Tandem Aldol−Tishchenko Reactions of Lithium Enolates: A Highly Stereoselective Method for Diol and Triol Synthesis

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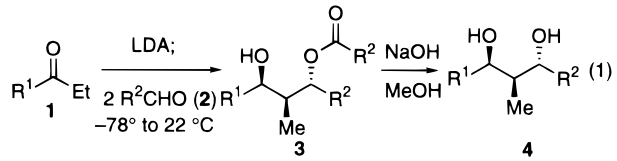
The reactions of metal enolates constitute important methods for the construction of carbon−carbon bonds.[1] Early investigations of aldol reactions employing lithium ketone enolates provided significant mechanistic information,[2] although these reactions are not generally as stereoselective as those of other enolates.[1,3] Recently, two intriguing reports described stereoselective reactions of lithium ketone enolates:[4,5] they react with 2 equiv of aldehyde to provide *anti*-1,3-diol derivatives by a sequence of aldol addition and intramolecular Tishchenko-type[6] reduction.[7−10] Although these reactions possess significant potential for organic synthesis, the generality of these transformations has not been investigated. We report here that the tandem[11] aldol−Tishchenko reaction of lithium enolates is a simple method for the synthesis of polyoxygenated organic compounds, creating three or five stereocenters in a single operation with high stereoselectivity. These tandem transformations compliment current aldol technology[1] because they represent a distinct approach to stereocontrol of enolate reactions, in that C−H bond formation, not C−C bond formation, determines the stereochemical outcome.

As part of research directed at utilizing silacyclopropane chemistry for organic synthesis,[12] we required a synthesis of aldol adducts of propiophenone and acetaldehyde to confirm stereochemical assignments. When the lithium enolate of propiophenone[2] was treated with 2.2 equiv of acetaldehyde at −78 °C followed by warming to 22 °C, a mixture of acetates (**3a**) was obtained; hydrolysis provided the diol **4a** as a 98:2 mixture of diastereomers in 41% yield (eq 1; Table 1, entry 1). The fact that no β-hydroxy ketones were isolated is consistent with the known reactivity of these enolates: standard aldol conditions involve the use of 1 equiv of aldehyde, low temperatures (−78 °C), and extremely short reaction times.[2] The aldol−Tishchenko reaction occurs with high selectivities and good yields for other aldehydes with little (<10%) acyl transfer (Table 1).[13] The reaction can be applied to 2-methyl-3-pentanone in place of propiophenone (Table 1, entries 4, 5). The stereochemistry of the products was determined by comparison to reference compounds and by analysis of the derived 1,3-diol acetonides by ^{13}C NMR spectroscopy.[14−16]

Table 1. Stereoselectivity of the Tandem Aldol−Tishchenko Reaction (eq 1)[a]

entry	ester/diol	R^1	R^2	yield of **3**, %	ds, %[b]	yield of **4**, %[c]
1	**3a**/**4a**	Ph	Me		98	41
2	**3b**/**4b**	Ph	Et	76	98	64
3	**3c**/**4c**	Ph	*i*-Pr	69	>99	62
4	**3d**/**4d**	*i*-Pr	Ph	73	87	72
5	**3e**/**4e**	*i*-Pr	*i*-Pr		>99	56[d]

[a] LDA as base, 2.2 equiv of aldehyde. These standard conditions were used unless otherwise noted. [b] Diastereoselectivity determined by analysis of the unpurified diol **4** by GC. [c] Overall yield from **1**. [d] LHMDS as base.



Experiments were conducted to provide insight into the reaction mechanism, which most likely includes an aldol addition step. Treatment of the aldol adduct *syn* -**5**[17] with LDA followed by 1.1 equiv of propionaldehyde under conditions similar to eq 1 resulted in a 1:1 ratio of diol **4c** and crossover product **4b** after hydrolysis (91% combined yield; eq 2). The same ratio of **4c** and **4b** was

(1) (a) For a recent review of stereoselective aldol reactions, see: Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.* **1994**, *1*, 317−338. (b) For a review of lithium enolate aldol reactions, see: Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 181−238.

(2) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066−1081.

(3) For recent investigations of aldol reactions employing lithium enolates, see: Evans, D. A.; Yang, M. G.; Dart, M. J.; Duffy, J. L. *Tetrahedron Lett.* **1996**, *37*, 1957−1960 and references cited therein.

(4) Baramee, A.; Chaichit, N.; Intawee, P.; Thebtaranonth, C.; Thebtaranonth, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 1016−1017.

(5) Horiuchi, Y.; Taniguchi, M.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1995**, *36*, 5353−5356.

(6) (a) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447−6449. (b) The method reported by Evans and Hoveyda has been applied to the synthesis of rapamycin: Romo, D.; Meyer, S. D.; Johnson, D. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 7906−7907.

(7) In a synthesis of zaragozic acid A, Heathcock observed diol monoesters when lithium enolates were treated with excess aldehyde: Caron, S.; Stoermer, D.; Mapp, A. K.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9126−9134.

(8) For a related transformation, see: Molander, G. A.; McKie, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 5821−5822.

(9) Other isolated examples of this reaction have been observed for other metal enolates. (a) Zinc: ref 5. (b) Samarium: Curran, D. P.; Wolin, R. L. *Synlett* **1991**, 317−318. (c) Nickel: Burkhardt, E. R.; Bergman, R. G.; Heathcock, C. H. *Organometallics* **1990**, *9*, 30−44.

(10) Recently, Mahrwald reported a titanium-catalyzed tandem aldol−Tishchenko reaction involving 3-pentanone and aldehydes: Mahrwald, R.; Costisella, B. *Synthesis* **1996**, 1087−1089.

(11) The utility of tandem reactions in synthesis has been discussed; see, for example: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (b) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307−338.

(12) (a) Bodnar, P. M.; Palmer, W. S.; Shaw, J. T.; Smitrovich, J. H.; Sonnenberg, J. D.; Presley, A. L.; Woerpel, K. A. *J. Am. Chem. Soc.* **1995**, *117*, 10575−10576. (b) Bodnar, P. M.; Palmer, W. S.; Ridgway, B. H.; Shaw, J. T.; Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **1997**, *62*, 4737−4745.

(13) Representative Experimental: Preparation of Ester **3b**. Freshly distilled diisopropylamine (0.57 mL, 4.4 mmol) was added to 10 mL of anhydrous THF. To the cooled (0 °C) solution was added 1.2 M *n*-BuLi in hexanes (3.6 mL, 4.3 mmol). After 10 min, the reaction mixture was cooled to −78 °C. To the cooled reaction mixture was added distilled propiophenone (0.50 mL, 3.8 mmol). After 20 min, distilled propionaldehyde (0.57 mL, 7.90 mmol) was added dropwise (1 min), and the resulting solution was stirred for 1 h at −78 °C. The reaction mixture was then warmed to 22 °C, stirred for 12 h, quenched with 20 mL of saturated aq $NaHCO_3$, extracted with CH_2Cl_2, filtered through cotton, and concentrated *in vacuo*. Purification by flash chromatography (90:10 to 70:30 hexanes:EtOAc) provided the product as a colorless oil (712 mg, 76% yield): IR (neat) 3506, 2974, 1703, 1603, 1081 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.91 (m, 1H), 4.80 (m, 1H), 2.81 (d, J = 3.7 Hz, 1H), 2.43 (q, J = 7.6 Hz, 2H), 1.93 (m, 1H), 1.76 (m, 1H), 1.63 (m, 1H), 1.20 (t, J = 7.5 Hz, 3H), 0.93 (t, J = 7.5 Hz, 3H), 0.76 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 142.8, 128.0, 126.7, 125.6, 77.3, 71.7, 43.4, 27.7, 24.8, 9.5, 9.3, 8.9; HRMS (CI) m/z calcd for $C_{15}H_{23}O_3$ $(M + H)^+$ 251.1647, found 251.1646. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.07; H, 8.81.

(14) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511−3515.

(15) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099−7100.

(16) The details are provided as Supporting Information.

(17) (a) Hamana, H.; Sasakura, K.; Sugasawa, T. *Chem. Lett.* **1984**, 1729−1732. (b) Evans, D. A.; Calter, M. A. *Tetrahedron Lett.* **1993**, *34*, 6871−6874.

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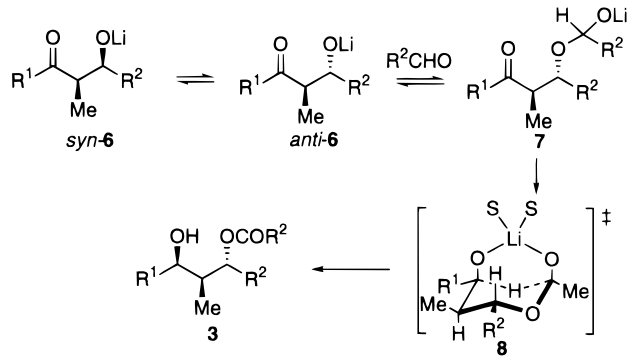
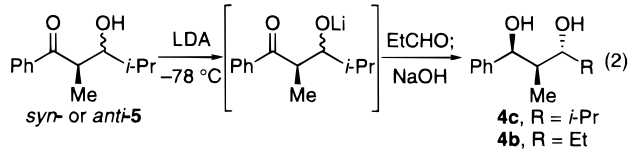
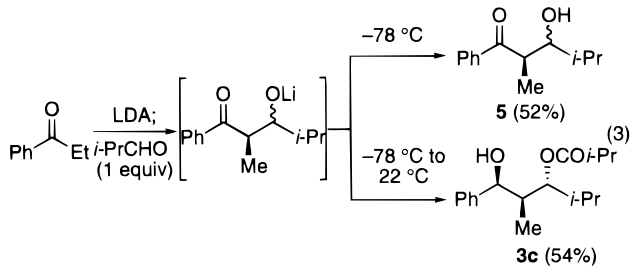
Scheme 1



obtained starting from *anti*-**5**.[18] Therefore, lithium aldolates are probably reactive intermediates in the tandem reaction. Since neither the stereochemical relationships of the products **4b**,**c** nor the nature of the alkyl group (*i*-Pr or Et) is dependent upon the structure of the aldolate, the aldol addition step must be reversible and not stereochemistry-determining.[4]

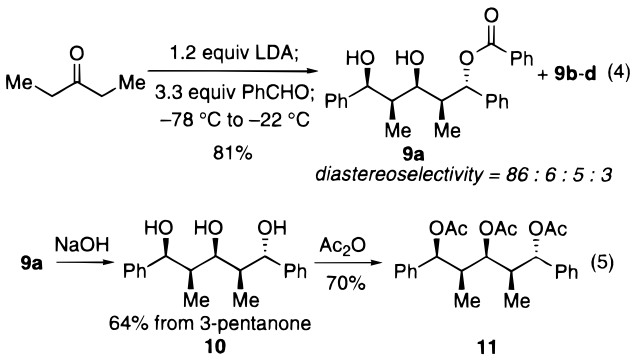


To determine the relative rates of the aldol addition and Tishchenko reduction steps, a solution of the aldolate was quenched at different temperatures. When isobutyraldehyde (1 equiv) was added to a solution of the enolate of propiophenone at −78 °C and the mixture was quenched after 10 s,[2] the expected aldol adducts **5** were formed (eq 3) with poor stereoselectivity (*anti*:*syn* = 46:54). If the solution of aldolate were warmed to 22 °C before quenching, the monoester **3c** was generated as a major product (54% yield based on 54% recovered propiophenone) along with the aldol adducts **5** (11% yield, *anti*:*syn* = 32:68). These results confirm that reduction is slower than aldol addition, but sufficient quantities of aldehyde are liberated from aldolates to carry out reduction.[6]



The high stereoselectivity of this reaction can be rationalized by a mechanism involving reversible aldol addition and hemiacetal formation, followed by rate- and stereochemistry-determining hydride transfer from a lithium hemiacetal (Scheme 1). The six-membered transition state for the Tishchenko reduction (**8**) resembles the transition structure identified computationally for hydride transfer between LiOMe and CH_2O[19] and proposed by Evans and Hoveyda for the anti selective samarium-catalyzed Tishchenko reduction of β-hydroxy ketones.[6,20] Since experiments indicate that the aldol addition step is reversible (eqs 2, 3), the methyl group can be placed in the equatorial position in the lowest energy transition state **8** leading to product. The mechanistic postulate of Scheme 1 differs from the one favored by Thebtaranonth et al., who proposed that both equivalents of aldehyde and the enolate are brought together simultaneously in a single transition state.[4]

Initial attempts to extend this reaction to 3-pentanone and benzaldehyde failed under the conditions developed for other ketones. If 3.3 equiv of benzaldehyde were employed, however, the diol benzoates **9a**−**d** were formed as an 86:6:5:3 mixture of diastereomers (by GC of the corresponding acetates **11**, *vide infra*) in 81% yield on a multigram scale (eq 4). The major diastereomer was proven to be **9a** by hydrolysis to afford triol **10** followed by acetylation (eq 5); the stereochemistry of **11** was determined by X-ray crystallography.[16] It is noteworthy that one product was formed almost exclusively, although 15 other stereoisomers of the triol monoester could possibly have been produced. This reaction can be considered to be a tandem sequence of two aldol additions, proton transfer, and intramolecular Tishchenko reduction steps.



These experiments demonstrate that the tandem lithium aldol−Tishchenko reaction can be used to form 1,3-diol derivatives with high stereochemical control. The stereoselectivity observed in the reaction appears to be a result of a rate-determining reduction which allows for the equilibration of aldolates. This operationally simple process is also applicable to the stereoselective formation of a 1,3,5-triol monoester in one step.

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Supporting Information Available: Full characterization data, stereochemistry proofs, and X-ray crystallographic data for **11** (20 pages).

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(18) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441−3442.

(19) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 906−908.

(20) We believe that formation of hemiacetal **7** is also reversible, since addition of the aldolates **6** to the aldehyde R^2CHO is likely to occur with little stereoselectivity at the newly formed hemiacetal stereocenter. Only one diastereomer of **7** is capable of undergoing hydride transfer by the six-membered transition state **8**.