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Stereoselective Synthesis of 2,3,4-Trisubstituted Tetrahydrofurans

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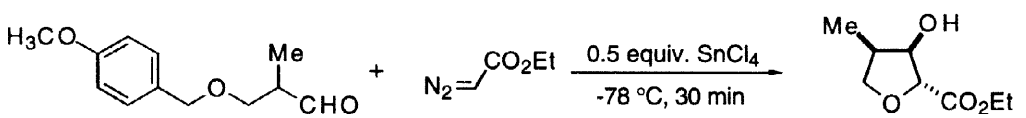
Abstract: The stereoselective synthesis of trisubstituted tetrahydrofurans from benzyl diazoacetate and α-alkyl-β-benzyloxyaldehydes or α-alkyl-β-(triethylsilyl)oxyaldehydes is described.

There are many tetrahydrofuran containing natural products, some of which possess biological activity and are of potential therapeutic interest.[1] As a result, the stereoselective construction of tetrahydrofurans has been the subject of extensive investigation.[2] We have recently shown that the treatment of β-benzyloxyaldehydes with ethyl diazoacetate in the presence of stannic chloride resulted in the formation of tetrahydrofurans with a high degree of stereoselectivity.[3] For example, aldehyde **1** afforded tetrahydrofuran **2** in 75% yield as a >10:1 mixture of stereoisomers (eq. 1).

(eq. 1)



1 **2**

The generality of this potentially powerful methodology has been the subject of continued research in our laboratory. In the course of this work, we were surprised to find that aldehyde **9** (P = PMB, *p*-methoxybenzyl), with an α-*t*-butyl group, afforded tetrahydrofuran **10** in only 8% yield (Table 1, entry 11). This result led us to study the generality of this reaction in the series of α-alkyl aldehydes, shown in Table 1, where the steric bulk of the α-alkyl substituent was varied from a methyl to a *t*-butyl group. Based on other work from our laboratory,[4] we elected to carry out this survey using both *p*-methoxybenzyl (PMB) and triethylsilyl (TES) protected alcohols.

The reaction of substrates with a PMB protecting group on the alcohol afforded tetrahydrofurans in 8-75% yield (Table 1). Substrates with a TES protecting group were easier to prepare and generally afforded tetrahydrofuran products in higher yields than the corresponding

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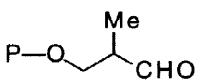
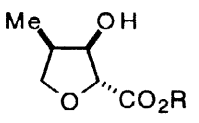
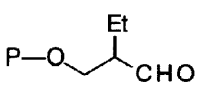
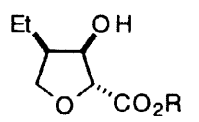
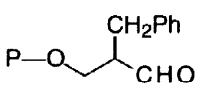
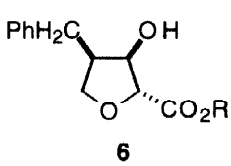
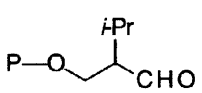
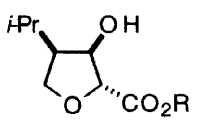
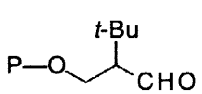
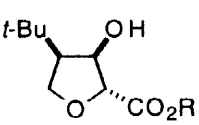
PMB protected alcohols. The exception to this trend was α-methyl aldehyde **1**, which afforded a higher yield of tetrahydrofuran **2** with the PMB protected alcohol (Table 1, entries 1, 2). The largest enhancement in yield was for the reaction of α-*t*-butyl aldehyde **9**, which increased from an 8% to an 87% yield of tetrahydrofuran **10**. The TES protected aldehydes generally afforded higher yields of tetrahydrofurans with boron trifluoride etherate than with stannic chloride (Table 1, entries 3, 4 and 7, 8).

Table 1. Stereoselective Synthesis of Tetrahydrofurans.

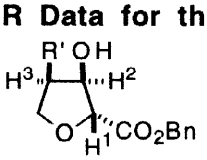
Entry	P—Aldehyde[a]		Conds.[b]	Ester—R $N_2 \gtrless CO_2-R$	THF	Yield[c]
1	PMB	 **1**	$SnCl_4$ (0.5)	Et	 **2**	75 (10:1)[d]
2	$SiEt_3$		$BF_3•OEt_2$ (1.0)	Bn		53 (7.2:1)[e]
3	$SiEt_3$	 **3**	$SnCl_4$ (0.2)	Bn	 **4**	44 (3.0:1)
4	$SiEt_3$		$BF_3•OEt_2$ (0.2)	Bn		66 (3.0:1)[e]
5	PMB		$SnCl_4$ (0.2)	Et		21 (4.5:1)[c]
6	PMB	 **5**	$SnCl_4$ (0.2)	Bn	 **6**	29 (4.5:1)
7	$SiEt_3$		$SnCl_4$ (0.2)	Bn		54 (3.0:1)[e]
8	$SiEt_3$		$BF_3•OEt_2$ (0.2)	Bn		72 (3.5:1)[e]
9	PMB	 **7**	$SnCl_4$ (0.5)	Et	 **8**	27 (>20:1)
10	$SiEt_3$		$BF_3•OEt_2$ (1.0)	Bn		67 (>20:1)
11	PMB	 **9**	$SnCl_4$ (0.5)	Bn	 **10**	8 (>10:1)
12	$SiEt_3$		$BF_3•OEt_2$ (1.0)	Bn		87 (>20:1)

[a]PMB = *p*-$(CH_3O)C_6H_4$. [b]Lewis acid followed by equiv. used; yields for 1.0 and 0.5 equiv of $BF_3•OEt_2$ were within 3% of each other. [c]Yield is followed by diastereomer ratio determined by HPLC analysis of the crude product mixture unless noted otherwise. [d]Diastereomer ratio determined by ^1H NMR integration (see ref 3). [e]The crude reaction mixture was treated with HF•pyridine to remove the silyl group from the secondary alcohol.

The reactions of aldehydes **3**, **5**, **7**, and **9** show a preference for increasing stereoselectivity with increasing steric bulk of the substituent α to the aldehyde. For example, the 4–*i*-propyl and 4–*t*-butyl tetrahydrofurans **8** and **10** were produced as single diastereoisomers (Table 1, entries 10 and 12). Even though the *i*-propyl tetrahydrofuran **8** was formed in only 67% isolated yield (Table 1, entry 10), a thorough GC-MS analysis of the reaction mixture failed to provide evidence for the formation of any diastereomeric tetrahydrofurans. The 67% yield appears to be due to decomposition of the aldehyde. The α-ethyl aldehyde **3** and α-benzyl aldehyde **5** afforded tetrahydrofurans **4** and **6** with 3.0:1 and 3.5:1 stereoselectivity respectively.[5] It is quite interesting that the trend of high stereoselectivity paralleling large steric bulk of the α-substituent of the aldehyde does not hold for α-methyl aldehyde **1**.[6]

The assignment of the stereochemistry of the major tetrahydrofuran diastereomers is based on ^{1}H NMR data and X-ray crystal structures. The X-ray structure of a derivative of **2**,[3] and of tetrahydrofuran **6** (R = Bn), showed the alkyl and hydroxyl groups in a cis-relationship, and trans to the ester.[5] The ^{1}H NMR spectrum of **2** and **6** (R = Bn) showed diagnostic H–H coupling constants and chemical shifts for hydrogens about the tetrahydrofuran and allowed the stereochemistry of the major isomers of the other tetrahydrofurans to be assigned as well. As shown in Table 2, the ^{1}H NMR data is self consistent and supports the stereochemical assignments.

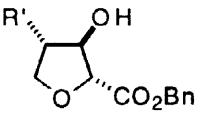
Table 2. Summary of ^{1}H NMR Data for the Major THF Diastereomers.



THF	H^1	H^2	H^3	$J(H^2–H^3)$
2, R' = Me	δ 4.43, d (J = 2.2 Hz)	δ 4.33, dd (J = 2.2, 5.3 Hz)	δ 2.32, m	5.3 Hz
4, R' = Et	δ 4.46, d (J = 0.9 Hz)	δ 4.33, dd (J = 0.8, 4.8 Hz)	δ 2.08, m	4.8 Hz
6, R' = Bn	δ 4.49, d (J = 0.8 Hz)	δ 4.31, br t (J = 4.8 Hz)	δ 2.52, m	4.8 Hz
8, R' = *i*-Pr	δ 4.51, s	δ 4.38, t (J = 4.4 Hz)	δ 1.81, m	4.4 Hz
10, R' = *t*-Bu	δ 4.44, s	δ 4.47, t (J = 4.8 Hz)	δ 1.88, m	4.8 Hz

The minor diastereomers were isolated in the case of tetrahydrofurans **2**, **4**, and **6** but could not be detected in the case of **8** and **10**. In each case, the minor diastereomer showed similar H—H coupling constants for hydrogens about the tetrahydrofuran, indicating they all possess the

same relative stereochemistry. The tentative stereochemical assignment of the minor diastereomer shown at the right is based on NOESY and 1D-NOE experiments.



It is interesting to note that the stereoselectivity of this tetrahydrofuran synthesis is virtually independent of the Lewis acid, bidentate $SnCl_4$ or monodentate $BF_3{\bullet}OEt_2$, and the alcohol protecting group. As shown in Table 1, the relative stereochemistry of the major diastereomer remains unchanged and consistent. A priori, we expected a change or possible reversal of stereoselectivity upon changing the Lewis acid and protecting group. We are continuing to study the mechanism of this reaction to gain insight into the source of the stereoselectivity.

In summary, we have shown that the synthesis of 2,3,4-trisubstituted tetrahydrofurans from diazoesters and α-alkyl-β-(triethylsilyl)oxyaldehydes is a highly stereoselective and general reaction. Further studies on this and related methodology are currently in progress.

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References and Notes

1. (a) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 3448-3467. (b) Kang, S. H.; Lee, S. B. *Tetrahedron Lett.* **1995**, *36*, 4089-4092, and references cited therein. (c) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: Boca Raton, 1995, pp 379.
2. For recent examples and leading references see: (a) Zhang, H. P.; Seepersaud, M.; Seepersaud, S.; Mootoo, D. R. *J. Org. Chem.* **1998**, *63*, 2049-2052. (b) Marshall, J. A.; Jiang, H. J. *Tetrahedron Lett.* **1998**, *39*, 1493-1496. (c) Craig, D; King, N. P.; Shaw, A. N. *Tetrahedron Lett.* **1997**, *38*, 8599-8602. (d) Petasis, N. A.; Lu, S.-P. *J. Am. Chem. Soc.* **1995**, *117*, 6394-6395. (e) Zhao, Y.; Beddoes, R. L.; Quayle, P. *Tetrahedron Lett.* **1994**, *35*, 4187-4188.
3. Angle, S. R.; Wei, G. P.; Ko, Y. K.; Kubo, K. *J. Am. Chem. Soc.* **1995**, *117*, 8041-8042.
4. Angle, S. R.; Bernier, D. S.; El-Said, N. A.; Jones, D. E.; Shaw, S. Z. *Tetrahedron Lett.* **1998**, *39*, 3919-3922.
5. A reaction was carried out with benzyl diazoacetate, aldehyde **5** and $BF_3{\bullet}OEt_2$ (1.0 and 0.2 equiv.); the stereoselectivity and yield remained unchanged.
6. This interesting stereochemical ambiguity is currently under investigation.