

Diastereoselective Construction of *syn*-1,3-Dioxanes via a Bismuth-Mediated Two-Component Hemiacetal/Oxa-Conjugate Addition Reaction

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S Supporting Information

ABSTRACT: The bismuth-mediated two-component hemiacetal/oxa-conjugate addition of δ -trialkylsilyloxy and δ -hydroxy α,β -unsaturated aldehydes and ketones with alkyl aldehydes provides the *syn*-1,3-dioxanes in a highly efficient and stereoselective manner. The key advantages of this protocol are its operational simplicity and its ability to directly access electron-withdrawing groups without recourse to oxidation state adjustments.

The stereoselective construction of *syn*-1,3-diols remains the focus of considerable attention due to the ubiquity of this motif in pharmacologically important molecules.^{1–4} In this context, the base-mediated combination of an aryl aldehyde with a δ -hydroxy α,β -unsaturated carboxylic acid derivative provides one of the most direct and convenient methods developed to date.^{4–6} Nevertheless, the analogous process with α,β -unsaturated aldehydes and ketones has not been forthcoming, despite the fact that this would circumvent the necessity for oxidation state adjustments.^{7–9} Additionally, the base-mediated process is limited to non-enolizable aromatic aldehydes, which requires multiple additions of the aryl aldehyde and base to minimize the effect of a competing Cannizzaro reaction.^{6,10} We envisioned that the acid-catalyzed version of this transformation would permit α,β -unsaturated aldehydes and ketones to be employed directly by using more electrophilic aliphatic aldehydes.¹¹ In a program directed toward the exploration of bismuth-mediated reactions, we have demonstrated that bismuth(III) salts facilitate a number of acid-catalyzed reactions with unique reactivity and selectivity because of their ability to modulate the acid concentration and thereby buffer the reaction.^{12,13} Herein, we now disclose the diastereoselective construction of *syn*-1,3-dioxanes **2** via a two-component hemiacetal/oxa-conjugate addition of δ -triorganosilyloxy and δ -hydroxy α,β -unsaturated aldehydes and ketones **1** with alkyl aldehydes (eq 1).

Table 1 outlines the development of the bismuth-mediated two-component hemiacetal/oxa-conjugate addition reaction.

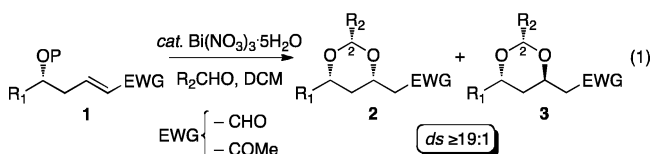


Table 1. Optimization and Aldehyde (R_2CHO) Scope for the Diastereoselective Two-Component Hemiacetal/Oxa-Conjugate Addition Reaction [eq 1; $R_1 = Ph(CH_2)_2$]^a

entry	homoallylic alcohol <i>rac</i> -1		aldehyde R_2	yield (%) ^b	<i>ds rac</i> -2/ <i>3</i> ^c
	P	EWG			
1	H	COMe	Me	99	$\geq 19:1$
2	H	COMe	Ph	—	—
3	H	CO ₂ Me	Ph	—	—
4 ^d	H	COMe	Me	34	$\geq 19:1$
5	H	COMe	^t Pr	98	$\geq 19:1$
6	H	COMe	^t Bu	90	$\geq 19:1$
7	H	COMe	H	98	$\geq 19:1$
8	TES	CHO	Me	68	17:1
9	H	CHO	Me	33	17:1
10	TES	CHO	Me ^e	83	$\geq 19:1$

^aAll reactions were carried out on a 0.5 mmol reaction scale utilizing 10 mol % bismuth(III) nitrate and the requisite aldehyde (5 equiv) in dichloromethane at ambient temperature. ^bIsolated yields. ^cRatios of diastereoisomers were determined by 500 MHz ¹H NMR analysis of the crude reaction mixtures. ^dReaction was conducted with 20 mol % nitric acid. ^e20 equiv.

Treatment of the δ -hydroxy α,β -unsaturated ketone *rac*-1a (P = H, EWG = COMe) with acetaldehyde and catalytic Bi(NO_3)₃·5H₂O furnished the *syn*-1,3-dioxane *rac*-2a in 99% yield with $\geq 19:1$ diastereoselectivity (entry 1). In contrast, the corresponding aryl aldehydes failed to react with either the α,β -unsaturated ketone or ester (entries 2 and 3), which is in full accord with our hypothesis.¹¹ Interestingly, the analogous process with nitric acid provided the 1,3-dioxane *rac*-2a in significantly lower yield, again illustrating the superiority of bismuth salts (entry 4). Further studies demonstrated that the reaction is applicable to a variety of aliphatic aldehydes (entries 5 and 6), in which even formaldehyde provided the *syn*-1,3-dioxane *rac*-2 (R₂ = H) in excellent yield (entry 7). Although the ability to form the *syn*-1,3-dioxane *rac*-2a from α,β -unsaturated methyl ketones circumvents the necessity to functionalize an ester or amide, the ability to employ an aldehyde directly would circumvent unnecessary oxidation state adjustments and thereby dramatically improve the synthetic utility of this process.⁷ Treatment of the

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δ -triethylsilyloxy α,β -unsaturated aldehyde *rac*-1k (P = TES, EWG = CHO) under the optimized reaction conditions furnished the 1,3-dioxanes *rac*-2k/3k in 68% yield, favoring the *syn* diastereoisomer *rac*-2k (entry 8). Interestingly, the δ -hydroxy α,β -unsaturated aldehyde *rac*-1k (P = H) provided the 1,3-dioxanes *rac*-2k/3k in significantly lower yield (entry 9). The marked difference in the efficiency is presumably the result of the triorganosilyl ether controlling the concentration of the secondary alcohol through the rate of protodesilylation.¹⁴ Finally, the efficiency and selectivity of this remarkable process was further improved by increasing the concentration of acetaldehyde to reduce competitive self-condensation (entry 10).

Table 2. Scope of the Diastereoselective Bismuth-Mediated Oxa-Conjugate Addition Reaction (eq 1; R₂ = Me)^a

entry	homoallylic alcohol <i>rac</i> -1			yield (%) ^b	<i>ds</i> <i>rac</i> -2/3 ^c
	R ₁	P	EWG		
1	Ph(CH ₂) ₂	H	COMe	a	99
2	PhCH ₂	H	COMe	b	97
3	Me	H	COMe	c	92
4	Br(CH ₂) ₅	H	COMe	d	99
5	ⁱ Pr	H	COMe	e	92
6	(CH ₃) ₂ CHCH ₂	H	COMe	f	96
7	(CH ₃) ₂ CH(CH ₂) ₂	H	COMe	g	98
8	BnOCH ₂	H	COMe	h	96 ^d
9	TBDPSO(CH ₂) ₂	H	COMe	i	95
10	Ph	H	COMe	j	97
11	Ph(CH ₂) ₂	TES	CHO	k	83
12	PhCH ₂	TES	CHO	l	64
13	Me	TES	CHO	m	56
14	Br(CH ₂) ₅	TES	CHO	n	74
15	ⁱ Pr	TES	CHO	o	72
16	(CH ₃) ₂ CHCH ₂	TES	CHO	p	75
17	(CH ₃) ₂ CH(CH ₂) ₂	TES	CHO	q	72
18	BnOCH ₂	TES	CHO	r	72
19	TBDPSO(CH ₂) ₂	TES	CHO	s	72
20	Ph	TES	CHO	t	70

^aAll reactions were carried out on a 0.5 mmol reaction scale utilizing 10 mol % bismuth(III) nitrate in dichloromethane at ambient temperature for 16–160 h. ^bIsolated yields. ^cRatios of diastereoisomers were determined by 500 MHz ¹H NMR analysis of the crude reaction mixtures.^{16,17} ^d95% on a 50 mmol scale.

Table 2 summarizes the application of the optimized reaction conditions (Table 1, entries 1 and 10) to a variety of δ -hydroxy and δ -triethylsilyloxy α,β -unsaturated ketones and aldehydes, respectively (vide supra). This study probed the effect of various substituents on the efficiency and selectivity of the process. For example, linear and branched alkyl derivatives, including benzyl and triorganosilyl¹⁵ protected hydroxyalkyl derivatives, provided excellent selectivity, albeit the aldehydes were generally less efficient because of competing side reactions (cf. entries 11–20 vs 1–10). Nevertheless, this work represents a direct and synthetically useful method for the stereoselective construction of *syn*-1,3-dioxanes.^{16–18} The overall process is operationally simple since it does not require the exclusion of air and moisture and can be conducted on a large scale with similar efficiency (entry 8).

To highlight the synthetic utility of this process, we elected to prepare the C18–C28 fragment of the polyene macrolide

RK-397 (Figure 1)^{19–22} using the iterative sequence outlined in Scheme 1. The enantiomerically enriched homoallylic alcohol (*R*)-4 was converted to the δ -triethylsilyloxy α,β -unsaturated

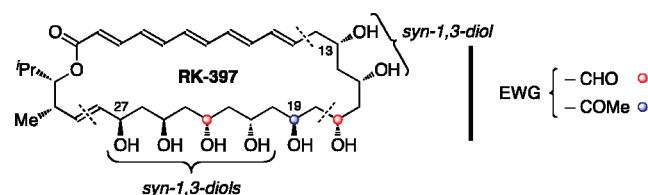
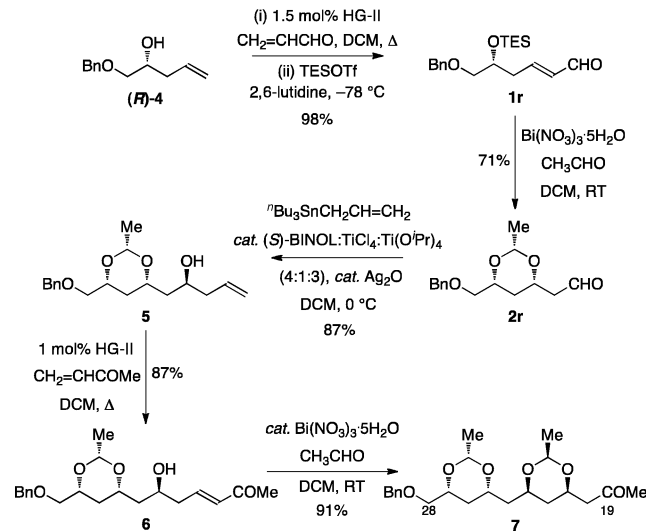


Figure 1. Mapping of *syn*-1,3-dioxanes 2 onto the polyene macrolide RK-397 using the bismuth-mediated two-component hemiacetal/oxa-conjugate reaction.

Scheme 1. Iterative Bismuth-Mediated Two-Component Hemiacetal/Oxa-Conjugate Reaction to *syn*-1,3-Dioxanes



aldehyde **1r** in 98% overall yield via cross-metathesis²³ with acrolein using the Hoveyda–Grubbs second-generation catalyst (HG-II),²⁴ followed by in situ protection of the secondary alcohol at low temperature to suppress the formation of the extended triethylsilyl enol ether. Treatment of **1r** under the optimized reaction conditions for the bismuth-mediated two-component hemiacetal/oxa-conjugate addition furnished the protected *syn*-1,3-dioxane **2r** in 71% yield with excellent diastereocontrol (*ds* $\geq 19:1$ by ¹H NMR). Enantioselective allylation of aldehyde **2r** (*ds* = 98:2 by HPLC), using Muruoka's protocol,²⁵ provided the homoallylic alcohol required to demonstrate the iterative process. Cross-metathesis with methyl vinyl ketone provided α,β -unsaturated ketone **6** (*E/Z* $\geq 19:1$ by ¹H NMR), which was treated under conditions analogous to those outlined for the δ -hydroxy α,β -unsaturated ketones to afford bis-protected *syn*-1,3-diol **7** in 91% yield with excellent diastereocontrol (*ds* $\geq 19:1$ by ¹H NMR). The advantage of this approach is the experimental simplicity coupled with the ability to directly utilize α,β -unsaturated aldehydes and ketones, which makes this an extremely attractive approach to *syn*-1,3-dioxanes.^{8h}

In conclusion, we have developed a highly diastereoselective bismuth-mediated two-component hemiacetal/oxa-conjugate addition reaction that provides *syn*-1,3-dioxanes under extremely mild conditions. This operationally simple protocol

provides the electron-withdrawing group in the aldehyde/ketone oxidation state, which alleviates the necessity for redox adjustments. The synthetic utility of this approach was highlighted in a five-step synthesis of the C18–C28 fragment of the polyene macrolide RK-397 in 48% overall yield. Finally, we envision that this approach will find favor in a number of synthetic applications that require either the aldehyde or ketone oxidation state.^{8,9}

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures, spectral data (including NOE data) for all new compounds, and a CIF file for *rac-2v*. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

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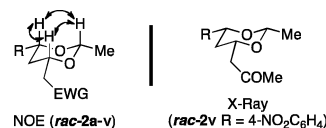
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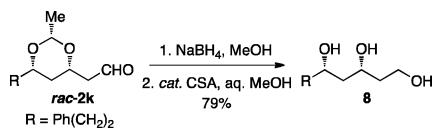
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- (14) The oxocarbenium ion intermediate is additionally stabilized by the triorganosilyl group.¹³
- (15) Although silyl migration/cyclization is a major side reaction in the base-catalyzed version using the *tert*-butyldimethylsilyl-protected hydroxymethyl derivative ($R_1 = \text{TBSOCH}_2$, EWG = CO_2Et), we observed only a trace amount ($\leq 5\%$) of triisopropylsilyl migration ($R_1 = \text{TIPSOCH}_2$, EWG = COMe , **2u**, 96%, $ds \geq 19:1$) with the new method. For more details, see: Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 1049.
- (16) The stereochemistry of the *syn*-1,3-dioxanes *rac-2a–v* was confirmed using nuclear Overhauser effect (NOE) experiments and further supported by the X-ray crystal structure of *rac-2v* (see the Supporting Information).



(17) The minor diastereoisomer **3a** interconverts to the more stable *syn*-1,3-dioxane **2a**, suggesting that the reaction proceeds under thermodynamic control. This result contrasts with the previous studies, which were under kinetic control.^{13c,d}

(18) Deprotection of the ethylidene acetal to provide the *syn*-1,3-diol can be readily accomplished using the following sequence: reduction of the aldehyde *rac-2k* with sodium borohydride followed by

treatment with catalytic camphorsulfonic acid in aqueous methanol furnished the triol **8** in 79% overall yield.



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