo complexation, although this apparently has no bearing on the diastereoselectivity of the reaction.

Using this system, we have determined that the selectivity in the asymmetric cleavage of chiral acetals is not due to preferential complexation to one of the acetal oxygens, but rather is due to a diastereoselective addition to a reactive intermediate which is most likely an oxocarbenium ion. However, this study does not address the subtleties of the reaction, such as the reason for an increase in the selectivity with the milder Lewis acids, or upon slow addition of the Lewis acid. Studies to probe these issues are currently under investigation.

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Supplementary Material Available: Listings of experimental details for the synthesis of the deuterated acetal (7 pages). Ordering information is given on any current masthead page.

(6) This compound was prepared in 10 steps starting from 2-butene-1,4-diol. See supplementary material for details.

(7) All reactions except for entry 3 proceeded in greater than 80% isolated yield.

(8) When the reaction is run to partial conversion (21% in the case of $TiCl_4$, see entry 3; 80% in the case of $TiCl_2(O\text{-}i\text{-}Pr)_2$ using 8 equiv of Lewis acid, entry not shown), the recovered acetal is not isomerized and the products display the same deuterium labeling results as in the case of reactions run to full conversion. This rules out the possibility of equilibration of the acetal prior to the reaction.

(9) Denmark has shown that BF_3 will undergo preferential complexation to the oxygen proximal to the axial methyl group of the acetals similar to **1** (see ref 4i). Our study demonstrates that the extent of the preference for complexation *along the reaction pathway* varies substantially according to the Lewis acid, but still favors complexation to the oxygen proximal to the axial methyl group.