Pergamon

Tetrahedron Letters 43 (2002) 1789–1792

TETRAHEDRON LETTERS

Glycolate aldol reactions with boron enolates of bis-4-methoxyphenyl dioxanone

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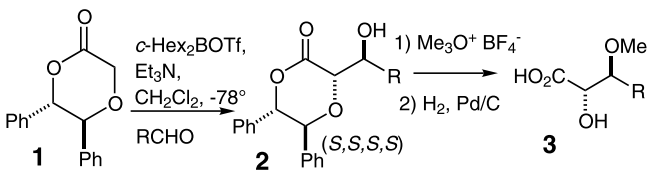
Received 29 November 2001; accepted 11 January 2002

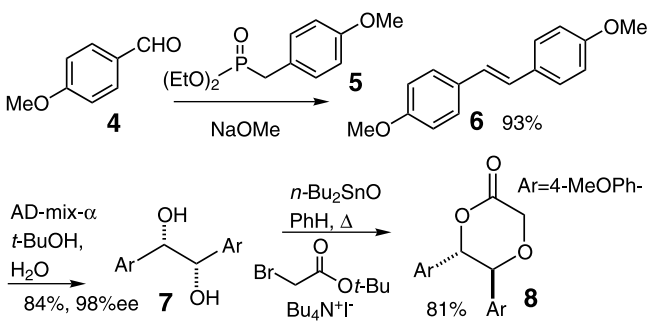
Abstract—The boron enolate of 5*S*,6*S*-bis-5,6-(4-methoxyphenyl)-2-dioxanone reacted with various aldehydes to produce *anti* glycolate aldol products in high yield with good selectivity. The outcome is consistent with an *E*-enolate reacting through a closed transition state. The adducts were protected and the auxiliary was conveniently removed with ceric ammonium nitrate to give useful intermediates.

Aldol reactions with glycolate esters and aldehydes have been used extensively to produce differentially protected 1,2-diol products. Various auxiliary and ligand based approaches have been successful with preformed enolates being the most common.[1] While some success has been found for *anti* stereoselection, the majority of cases involve *syn* outcomes using oxazolidinone-based glycolates.[2] A systematic study examining a range of aldehydes with norephedrine glycolate esters to produce *syn* products was recently reported by us.[3] In contrast to stoichiometric approaches, catalytic glycolate aldols have been very limited with only a few cases reported. Kobayashi's tin glycolates with good selectivity for either the *syn* or *anti* diols remain the prime examples.[4] Recently proline catalysis has been extended to hydroxy-ketone aldol reactions with success.[5] The alternative approach using osmium-catalyzed asymmetric dihydroxylation (AD) works very well for *syn* diols from *E* olefins but is not useful for applications with *Z*-alkenes leading to *anti* diols.[6] We recently reported the use of 5,6-diphenyl-2-dioxanone **1** to produce *anti* products **2** with aldehydes under aldol conditions (Scheme 1).[7] The removal of the auxiliary was limited to hydrogenation with palladium on carbon catalysis. We now report the synthesis and aldol reactivity of 5*S*,6*S*-bis-5,6-(4-methoxyphenyl)-2-dioxanone that can now be easily removed under oxidative cleavage conditions to generate differentially protected diol ester products.

The new dioxanone was made in analogous fashion to the previous diphenyl substrate beginning with formation of *E*-4,4′-dimethoxy stilbene **6** (Scheme 2). 4-Methoxybenzaldehyde was reacted with benzyl phosphonate **5**, obtained from an Arbuzov reaction with ethyl phosphite, under basic conditions to give **6** as a single isomer in 93% yield as a white crystalline solid (mp 211–214°C).[8] Treatment with Sharpless' AD-mix-α reagent[6] in a water-*t*-butyl alcohol mixture using the standard conditions gave the *S*,*S* diol **7** in 84% yield with 98% ee following recrystallization from ethyl acetate–hexanes.[9] The selectivity in this case was established by ^{1}H NMR of a mono Mosher's ester formed



Scheme 1.



Scheme 2.

Keywords: aldol reaction; glycolate; enolate; diols; diastereoselection.

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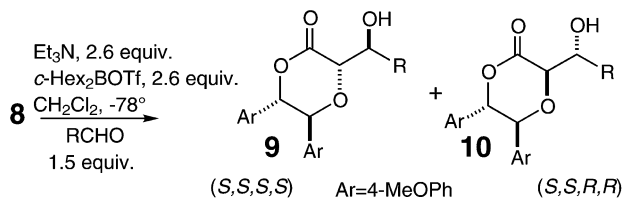
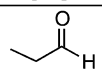
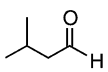
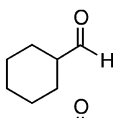
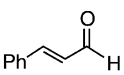
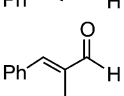
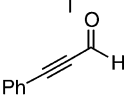
0040-4039/02/$ - see front matter
PII: S0040-4039(02)00152-1

from diol **7**.[10] Diol **7** was treated with di-*n*-butyl tin oxide in benzene heated at reflux followed by addition of *t*-butyl bromoacetate.[11] The desired 5,6-bis-(4-methoxyphenyl)-dioxanone **8** was obtained in 81% yield following silica gel chromatography.[12] Yields have remained consistent for this three-step sequence on scales of 5–10 g.

Aldol reactions were performed using optimized conditions, which include triethylamine and dicyclohexylboron triflate in methylene chloride at −78°C (Table 1).[13] The boron enolate formation was allowed to occur for a period of 3 h prior to addition of the aldehyde that was used as 1.5 equivalents. After a reaction time of 30 min, followed by standard quenching, work-up, and purification, the aldol products were obtained in good to excellent yields based on the auxiliary. The observed ratios for the major *anti* isomers **9** and **10** were determined by ^{1}H NMR by integrating the well-resolved signals corresponding to the protons located at the α and β ester positions. Only trace amounts of *syn* isomers were detected in a few cases. Normally, only the two *anti* diastereomers were detected. The selectivity was found to be excellent at 12:1 and 11:1 for alkyl aldehydes including α- and β-branched examples indicated. Previously the selectivity for isovaleraldehyde with the 5,6-diphenyldioxanone enoloate was found to be somewhat lower with 8:1 selectivity.[7a] This new bis-methoxyphenyl dioxanone has recently been used to produce an advanced intermediated in the synthesis of the ansamycin antibiotic geldanamycin.[7b] The β-branched aldehyde for that case gave *anti* product with 15:1 selectivity. Cyclohexane carboxaldehyde in this case gave product with reduced 7:1 selectivity (Table 1). Aromatic aldehydes also showed reduced selectivity. Benzaldehyde gave only 2:1 selectivity and cinnamaldehyde was moderate at 4:1. Other conditions using the lithium enolate, generated from treatment with LDA, or use of Lewis acids together with amine bases have not been successful.

Table 1. *anti* aldol reactions with dioxanone **8**



RCHO	yield[a]	dr[b]
	82%	11:1
	91%	11:1
	83%	12:1
	78%	7:1
	81%	2:1
	87%	4:1
	92%	4:1
	94%	5:1

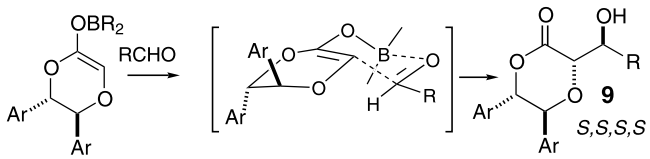
[a]Yields reported are for chromatographed, pure materials.

[b]Diastereomeric ratios were determined by ^{1}H NMR.

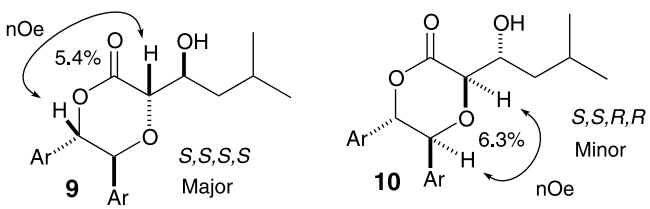
The major *S*,*S*,*S*,*S* isomer was established previously using single-crystal X-ray analysis.[7a] The origin for the selectivity is a consequence of the aldehyde attack occurring upon the *re* face of the enolate opposite from the C-5 4-methoxyphenyl group (Scheme 3). With the enolate locked in the *E*-configuration, the closed Zimmerman–Traxler aldol transition state arrangement generates *anti* aldol product with boron acting as Lewis acid with the aldehyde in a 6-ring chair conformation.[14]

The absolute stereochemistry was established previously using X-ray analysis and direct comparison to products prepared following independent procedures.[7a] Now with the new aldol products, homonuclear ^{1}H NMR NOE measurements were made on the two *anti* product isomers to confirm the stereochemistry (Scheme 4). Irradiation of the ^{1}H signals corresponding to the benzylic lactone ring protons gave clear evidence for the stereochemistry as observed previously. The major *S*,*S*,*S*,*S* isomer showed a 5.4% enhancement for the α-ester proton upon irradiation of the C-6 hydrogen, indicating a *cis* relationship. In addition, a 6.3% enhancement was seen at this position with the minor *S*,*S*,*R*,*R* isomer upon C-5 irradiation.[15]

The advantage now offered by the bis-(4-methoxyphenyl)-dioxanone auxiliary is ease of removal using oxidative cleavage conditions in place of the high-pressure hydrogenation conditions required previously. Three products **10** from Table 1 were trans-

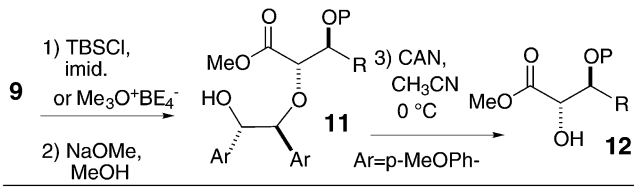


Scheme 3.



Scheme 4.

Table 2. Protection and auxiliary removal with aldol adducts **9**



R	P, yield[a]	ester yield	CAN removal
	Me, 81%	85%	81%
	TBS, 77%	75%	89%
	TBS, 85%	77%	70%

[a]All yields are for isolated, chromatographed materials

formed by protecting the β-hydroxyl with two groups, either as a methyl ether using Meerwein's salt or as a *tert*-butyldimethylsilyl (TBS) ether (Table 2). The lactone was then ring opened to the methyl ester **11** using sodium methoxide (0.01 equiv.) in a 1:1 methanol–THF mixture with stirring overnight. Ceric ammonium nitrate (CAN, 2.5 equiv.) was then used in a 9:1 acetonitrile–water mixture at 0°C for 2 h to cleave the activated 4-methoxybenzyl ether generating hydroxy ester product together with two equivalents of 4-methoxybenzaldehyde. Chromatography then gave pure differentially protected *anti* diol ester products in good overall yield for the three-step sequence. Other substrates and protecting groups are expected to give similar results.

The new 5*S*,6*S*-bis-5,6-(4-methoxyphenyl)-2-dioxanone, readily made in two steps using catalytic AD-mix-α reagent and a simple stilbene, produces *anti* glycolate aldol products with a wide range of aldehydes. The auxiliary is readily removed with CAN following protection to give synthetically useful *anti* diol intermediates. Efforts to further improve the selectivity and apply the auxiliary to other transformations are underway.

Acknowledgements

We wish to thank the National Institutes of Health (GM57275) and the Brigham Young University Cancer Center for funding and Dr. Bruce Jackson for mass spectroscopy and Dr. Li Du for NMR assistance.

References

1. (a) Gennari, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 2.4; (b) Cameron, J. C.; Paterson, I. *Org. React*. **1997**, *51*, 1.
2. *syn* Versions: (a) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc*. **1988**, *110*, 2506–2513; (b) Ku, T. W.; Kondrad, K. H.; Gleason, J. G. *J. Org. Chem*. **1989**, *54*, 3487–3489; (c) Andrus, M. B.; Schreiber, S. L. *J. Am. Chem. Soc*. **1993**, *115*, 10420–10421; (d) Evans, D. A.; Barrow, J. C.; Leighton, J. L.; Robichaud, A. J.; Sefkow, M. *J. Am. Chem. Soc*. **1994**, *116*, 12111–12112; (e) Crimmins, M. T.; Choy, A. L. *J. Org. Chem*. **1997**, *62*, 7548–7549; (f) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc*. **1999**, *121*, 5653–5660; (g) Haight, D.; Birrell, H. C.; Cantello, B. C. C.; Eggleston, D. S.; Haltiwanger, R. C.; Hindley, R. M.; Ramaswany, A.; Stevens, N. C. *Tetrahedron: Asymmetry* **1999**, *10*, 1353–1367. *anti*: (h) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc*. **1990**, *112*, 7001–7011; (i) Evans, D. A.; Gage, J. R.; Leighton, J. L.; Kim, A. S. *J. Org. Chem*. **1992**, *57*, 1961–1963; (j) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc*. **1986**, *108*, 6757–6761; (k) Li, Z.; Wu, R.; Michalczyk, R.; Dunlap, R. B.; Odom, J. D.; Silks, L. A., III *J. Am. Chem. Soc*. **2000**, *122*, 386–387.
3. Andrus, M. B.; Soma Sekhar, B. B. V.; Turner, T. M.; Meredith, E. L. *Tetrahedron Lett*. **2001**, *42*, 7197–7201.
4. (a) Kobayashi, S.; Kawasuji, T. *Tetrahedron Lett*. **1994**, *35*, 3329–3332; (b) Kobayashi, S.; Hayashi, T. *J. Org. Chem*. **1995**, *60*, 1098–1101; (c) Gennari, C.; Vulpetti, A.; Pain, G. *Tetrahedron* **1997**, *53*, 5909–5914.
5. List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc*. **2000**, *122*, 2395–2396.
6. (a) Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc*. **1992**, *114*, 7568–7569; (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483–2523.
7. (a) Andrus, M. B.; Soma Sekhar, B. B. V.; Meredith, E. L.; Dalley, N. K. *Org. Lett*. **2000**, *2*, 3035–3037; (b) Andrus, M. B.; Meredith, E. L.; Soma Sekhar, B. B. V. *Org. Lett*. **2001**, *3*, 259–262. For other cyclic glycolate aldol approaches, see: (c) Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2704–2709; (d) Pearson, W. H.; Cheng, M.-C. *J. Org. Chem*. **1987**, *52*, 3176–3178; (e) Comins, D. L.; Kuethe, J. T.; Lakner, F. J. *J. Am. Chem. Soc*. **1999**, *121*, 2651–2652; (f) Evans, D. A.; Hu, E.; Tedrow, J. S. *Org. Lett*. **2001**, *3*, 3133–3136; (g) Dixon, D. J.; Ley, S. V.; Polara, A.; Sheppard, T. *Org. Lett*. **2001**, *3*, 3749–3752.
8. Preparation of *trans*-4,4′-dimethoxy-stilbene **6**. Diethyl 4-methoxybenzylphosphonate **5** (10 g, 38.7 mmol) in DMF (96.8 mL) was treated with NaOMe (6.27 g, 116 mmol) at rt for 20 min and *p*-anisaldehyde **4** (5.66 mL, 46.5 mmol) was added. The solution was allowed to stir for an additional 30 min, then warmed to 100°C for 7 h. The reaction was cooled to rt and stirred overnight then the reaction was quenched with cold H_2O. White crystals were collected and washed with cold acetone (8.75 g, 93% yield); mp 211–214°C; R_f=0.43 (30% EtOAc/hexanes); ^1H NMR (300 Hz, $CDCl_3$) δ 7.44–7.41 (m, 4H), 6.93–6.87 (m, 6H), 3.83 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 159.3, 130.7, 127.7, 126.4, 114.4, 100.3, 55.6; HRMS EI (M+Na) calcd for $C_{16}H_{16}O_2$ 240.1150, found 240.1152.
9. Mp 102–105°C, $[\alpha]_D=-112$ (*c* 1.50, CH_2Cl_2).
10. Mosher, H. S.; Dale, J. A. *J. Org. Chem*. **1970**, *35*, 4002–4008.
11. (a) Burke, S. D.; Sametz, G. M. *Org. Lett*. **1999**, *1*, 71–74; (b) David, S.; Thieffry, A.; Veyrieres, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1796–1798.

12. See Ref. 7a for the procedure. Data for dioxanone **8**: mp 116–118°C, $[\alpha]_D = -125$ (*c* 1.68, CH_2Cl_2); $R_f = 0.14$ (30% EtOAc/hexanes); ^1H NMR (300 Hz, $CDCl_3$) δ 7.01–6.95 (m, 4H), 6.81–6.76 (m, 6H), 5.42 (d, $J = 9.3$ Hz, 1H), 4.76 (d, $J = 17.8$ Hz, 1H), 4.60–4.54 (m, 2H), 3.78 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 167.5, 160.2, 160.1, 128.9, 128.8, 127.4, 127.1, 114.0, 114.0, 86.4, 80.5, 66.5, 55.5.
13. General procedure: A solution of **8** (100 mg, 0.33 mmol) in dry CH_2Cl_2 (15 mL) was cooled to −78°C under nitrogen gas and triethylamine (0.12 mL, 0.87 mmol) was added dropwise over 5 min. *c*-Hex_2BOTf (1 M solution in hexanes, 0.80 mL, 0.80 mmol) diluted in 1 mL dry CH_2Cl_2 was added dropwise over 5 min. The solution was allowed to stir at −78°C for 3 h. Aldehyde (0.50 mmol) was added dropwise over 5 min and the solution was allowed to stir for 0.5 h. The solution was quenched with a pH 7 buffer solution (2 mL), MeOH (0.4 mL), and 30% hydrogen peroxide (0.2 mL). The solution was warmed to rt, diluted with ether (75 mL), and washed with sat. $NaHCO_3$ (5 mL). The aqueous phase was extracted with ether (4×30 mL) and the organic layers were washed with dilute HCl (10 mL) and brine (20 mL). The organic layer was dried with $MgSO_4$, concentrated under vacuum, and silica gel radial chromatography gave the desired aldol products as a mixture whose diastereomeric ratio was determined by ^1H NMR. Further purification with a less polar eluent could be used to furnish individual diastereomers. The following data from isovaleraldehyde is typical: major isomer **9** (3*S*,5*S*,6*S*)-[(*S*)-1-hydroxy-3-methylbutyl]-5,6-bis-(4-methoxyphenyl)-1,4-dioxan-2-one. White crystalline solid (113 mg, 86% yield); mp 106–108°C; $[\alpha]_D = -132$ (*c* 31.6, CH_2Cl_2); $R_f = 0.20$ (30% EtOAc/hexanes); ^1H NMR (300 Hz, $CDCl_3$) δ 7.02–6.95 (m, 4H), 6.79–6.74 (m, 4H), 5.39 (d, $J = 9.3$ Hz, 1H), 4.94 (d, $J = 9.0$ Hz, 1H), 4.50 (d, $J = 5.1$ Hz, 1H), 4.25–4.17 (m, 1H), 3.75 (s, 6H), 2.83 (d, $J = 5.1$ Hz, 1H), 1.97–1.83 (m, 1H), 1.97–1.82 (m, 2H), 0.95 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.3, 160.2, 160.0, 129.0, 129.0, 128.2, 126.8, 114.0, 114.0, 85.2, 78.2, 77.2, 71.8, 55.4, 42.6, 24.5, 23.9, 21.7; HRMS FAB (M+Na) calcd for $C_{23}H_{28}O_6Na$ 423.1784, found 423.1785. Minor isomer **10** (3*R*,5*S*,6*S*)-[(*R*)-1-hydroxy-3-methylbutyl]-5,6-bis-(4-methoxyphenyl)-1,4-dioxan-2-one. White solid; $[\alpha]_D = -80.6$ (*c* 5.06, CH_2Cl_2); $R_f = 0.16$ (30% EtOAc/hexanes); ^1H NMR (300 Hz, $CDCl_3$) δ 6.99–6.93 (m, 4H), 6.79–6.75 (m, 4H), 5.38 (d, $J = 9.6$ Hz, 1H), 4.61 (d, $J = 9.3$ Hz, 1H), 4.49 (d, $J = 4.5$ Hz, 1H), 4.32–4.22 (m, 1H), 3.77 (s, 6H), 2.77 (d, $J = 6.3$ Hz, 1H), 1.99–1.85 (m, 1H), 1.78–1.69 (m, 1H), 1.55–1.46 (m, 1H), 1.00–0.96 (dd, $J = 6.6$, 5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 168.9, 160.2, 160.0, 128.8, 127.4, 126.8, 114.0, 114.0, 86.6, 80.5, 80.1, 71.1, 55.4, 41.7, 24.6, 23.9, 21.7; HRMS FAB (M+Na) calcd for $C_{23}H_{28}O_6Na$ 423.1784, found 423.1765. All other compounds were adequately characterized by ^1H, ^{13}C NMR and HRMS.
14. (a) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920; (b) Fenzl, W.; Koster, R. *J. Liebigs Ann. Chem.* **1975**, 1322; (c) Masamune, S. *Aldrichim. Acta* **1978**, *11*, 23.
15. An X-ray structure was solved for an intermediate following the aldol reaction with this dioxanone in the route to geldanamycin. See Ref. 7b.