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L-Selectride-Mediated Highly Diastereoselective Asymmetric Reductive Aldol Reaction: Access to an Important Subunit for Bioactive Molecules

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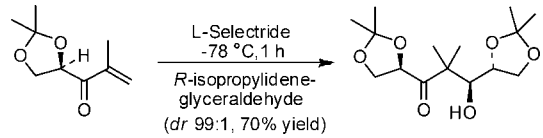
ABSTRACT



L-Selectride reduction of a chiral or achiral enone followed by reaction of the resulting enolate with optically active α-alkoxy aldehydes proceeded with excellent diastereoselectivity. The resulting α,α-dimethyl-β-hydroxy ketones are inherent to a variety of biologically active natural products.

Asymmetric aldol reactions leading to the stereocontrolled generation of β-hydroxy carbonyl derivatives are among the most important reactions in organic synthesis.[1] Consequently, a number of effective methodologies have been developed over the years. In a series of elegant studies, Stork and co-workers have shown that lithium−ammonia reduction of enones leads to stoichiometric generation of enolates.[2] Since then, reductive aldol reaction in which conjugate reduction followed by an aldol reaction of the resulting enolate led to the development of a wide variety of methodologies for the synthesis of β-hydroxy carbonyl derivatives.[3] In recent years, impressive progress has been made in both catalytic[4] and enantioselective[5] reductive aldol processes. In the context of our enantioselective synthesis of (+)-peloruside A, we recently carried out an L-Selectride mediated reductive aldol coupling of enone **1** and aldehyde **2** to provide aldol product **3** and its diastereomer as a 4:1 mixture in 92% yield at −78 °C for 1 h (Figure 1).[6,7] The major aldolate **3** was

(1) Mahrwald, R. *Modern Aldol Reactions*; Wiley-VCH: Germany, 2004; Vol. 1−2.

(2) (a) Stork, G.; Darling, S. D. *J. Am. Chem. Soc.* **1960**, *82*, 1512. (b) Stork, G.; Rosen, P.; Goldman, N. L. *J. Am. Chem. Soc.* **1961**, *83*, 2965. (c) Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J. *J. Am. Chem. Soc.* **1965**, *87*, 275.

(3) For recent reviews on reductive aldol reactions, see: (a) Han, S. B.; Hassan, A.; Krische, M. J. *Synthesis* **2008**, *17*, 2669. (b) Garner, S.; Krische, M. J. In *Modern Reduction Methods*; Andersson, P., Munslow, I., Eds.; Wiley-VCH: Weinheim, 2008; p 387. (c) Nishiyama, H.; Shiomi, T. *Top. Curr. Chem.* **2007**, *279*, 105.

(4) For recent metal-catalyzed reductive aldol reactions, see: (a) Shiomi, T.; Nishiyama, H. *Org. Lett.* **2007**, *9*, 1651. (b) Han, S. B.; Krische, M. J. *Org. Lett.* **2006**, *8*, 5657. (c) Jung, C. K.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 17051. (d) Baik, T. G.; Luis, A. L.; Wang, L. C.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 5112. (e) Lam, H. W.; Joensuu, P. M.; Murray, G. J.; Fordyce, E. A. F.; Prieto, O.; Luebbers, T. *Org. Lett.* **2006**, *8*, 3729. (f) Doi, T.; Fukuyama, T.; Minamino, S.; Ryu, I. *Synlett* **2006**, *18*, 3013. (g) Deschamp, J.; Chuzel, O.; Hannedouche, J.; Riant, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 1292. (h) Welle, A.; Diez-Gonzalez, S.; Tinant, B.; Nolan, S. P.; Riant, O. *Org. Lett.* **2006**, *8*, 6059. (i) Chrovian, C. C.; Montgomery, J. *Org. Lett.* **2007**, *9*, 537, and references cited therein.

(5) Bee, C.; Han, S. B.; Hassan, A.; Lida, H.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 2746.

(6) West, L. M.; Northcote, P. T.; Battershill, C. N. *J. Org. Chem.* **2000**, *65*, 445.

(7) Ghosh, A.; Xu, X.; Kim, J-H.; Xu, C-X. *Org. Lett.* **2008**, *10*, 1001.

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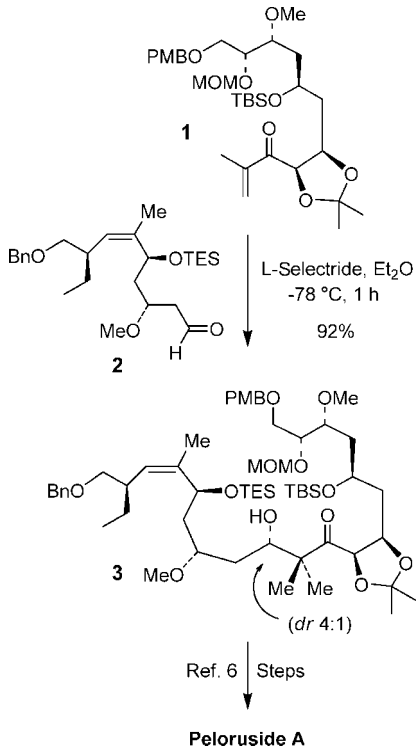
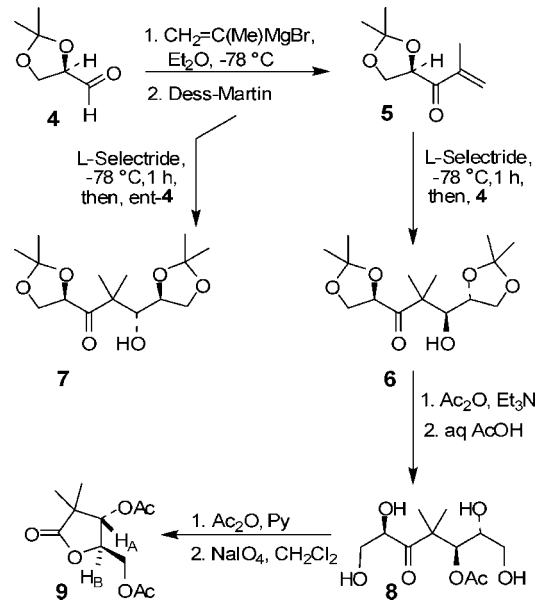


Figure 1. Reductive aldol reaction of **1** and **2**.

subsequently converted to peloruside A. The overall process is quite practical and offers significant improvement over the direct aldol reaction of a related ketone enolate and aldehyde reported recently.[8] Of particular importance, these α,α-dimethyl β-hydroxy carbonyl derivatives are structural features of numerous bioactive natural products like epothilones,[9] mycalamide A,[10] and peloruside A.[6] Encouraged by the reasonable diastereoselectivity of the L-Selectride mediated reductive aldol process, we have now examined the stereochemical outcome with a variety of chiral and achiral enones and aldehydes bearing an α- β-alkoxy stereocenter. Herein, we report the results of our investigations. Excellent levels of diastereoselectivity are attainable when the enolate from L-Selectride reduction is reacted with aldehydes containing an α-chiral center.

Our preliminary investigations focused on reactions with model enone **5** and optically active isopropylidene glyceraldehyde **4**. As shown in Scheme 1, enone **5** was prepared in a two-step sequence involving: (1) reaction of isopropenyl magnesium bromide in diethyl ether followed by Dess−Martin oxidation[11] of the resulting diastereomeric alcohols to enone

Scheme 1. Asymmetric Reductive Aldol Reaction of Chiral Enone with Chiral Aldehydes

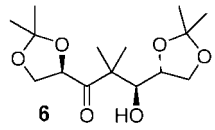
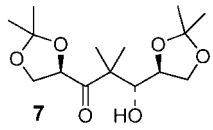
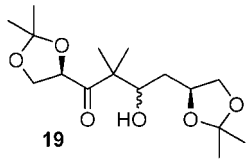
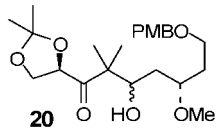
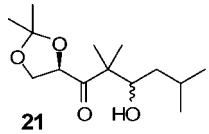
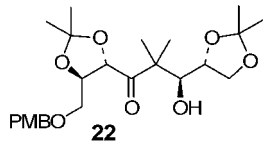
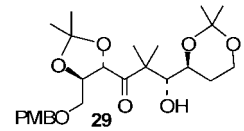
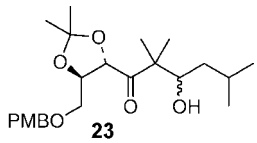
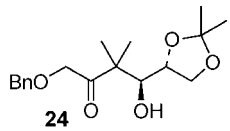
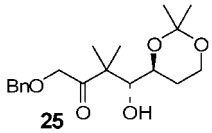


5 in 63% yield over two steps. Enone **5** was treated with 1.1 equiv of L-Selectride at −78 °C for 10 min to form the corresponding lithium enolate. To the resulting enolate, 2 equiv of isopropylidene-D-glyceraldehyde in diethyl ether was added via cannula. The reaction mixture was allowed to stir at −78 °C for 1 h. After this period, the reaction was quenched at −78 °C with aqueous NH_4Cl solution and warmed to 23 °C. Standard workup and flash chromatography afforded aldol product **6** in 70% yield as a single *anti*-diastereomer (by ^1H and ^{13}C NMR and HPLC analysis). Since enone **5** contains a chiral center, we then examined a stereodifferentiating experiment with L-glyceraldehyde *ent*-**4**. As shown in Table 1, reaction with *ent*-**4** also proceeded with excellent diastereoselectivity, indicating that the presence of enone chirality has no effect on anti-diastereoselectivity.

To determine the stereochemical course of the reductive aldol reaction, aldol product **6** was converted to known 3,5-diacetoxy γ-lactone **9** as follows. Protection of the hydroxyl group as an acetate followed by removal of isopropylidene groups by exposure to 40% aqueous acetic acid at 80 °C provided the corresponding tetrol **8** in 76% yield over two steps. Reaction of **8** with 2 equiv of acetic anhydride in pyridine provided the corresponding triacetoxy α-hydroxy ketone in 45% yield. Reaction of hydroxyketone with sodium periodate afforded γ-lactone **9** in 45% yield. The ^1H NMR coupling constant ($J = 5.7$ Hz) between H_A and H_B as well as their chemical shifts were found to be consistent with an *anti*-isomer.[12] Similarly, aldol product **7** was converted to *ent*-**9** lactone to confirm the assignment of stereochemistry for **7**. The stereochemical course of the aldol process can be explained by using a related model described by Mukaiyama and co-workers.[13] As shown in Figure 2, L-Selectride

(8) Liu, B.; Zhou, W-S. *Org. Lett.* **2004**, *6*, 71.
(9) Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem.* **1996**, *108*, 1671; *Angew. Chem., Int. Ed Engl.* **1996**, *35*, 1567. Gerth, K.; Bedorf, N.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot.* **1996**, *49*, 560.
(10) West, L. M.; Northcote, P. T.; Battershill, C. N. *J. Org. Chem.* **2000**, *65*, 445.
(11) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(12) Kita, Y.; Tamura, O.; Itoh, F.; Yasuda, H.; Kishino, H.; Ke, Y.-Y.; Tamura, Y. *J. Org. Chem.* **1988**, *53*, 554.
(13) Suzuki, K.; Yuki, Y.; Mukaiyama, T. *Chem. Lett.* **1981**, 1529.

Table 1. Reductive Aldol Reactions of a Variety of Enones and Aldehydes

enone	aldehyde	aldol product	*dr* [a](yield %)[b]
5	**4**	 **6**	99:1 (70)
5	ent-**4**	 **7**	99:1 (67)
5	**15**	 **19**	42:58 (84)
5	**16**	 **20**	58:42 (63)
5	**17**	 **21**	1:1 (50)
11	**4**	 **22**	99:1 (74)
11	**18**	 **29**	4:1[c] (64)
11	**17**	 **23**	62:38 (50)
13	**4**	 **24**	99:1[d] (72)
13	**18**	 **25**	99:1 (65)

[a] Ratios were determined by ^{1}H and ^{13}C NMR analysis [b] Yields are after silica gel chromatography. [c] Ratios are from isolated yields. [d] HPLC analysis corresponds to ^{1}H and ^{13}C NMR ratio.

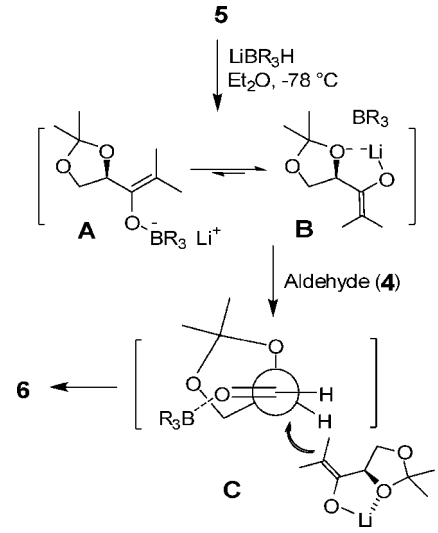


Figure 2. Stereochemical model for aldol reactions.

reduction of **5** may lead to the formation of intermediate enolates **A** and **B**, and equilibrium may favor enolate **B** because of metal chelation. Enolate addition to aldehyde **4** may proceed through **C** and provide *anti*-alcohol **6** selectively.[14]

We have investigated diastereoselectivity associated with an aldol reaction containing a β-alkoxy stereocenter on the aldehyde component. As shown, the reaction of **5** and isopropylidene butyraldehyde **15** proceeded with limited diastereoselectivity. We have further examined aldol reaction of enone **5** with aldehyde **16**. Limited diastereoselectivity was also observed for the β-methoxy aldehyde substrate. Similarly, reaction with isovaleraldehyde **17** proceeded with limited diastereoselectivity.

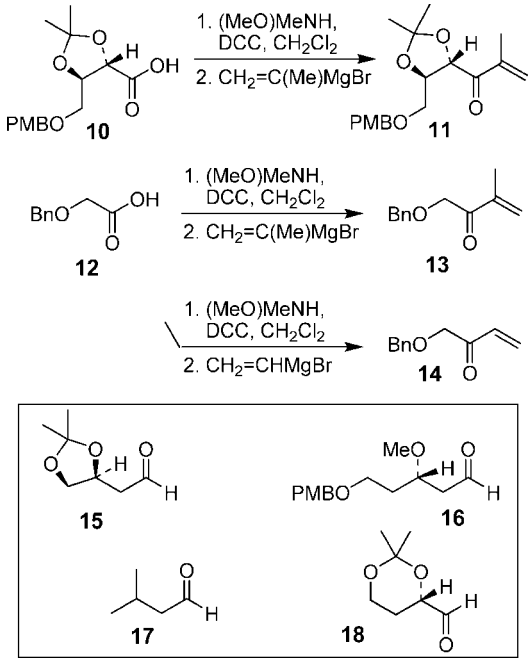
We have prepared chiral enone **11** and achiral enone **13** and examined reductive aldol reactions with aldehydes containing α-chiral centers. Enone **11** was synthesized by conversion of known[15] carboxylic acid **10** to its corresponding Weinreb amide[16] followed by reaction with isopropenyl Grignard reagent. Similarly, enones **13** and **14** were prepared from benzyloxyacetic acid **12**. Aldol reaction of **11** with *R*-glyceraldehyde (**4**) again proceeded with excellent diastereoselectivity. As an orthogonal measure of the diastereoselectivity of this reaction, we utilized HPLC to follow this reductive aldol reaction. HPLC was able to indirectly follow the conversion of the enone to the enolate. Analysis of the crude reaction mixture after quenching with sat. NH_4Cl revealed a single major peak. To ensure that the other diastereomer was indeed being separated by our chromatographic conditions, we repeated the reaction at a higher temperature in hopes of generating the other diastereomer. After forming the enolate in >98% yield at −78 °C, we allowed the addition of aldehyde **4** to occur at 23 °C. HPLC

(14) The coordination by trialkylborane with carbonyl oxygen is presumably weak.

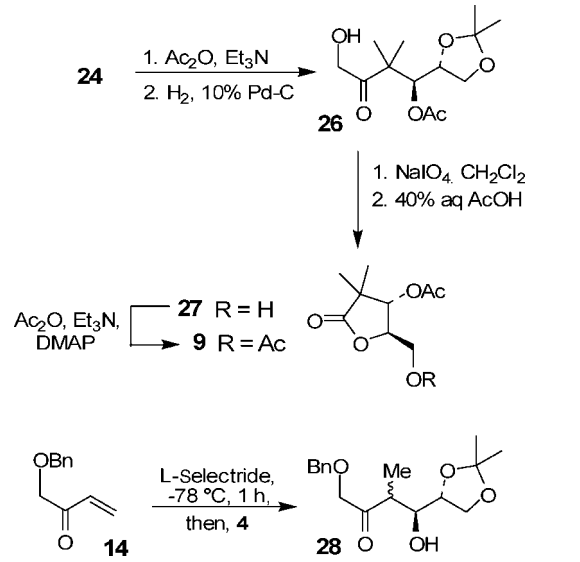
(15) (a) Kigoshi, H.; Kita, M.; Ogawa, S.; Masahiro, I.; Uemura, D. *Org. Lett.* **2003**, *5*, 957. (b) Saito, S.; Ishikawa, T.; Moriwake, T. *J. Org. Chem.* **1994**, *59*, 4375.

(16) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

Scheme 2. Synthesis of Enones **10**, **12**, and **13**



Scheme 3. Synthesis of **9** and Aldol Reaction of **14**



analysis of the crude reaction showed elevated levels of byproducts. Purification of the material allowed the isolation of the diastereomer, and subsequent HPLC analysis confirmed its retention time. To our delight, the diastereomers of **22** were adequately resolved. Furthermore, the diastereoselectivity of the reaction was confirmed to be 99:1 at −78 °C and 92:8 at 23 °C. Interestingly, the reaction of **11** with isovaleraldehyde **17** provided a 60:40 mixture of diastereomers, indicating that the β-chiral center on the enone may be responsible for a weak directing effect. Since the α-chiral center of the aldehyde is directly responsible for the excellent observed diastereoselectivity, we then examined an aldol reaction with an enolate derived from achiral enone **13**. As can be seen, reactions with both isopropylidene glyceraldehyde **4** and isopropylidene butyraldehyde **18** provided respective *anti*-diastereomers **24** and **25** as a single product in very good yields.

The assignment of stereochemistry for **24** was made after its conversion to diacetoxy γ-lactone **9** as shown in Scheme 3. The free hydroxyl group in **24** was protected as its acetate. Catalytic hydrogenation over 10% Pd−C provided the hydroxyl ketone **26**. Sodium periodate cleavage followed by removal of the isopropylidene group by exposure to 40% aqueous acetic acid at 80 °C afforded γ-lactone **27**. It was then protected as its acetate to give γ-lactone **9**. The stereochemical outcome of this aldol addition thus indicates *anti* addition of the enolate to the isopropylidene glyceraldehyde. We have also investigated *syn*/*anti* aldol diastereoselectivity by reductive aldol reaction of enone **14** and aldehyde **4**. However, generation of enolate and its subsequent addition to aldehyde provided a complex mixture of products. Further optimization of conditions is being investigated.

In conclusion, we have developed highly diastereoselective reductive aldol methodology. Reactions involved an L-Selectride reduction of chiral or achiral isopropenyl ketones followed by reaction of the resulting enolates with aldehydes containing an alkoxy stereocenter. The stereochemical course of the reaction can be rationalized using a transition state model proposed by Mukaiyama and co-workers. Further exploration of this methodology is currently ongoing in our laboratory.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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