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Diastereoselective Synthesis of Vicinal Tertiary Diols

Brad M. Loertscher, Phil R. Young, Patrick R. Evans, and Steven L. Castle*

Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah 84602, United States

scastle@chem.byu.edu

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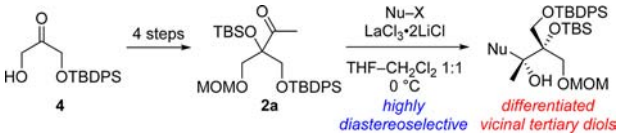
ABSTRACT



A strategy for the synthesis of differentiated vicinal tertiary diols is described. The key step is a high-yielding, diastereoselective $LaCl_3 \cdot 2LiCl$-mediated addition of a Grignard or organolithium reagent to ketone 2a. The reaction is believed to proceed via a 1,3-chelated intermediate. One of the adducts has been transformed into a functionalized cyclopentenone resembling the core structure of pactamycin.

Vicinal tertiary diols and their derivatives occupy a prominent place in organic chemistry, in part because of their presence in bioactive natural products such as zaragozic acid C,[1] pactamycin,[2] and ryanodine[3] (Figure 1). A variety of methods[4] including dihydroxylations,[5] pinacol couplings,[6] and rearrangements[7] have been utilized for their synthesis. However, most of these protocols were developed for specific applications and have not been generalized. Accordingly, there is a clear need for an efficient, stereoselective, and broadly applicable strategy for constructing vicinal tertiary diols.

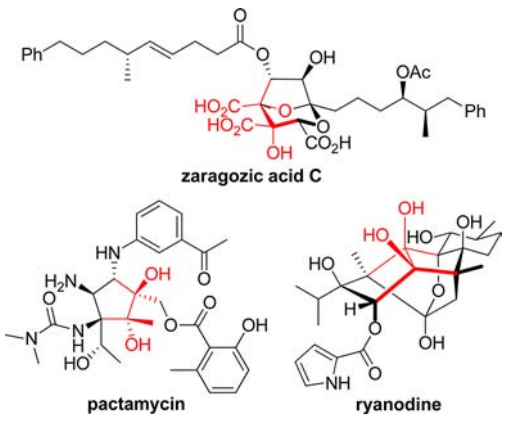


Figure 1. Naturally occurring vicinal tertiary diols.

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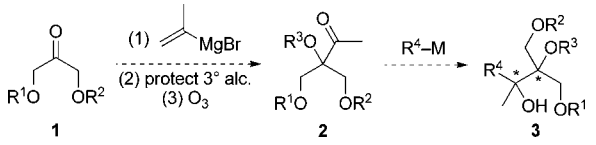
We recognized that sequential additions of Grignard reagents or related nucleophiles to ketones would provide a straightforward means of accessing the desired compounds. This strategy is outlined in Scheme 1. Addition of isopropenylmagnesium bromide to differentiated dihydroxyacetone derivative **1** would furnish a tertiary alcohol. Protection of this alcohol and ozonolysis of the alkene would provide ketone **2**. Then, addition of Grignard or organolithium reagents to the ketone would deliver the targeted vicinal tertiary diols **3**. The judicious choice of protecting groups R^1-R^3 would permit selective elaboration of these compact, highly functionalized adducts. We were intrigued by the simple and direct nature of this route combined with the expected utility of the products. Nucleophilic additions to protected α-*tert*-hydroxy ketones have been reported, primarily in the context of total synthesis efforts.[4a,8] However, to the best of our knowledge a study of the stereoselectivity, scope, and limitations of additions to simple ketones of type **2** has not been described. With the goal of developing a broadly useful method for constructing vicinal tertiary diols, we set out to identify suitable protecting groups R^1-R^3 capable of enabling high-yielding, diastereoselective additions of Grignard and organolithium reagents to **2**.

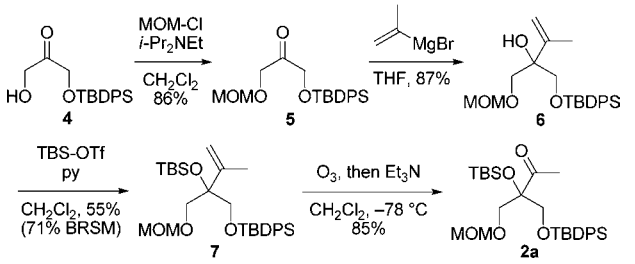
Scheme 1. Proposed Synthetic Strategy



A set of ketones bearing different protecting groups was synthesized, and the preparation of **2a** is shown in Scheme 2 as a representative example.[9] Methoxymethylation of known 1,3-dihydroxyacetone derivative **4**[10] provided the differentially protected intermediate **5**. Addition of isopropenylmagnesium bromide to **5** was facile, but TBS protection of the resulting tertiary alcohol **6** was sluggish, furnishing **7** in moderate yield along with some recovered starting material. Then, ozonolysis of the 1,1-disubstituted alkene delivered methyl ketone **2a**.

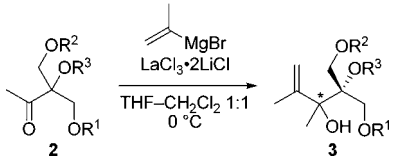
Upon examining the addition of isopropenylmagnesium bromide to ketone **2a**, we discovered that $LaCl_3\cdot 2LiCl$[11] was essential to obtaining high yields of the adduct **3a**

Scheme 2. Synthesis of Ketone **2a**



(Table 1). Notably, this additive was significantly more effective than $CeCl_3$.[12] We were pleased to find that alcohol **3a** could be obtained in excellent (19:1) dr when the reaction was conducted in a $THF-CH_2Cl_2$ mixed solvent system. Additions performed in pure THF were characterized by lower dr values (ca. 7–10:1),[13] so the mixed solvent system was employed to study additions to ketones **2b–g**. Replacing the TBDPS ether of **2a** with a smaller TBS ether (i.e., **2b)** afforded decreased diastereoselectivity. Substitution of a benzyl ether for the MOM group led to similar or slightly attenuated dr values (cf., **2a** and **2e**, **2b** and **2c**). A bulkier BOM group could be used in place of the MOM group with excellent results (cf., **2a** and **2g**). Importantly, all of the ketones examined underwent $LaCl_3\cdot 2LiCl$-promoted Grignard addition with high yields and synthetically useful levels of diastereoselectivity with the sole exception of **2d**. Presumably, the presence of two protecting groups capable of chelation allows nucleophilic addition to this substrate to occur via competing pathways.

Table 1. $LaCl_3\cdot 2LiCl$-Mediated Grignard Additions to **2a–g**



ketone	R^1	R^2	R^3	% yield[a]	dr[b]
2a[c]	MOM	TBDPS	TBS	96	19:1
2b	MOM	TBS	TBS	90	5.1:1
2c	Bn	TBS	TBS	89	5.8:1
2d	Bn	TBS	MOM	74	1.6:1
2e	Bn	TBDPS	TBS	98	10:1
2f	Bn	TBS	TES	76	7.7:1
2g	BOM	TBDPS	TBS	91	19:1

[a] Combined isolated yields of both diastereomers. [b] Determined by ^{1}H NMR. [c] $THF-CH_2Cl_2$ 3:1 was employed as solvent.

(8) (a) Clark, D. A.; de Riccardis, F.; Nicolaou, K. C. *Tetrahedron* **1994**, *50*, 11391. (b) Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1995**, *117*, 8106. (c) Kawata, S.; Yoshimura, F.; Irie, J.; Ehara, H.; Hirama, M. *Synlett* **1997**, 250. (d) Hodgson, D. M.; Bailey, J. M.; Villalonga-Barber, C.; Drew, M. G. B.; Harrison, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3432. (e) Sumiya, T.; Ishigami, K.; Watanabe, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5527. (f) Tatsuta, K.; Tanaka, H.; Tsukagoshi, H.; Kashima, T.; Hosokawa, S. *Tetrahedron Lett.* **2010**, *51*, 5546.

(9) See the Supporting Information for the synthesis of ketones **2b–2g**.

(10) Sharma, R.; Lee, J.; Wang, S.; Milne, G. W. A.; Lewin, N. E.; Blumberg, P. M.; Marquez, V. E. *J. Med. Chem.* **1996**, *39*, 19for an improved synthesis of **4**.

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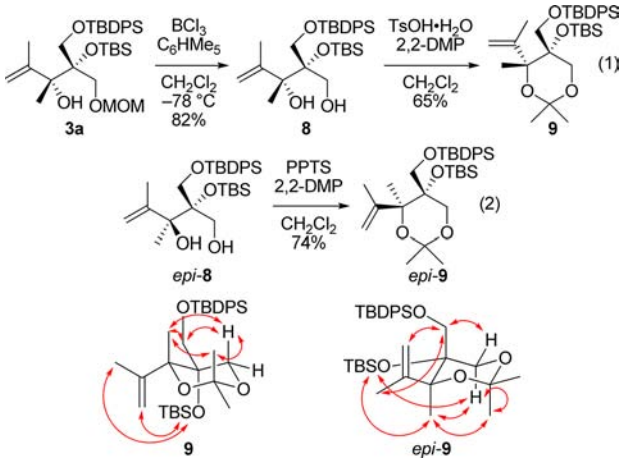
(13) Since the lanthanum salt and Grignard reagents were dispensed as commercially available solutions in THF (0.6 and 0.5 M, respectively), the reaction was never performed in pure CH_2Cl_2.

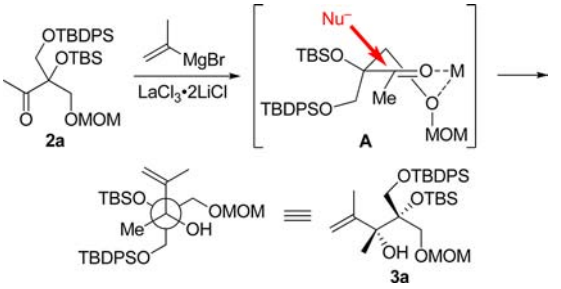
The relative stereochemistry of alcohol **3a** was assigned as outlined in Scheme 3. Selective removal of the MOM ether failed under a variety of conditions but was accomplished via the protocol of Tokuyama and Fukuyama, which enlists pentamethylbenzene as a cation scavenger and BCl_3 as a Lewis acid.[14] This method was initially devised for the deprotection of aryl benzyl ethers, and we are unaware of any prior examples of its use for MOM ether cleavage. Notably, unreacted pentamethylbenzene could be recovered cleanly from the reaction mixture. Then, formation of a six-membered cyclic acetonide from the resulting diol **8** furnished **9**. Diol *epi*-**8**, which was derived from MOM deprotection of a mixture of **3a** and its epimer followed by chromatographic separation, was transformed into the corresponding acetonide *epi*-**9**. Interestingly, the ketalization of *epi*-**8** proceeded in the presence of PPTS, whereas $TsOH \cdot H_2O$ was required to promote ketalization of its diastereomer **8**. The NOESY spectra of **9** and *epi*-**9** displayed several diagnostic through-space correlations as illustrated in Scheme 3, thereby enabling us to determine the relative stereochemistry of the vicinal tertiary diol moiety.

Scheme 3. Assignment of Relative Stereochemistry



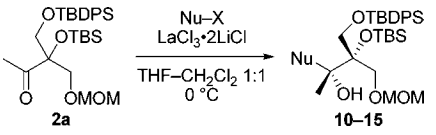
The observed diastereoselectivity in the $LaCl_3 \cdot 2LiCl$-promoted Grignard addition to ketone **2a** is consistent with the pathway depicted in Scheme 4. The improved dr obtained with the noncoordinating cosolvent CH_2Cl_2 suggests that 1,3-chelation control[15] may be operative. Thus, addition of the nucleophile to the less-hindered face of 1,3-chelated intermediate **A** provides the observed product **3a**. When the reaction is conducted in pure THF, a less-selective nonchelated addition process may become competitive because of disruption of **A** by the coordinating solvent. Although other alcohol protecting groups might be suitable, from the ketones **2a**–**g** examined to date it is clear that the combination of the bulky TBDPS ether and the somewhat smaller TBS ether enables a high degree of diastereocontrol.

Scheme 4. Rationale for Stereocontrol



The scope of diastereoselective additions to ketone **2a** was then explored with various nucleophiles. Alkyl and allyl nucleophiles furnished the tertiary alcohol adducts in excellent yields and dr's (no minor isomers were detected), and an alkyllithium reagent was viable as long as the reaction was performed in pure THF (Table 2, entries 1–3). In contrast, phenyl and vinyl Grignard reagents reacted with attenuated levels of diastereoselectivity (entries 4 and 5). Although an alkynyllithium reagent did not undergo addition to **2a** (entry 6), ethynylmagnesium bromide furnished adduct **15** in good yield and dr (entry 7).

Table 2. Additions of Selected Nucleophiles to Ketone **2a**



entry	Nu–X	product	% yield[a]	dr[b]
1[c]	Bu–Li	**10**	99	>19:1
2	Bu–MgCl	**10**	99	>19:1
3	Allyl–MgBr	**11**	93	>19:1
4	Ph–MgCl	**12**	98	5.1:1
5	Vinyl–MgBr	**13**	98	5.0:1
6	TMSC≡C—Li	**14**	nr[d]	–
7	HC≡C—MgBr	**15**	64	10:1

[a] Combined isolated yields of both diastereomers. [b] Determined by ^1H NMR. [c] Pure THF was employed as the solvent, and the reaction was conducted at −20 °C. [d] No reaction occurred in either THF–CH_2Cl_2 1:1 or pure THF.

Differentiated vicinal tertiary diols **3** and **10**–**15** contain several functional groups that are amenable to further elaboration. To demonstrate the synthetic potential of these compounds, diol **8** (derived from adduct **3a**, see Scheme 3) was transformed into cyclopentenone **18**, which contains the vicinal tertiary diol subunit of the cyclopentane

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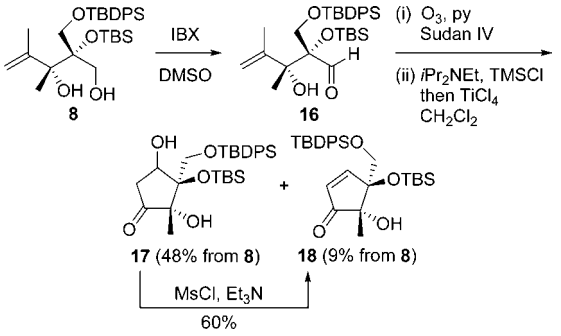
(15) (a) Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 4019. (b) Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035. (c) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729. (d) Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847. (e) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506. (f) Carreira, E. M.; Kvaerno, L. *Classics in Stereoselective Synthesis*; Wiley-VCH: Weinheim, 2009; pp 29–37.

Scheme 5. Synthesis of Cyclopentenone **18**



core of pactamycin.[16,17] Oxidation of the primary alcohol by IBX furnished aldehyde **16**, which was subjected to a one-pot ozonolysis/aldol cyclization process. Diol **17** was obtained in 48% overall yield from **8** along with a small amount (9%) of cyclopentenone **18**. Selective dehydration of **17** produced **18** in 60% yield, raising the overall yield of **18** to 38% from **8** (Scheme 5).

In conclusion, we have devised a strategy for the diastereoselective synthesis of differentiated vicinal tertiary diols. A range of Grignard and organolithium reagents can be employed in high-yielding $LaCl_3 \cdot 2LiCl$-promoted additions to ketone **2a**, which in turn is available via a short sequence from a known 1,3-dihydroxyacetone derivative. We propose that a 1,3-chelated intermediate is responsible for the high diastereoselectivities of the addition reactions. To illustrate the utility of this method, we converted adduct **3a** into cyclopentenone **18**, which resembles the congested cyclopentane core of pactamycin. In order to access targets such as zaragozic acid C and ryanodine, more elaborate ketones replacing the methyl group of **2a** with functionalized alkyl groups would be required. Although our study was limited to racemic compounds, **2a** or related ketones should be accessible in optically active form via enantioselective cyanosilylation[18] or enzymatic desymmetrization.[19] Future work will involve the application of this strategy to the construction of complex natural products.

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Supporting Information Available. Experimental procedures, characterization data, and NMR spectra for all new compounds, and details of the synthesis of ketones **2b**–**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) For synthetic studies targeting pactamycin, see (a) Tsujimoto, T.; Nishikawa, T.; Urabe, D.; Isobe, M. *Synlett* **2005**, 433. (b) Matsumoto, N.; Tsujimoto, T.; Nakazaki, A.; Isobe, M.; Nishikawa, T. *RSC Adv.* **2012**, *2*, 9448. (c) Knapp, S.; Yu, Y. *Org. Lett.* **2007**, *9*, 1359. (d) Ref 5e. (e) Ref 4f.

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The authors declare no competing financial interest.