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Stereoselective synthesis of 4-aryl-2-(benzyloxy)carbonyl-3-hydroxy tetrahydrofurans from aryl epoxides

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Abstract

The stereoselective synthesis of 4-aryl substituted tetrahydrofurans from benzyl diazoacetate and aryl epoxides is described. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: aryl epoxides; tetrahydrofurans; stereoselective; asymmetric synthesis.

The biological importance of tetrahydrofuran natural products and synthetic variants, such as *C*-glycosides, has prompted an extensive investigation into their asymmetric, stereocontrolled synthesis.[1] We have recently described a novel stereoselective synthesis of 4-alkyl substituted tetrahydrofurans from α-alkyl-β-(triethylsilyl)oxyaldehydes and diazoesters that affords tetrahydrofurans with a high degree of stereoselectivity.[2,3] We sought to expand this methodology to the asymmetric synthesis of tetrahydrofurans from optically active epoxides in a single synthetic step by exploiting the known[4,5] rearrangement of epoxides to β-silyloxyaldehydes, which can be accomplished in high yields with complete retention of optical activity. This process might provide ready access to β-silyloxyaldehydes which, in the presence of diazoesters, could then react to afford tetrahydrofurans. We report herein our progress toward this goal.

Our results are summarized in Table 1. Treatment of epoxide (−)-**1** with $BF_3{\cdot}OEt_2$ (0.2 equiv.) and benzyl diazoacetate (1.5 equiv., −78°C, 45 min) afforded (+)-**3** $[\alpha]_D^{25}$ +10.4 ($c = 0.0105$, $CHCl_3$) in 65% yield[6] and >95% ee[7] (Table 1, entry 1). Epoxide (+)-**1** was treated with $BF_3{\cdot}OEt_2$ (0.2 equiv.) and benzyl diazoacetate to afford (−)-**3** $[\alpha]_D^{25}$ −10.6 ($c = 0.0105$, $CHCl_3$) in 66% yield and >95% ee[7] (entry 2). Increasing the amount of $BF_3{\cdot}OEt_2$ to 0.5 equiv. (entry 3) led to a slight decrease in the yield of (−)-**3**.

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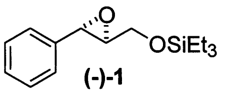
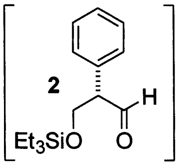
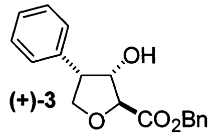
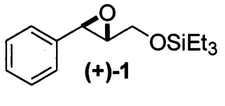
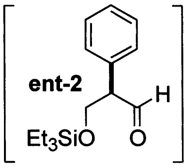
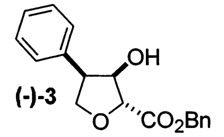
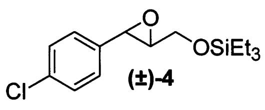
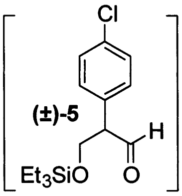
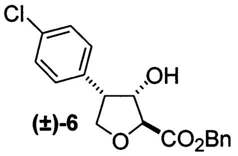
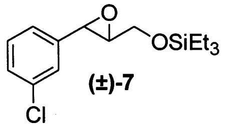
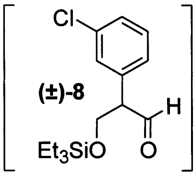
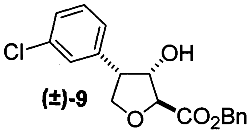
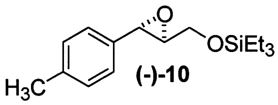
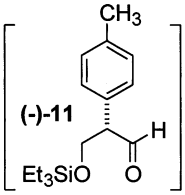
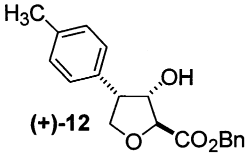
Table 1
Asymmetric, stereoselective synthesis of 4-aryl tetrahydrofurans

Entry	Aryl Epoxide	Conditions[a]	Aldehyde	Tetrahydrofuran	Yield
1	 **(-)-1**	$BF_3{\cdot}OEt_2$ (0.2)[b]	 **2**	 **(+)-3**	65
2	 **(+)-1**	$BF_3{\cdot}OEt_2$ (0.2)[b]	 **ent-2**	 **(-)-3**	66
3		$BF_3{\cdot}OEt_2$ (0.5)[b]			55
4	 **(±)-4**	$BF_3{\cdot}OEt_2$ (0.2)[b]	 **(±)-5**	 **(±)-6**	32
5		$BF_3{\cdot}OEt_2$ (0.5)[b]			74
6	 **(±)-7**	$BF_3{\cdot}OEt_2$ (0.5)[b]	 **(±)-8**	 **(±)-9**	20
7		MABR (2.0) $BF_3{\cdot}OEt_2$ (0.5)[b]			20
8		MABR (2.0) $BF_3{\cdot}OEt_2$ (0.5)[c]			41
9		MABR (2.0) $BF_3{\cdot}OEt_2$ (1.0)[c]			41
10	 **(-)-10**	$BF_3{\cdot}OEt_2$ (0.5)[b]	 **(-)-11**	 **(+)-12**	14
11		MABR (2.0) $BF_3{\cdot}OEt_2$ (0.2)[c]			23
12		MABR (2.0) $BF_3{\cdot}OEt_2$ (0.5)[c]			52

[a] 1.5 equiv. of benzyl diazoacetate was used in every reaction shown above; Lewis acid followed by equiv. used. [b] Aldehyde intermediate was not isolated. [c] The aldehyde intermediate was first prepared using methylaluminum bis(4-bromo-2,6-diisopropylphenoxide) MABR catalyst (2 equiv.), isolated, purified on silica gel (25:1 hexanes/Et_2O) and used for the tetrahydrofuran reaction.

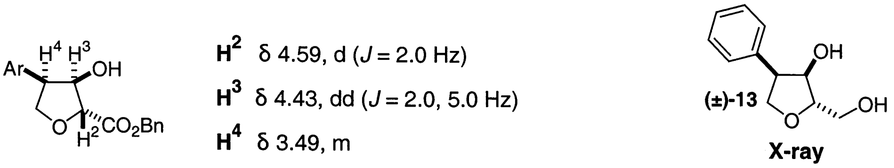
Reaction of *p*-Cl phenyl epoxide (±)-**4** with $BF_3{\cdot}OEt_2$ (0.2 equiv.) and benzyl diazoacetate (1.5 equiv.) at −78°C for 4 h, afforded tetrahydrofuran (±)-**6** in 32% yield. Increasing the amount of $BF_3{\cdot}OEt_2$ to 0.5 equiv. (−78°C, 45 min) afforded tetrahydrofuran (±)-**6** in 74% yield. This significant improvement in the yield with a small change in the amount of Lewis acid, relative to the lack of effect on epoxide **1**, shows that the reaction is sensitive to minor changes in the substitution on the aromatic ring.

Epoxides (±)-**7** and (−)-**10** were treated with $BF_3{\cdot}OEt_2$ (0.5 equiv.) and benzyl diazoacetate at −78°C to afford tetrahydrofuran products (±)-**9** and (+)-**12** in 20 and 14% yield, respectively. Treatment of *p*-CH_3 phenyl epoxide (−)-**10** with $BF_3{\cdot}OEt_2$ (0.2 equiv.) at −78°C for 45 min, in the absence of benzyl diazoacetate, afforded an intractable mixture of products, containing <10% of aldehyde (−)-**11** (^1H NMR analysis of the crude reaction mixture). These results lead to the conclusion that the reason for the modest yields of tetrahydrofurans with $BF_3{\cdot}OEt_2$ is due to poor conversion of epoxides (±)-**7** and (−)-**10** to aldehydes (±)-**8** and (−)-**11**. It is interesting to note that minor variations in the substitution on the aromatic ring have such a major impact on the epoxide to aldehyde rearrangement. As an alternative to $BF_3{\cdot}OEt_2$, methylaluminum bis(4-bromo-2,6-diisopropylphenoxide), MABR (2 equiv.),[4] was reacted with epoxide (−)-**10** at −78°C for 1 h (in the absence of benzyl diazoacetate) to afford aldehyde (−)-**11** in 80% yield. Treatment of *m*-Cl phenyl epoxide (±)-**7** under the same conditions afforded aldehyde (±)-**8** in 74% yield.

While MABR was an excellent Lewis acid for the epoxide to aldehyde rearrangement, it did not result in the formation of tetrahydrofurans when benzyl diazoacetate was included in the reaction.[8] In an attempt to effect a one-pot epoxide to tetrahydrofuran reaction, the sequential addition of MABR and $BF_3{\cdot}OEt_2$ was investigated. Epoxide (±)-**7** was treated with MABR (2 equiv., −78°C, 2 h) followed by sequential addition of benzyl diazoacetate (1.5 equiv.) and $BF_3{\cdot}OEt_2$ (0.5 equiv.), to afford tetrahydrofuran (±)-**9** in 20% yield (entry 7).

The conversion of epoxides (±)-**7** and (−)-**10** to tetrahydrofurans (±)-**9** and (+)-**12** could be effected more efficiently in a two-step process via (1) treatment of the epoxides with MABR (2 equiv., −78°C, 1 h) followed by, (2) treatment of the resulting aldehydes with $BF_3{\cdot}OEt_2$ (0.5 equiv.) and benzyl diazoacetate (1.5 equiv.) at −78°C. This procedure afforded tetrahydrofurans (±)-**9** and (+)-**12** in 41 and 52% overall yield, respectively, from the corresponding epoxides (Table 1, entries 8 and 12). Increasing the amount of $BF_3{\cdot}OEt_2$ to 1.0 equiv. (entry 9) for the conversion of (±)-**8** to (±)-**9** via the two-step process showed no effect on the yield of tetrahydrofuran (±)-**9**. Whereas, decreasing the amount of $BF_3{\cdot}OEt_2$ to 0.2 equiv. (entry 11) for the conversion of (−)-**11** to (+)-**12** led to a marked decrease in the yield of tetrahydrofuran (23% from (−)-**10**). The optical rotations of (+)-**12** prepared in the single pot reaction (entry 10) and the two-step procedure (entry 12) were identical, $[\alpha]^{25}_{D}$ +7.5 ($c = 0.0033$, $CHCl_3$). Given the lack of racemization seen for (−)-**1** and (+)-**1**, it appears that α-aryl aldehyde (−)-**11** does not racemize under the reaction conditions.

Tetrahydrofurans **3**, (±)-**6**, (±)-**9**, and (+)-**12** all appear to have the same relative stereochemistry about the tetrahydrofuran ring, as evidenced by the identical ^1H NMR chemical shifts and coupling constants for resonances corresponding to H^2, H^3 and H^4 (Fig. 1). We were able to unambiguously determine the stereochemistry of tetrahydrofuran (±)-**3** by an X-ray crystal structure of diol (±)-**13** (prepared from (±)-**3**; $LiAlH_4$ 6 equiv.; Et_2O), which showed a 2,3-*trans*-3,4-*cis* orientation about the tetrahydrofuran ring.



H^2 δ 4.59, d (J = 2.0 Hz)
H^3 δ 4.43, dd (J = 2.0, 5.0 Hz)
H^4 δ 3.49, m

Figure 1. Summary of key ^1H NMR data

Tetrahydrofurans (±)-**6**, (±)-**9** and (+)-**12** must also possess this same 2,3-*trans*-3,4-*cis*-relative stereochemistry. This stereochemical assignment is consistent with our previous work with the synthesis of 2,3,4-trisubstituted tetrahydrofurans from aldehydes.[2]

In conclusion, we have developed a novel method for the asymmetric synthesis of 4-aryl-2-(benzyloxy)carbonyl-3-hydroxy tetrahydrofurans from optically active aryl epoxides. This method should be adaptable to the synthesis of several unique tetrahydrofuran natural products and *C*-glycosides. A further study on this is currently under investigation and will be reported in due course.

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6. All new compounds were pure by chromatography and were characterized by ^{1}H NMR, ^{13}C NMR, IR, MS and HRMS.
7. The %ee was determined by ^{1}H NMR Eu(hfc)$_3$ study where racemic material was used to establish the limits of detection.
8. Treatment of (±) epoxide **1** with MABR (2.0 equiv.) (−78°C, 1 h), followed by addition of benzyl diazaoacetate (1.0 equiv.) with stirring for an additional 1 h at −78°C, afforded (±) aldehyde **2** and unreacted benzyl diazoacetate. No tetrahydrofuran could be seen in the crude reaction mixture by ^{1}H NMR and TLC analysis.