ORGANIC LETTERS

2000
Vol. 2, No. 14
2165−2167

Diastereoselective Alkylations of Oxazolidinone Glycolates: A Useful Extension of the Evans Asymmetric Alkylation

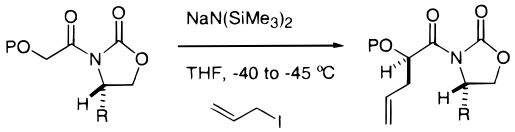
Michael T. Crimmins,* Kyle A. Emmitte, and Jason D. Katz

Venable and Kenan Laboratories of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290

crimmins@email.unc.edu

Received May 22, 2000

ABSTRACT

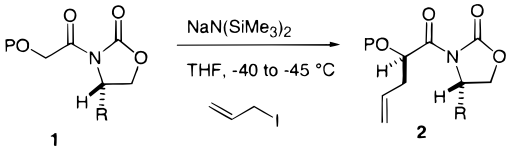


The diastereoselective alkylation of glycolate oxazolidinones has been demonstrated as a method for the enantioselective preparation of α-alkoxy carboxylic acid derivatives and selectively protected 1,2-diols. Various protecting groups on the glycolate hydroxyl and multiple substitution patterns on allylic iodides are tolerated in the alkylation. Yields for the alkylations are typically 70–85% with diastereoselectivities of >98:2.

The enantioselective construction of chiral α-hydroxy acids and chiral 1,2-diols has been extensively studied because of their importance in asymmetric synthesis.[1,2] The manipulation of tartaric acid, malic acid, and glycidol for complex synthesis supports the utility of these chiral building blocks.[3] Various methods including asymmetric dihydroxylations,[4] asymmetric enolate hydroxylations,[5] and asymmetric glycolate alkylations[6−14] have been employed for the preparation of α-hydroxy acids and their derivatives. The asymmetric glycolate alkylation is an attractive approach because of the relative ease of interchanging the alkyl group as well as the protecting group on the glycolate hydroxyl. Chiral auxiliaries attached to the carbonyl, the hydroxyl group, and to both have been employed in diastereoselective alkylations of chiral glycolates.[6−14]

For ongoing studies, we required access to both simple α-alkoxy carboxylic acid derivatives and more complex α,α′-disubstituted ether derivatives.[15,16] The asymmetric glycolate alkylation offered an attractive solution to both these needs. As such, we required a highly diastereoselective asymmetric glycolate enolate which allowed for easy interchange of the hydroxyl protecting group (P, Scheme 1). The well-

Scheme 1



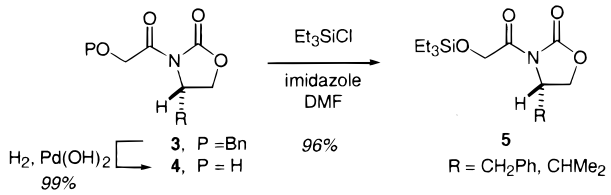
(1) Coppola, G. M.; Schuster, H. F. *Hydroxy Acids in Enantioselective Synthesis*; VCH: Weinheim, 1997.
(2) Hannession, S. *Total Synthesis of Natural Products. The Chiron Approach*; Pergamon Press: New York, 1983; Chapter 2.
(3) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Soo, Y. K.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780. Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437−475.
(4) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.
(5) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346−4348.
(6) Frater, G. Y.; Muller, U.; Gunther, W. *Tetrahedron Lett.* **1981**, *22*, 4221−4224.
(7) d'Angelo, J.; Pages, O.; Maddaluno, J.; Dumas, F. Revial, G. *Tetrahedron Lett.* **1983**, *24*, 5869−5872.
(8) Helmchen, G.; Wierzchowski, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 60−61.
(9) Kelly, T. R.; Arvanitis, A. *Tetrahedron Lett.* **1984**, *25*, 39−42.

10.1021/ol006091m CCC: $19.00
Published on Web 06/16/2000

documented Evans alkylation[17] of *N*-acyl 4-substituted oxazolidinones (R = Bn, $CHMe_2$, Scheme 1) seemed a logical choice. A survey of the literature uncovered only a single, fairly complex example[18] of a glycolate oxazolidinone alkylation with methallyl bromide.[19] This was surprising given the extensive application of 4-substituted oxazolidinone auxiliaries in asymmetric synthesis.[20] They are readily available (both commercially and synthetically), easily removed, and can be recovered and recycled. We have previously reported the use of asymmetric glycolate alkylations for some specific applications.[15,16] Here, we report on the utility and generality of asymmetric alkylations of sodium enolates of numerous glycolate oxazolidinones with a variety of allylic iodides for the preparation of α-hydroxy carboxylic acids and 1,2-diols with selective protection of the secondary alcohol.

A variety of oxazolidinone glycolates can be prepared by one of three methods: (1) acylation of the auxiliary with the appropriate alkoxyacetyl chloride (P = Me, Bn),[17,21] (2) one-pot preparation from the alkoxycarboxylic acid through the in situ formation of the mixed pivalic anhydride (P = PMB, allyl, complex alkyl),[22,23] or (3) protection of the parent glycolate oxazolidinone (P = Et_3Si, MOM, *t*-$BuMe_2Si$, *t*-$BuPh_2Si$). The latter method functions well for the preparation of less hindered silyl ethers and other acid sensitive protecting groups. The parent glycolate **4** was prepared in 99% yield by exposure of benzyl ether **3**[20] to hydrogen and $Pd(OH)_2$ in ethyl acetate. Treatment of oxazolidinone glycolate **4** with triethylsilyl chloride and imidazole produced silyl ether **5** in 96% yield. The methoxymethyl ether, the *tert*-butyldimethylsilyl ether, and the *tert*-butyldiphenylsilyl ether were prepared in a similar manner (Scheme 2).

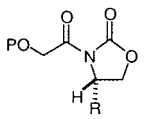
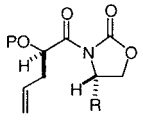
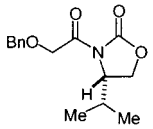
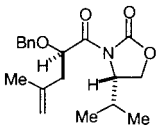
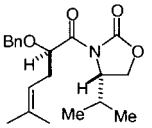
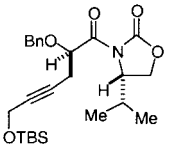
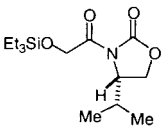
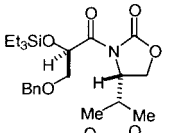
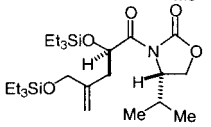
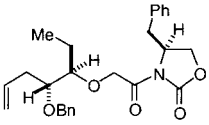
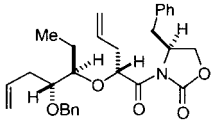
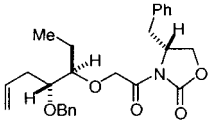
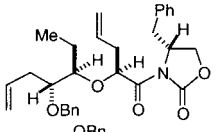
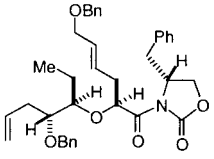
Scheme 2



Generation of the sodium enolate of the acyl oxazolidinone [1.5 equiv of $NaN(SiMe_3)_2$, −78 °C, 30 min] followed by addition of 3−5 equiv of the required alkylating agent, and warming the reaction mixture to − 40 to − 45 °C, results in relatively rapid (1−3 h) alkylation of the enolate with excellent diastereoselectivity (generally >96% de). Purification of the products by flash chromatography provided the alkylated product in 70−85% yield essentially diastereomerically pure (>99:1).[24]

As illustrated in Table 1, a wide range of protecting groups (or ethers) is tolerated on the glycolate hydroxyl. Benzyl, *p*-methoxybenzyl, MOM, allyl, trialkylsilyl, and complex

Table 1. Asymmetric Glycolate Alkylations[28]

entry	glycolate	product	yield (d.r.)
			
1	R = CH_2Ph	P = Bn	75% (>98:2)
2	R = CH_2Ph	P = Et_3Si	73% (>98:2)
3	R = CH_2Ph	P = *t*-$BuPh_2Si$	78% (>98:2)
4	R = CH_2Ph	P = Me	30% (>98:2)
5	R = CH_2Ph	P = PMB	73% (>98:2)
6	R = CH_2Ph	P = CH_2=$CHCH_2$	64% (>98:2)
7	R = $CHMe_2$	P = Bn	82% (>98:2)
8	R = $CHMe_2$	P = Et_3Si	88% (>98:2)
9	R = $CHMe_2$	P = *t*-$BuMe_2Si$	84% (>98:2)
10	R = $CHMe_2$	P = Me	41% (>98:2)
11	R = $CHMe_2$	P = MOM	53% (>98:2)
12			81% (>98:2)
13			84% (>98:2)
14			54%(>98:2)
15			66% (>98:2)
16			80% (>98:2)
17			71% (97:3)
18			71% (97:3)
19			75% (97:3)

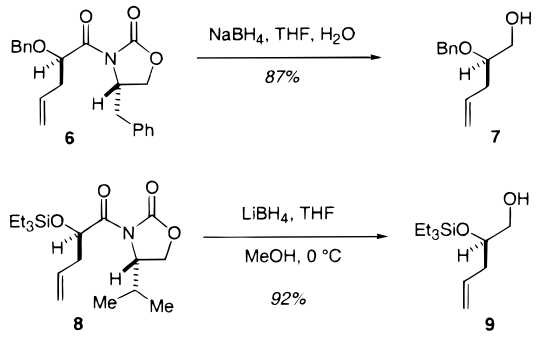
(10) Enomoto, M.; Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *25*, 1343−1344.
(11) Ludwig, J. W.; Newcomb, M.; Bergbreiter, D. E. *Tetrahedron Lett.* **1986**, *26*, 2731−2734.
(12) Pearson, W. H.; Cheng, M.-C. *J. Org. Chem.* **1986**, *51*, 3746−3748.
(13) Cardillo, G.; Orena, M.; Romero, M.; Sandri, S. *Tetrahedron* **1989**, *45*, 1501−1508.
(14) Jung, J. E.; Ho, H.; Kim, H.-D. *Tetrahedron Lett.* **2000**, *41*, 1793−1796.
(15) Crimmins, M. T.; Emmitte, K. A. *Synthesis* **2000**, 899−903.
(16) Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029−2032.

alkyl ethers all function well in this regard. Both relatively simple (entries 1−14) and highly complex examples proceed with similar yields and levels of diastereoselection. One of the more attractive aspects of this procedure is the ability to selectively prepare α,α′- disubstituted ethers with high levels of diastereocontrol (entries 17−19).

Several points regarding the procedure are worthy of note. In our experience,[25] the use of the allylic iodides is essential since rates of alkylation with allylic bromides are slow and yields drop substantially due to competitive deacylation of the enolates. Excess iodide (3−5 equiv) is also preferred to achieve acceptable rates. For most cases, rates are sluggish at −78 °C and warming the reaction to −40 to −45 °C appears to be optimal for most examples. The methyl ether is relatively unstable at -45 °C, and the alkylation is better accomplished at −78 °C. The methyl ether resulted in substantial deacylation of the auxiliary even at −78 °C and produced a somewhat impure product in modest yields (entries 4 and 10).[26] The MOM ether (entry 11) and allyl ether (entry 6) showed similar trends, but to a lesser extent. It is also of particular interest that the valine-derived enolates (R = $CHMe_2$) are slightly more reactive and tend to give somewhat improved yields when compared to the phenylalanine-derived (R = CH_2Ph) auxiliaries (compare, for example, entries 1 vs 7 and 2 vs 8). Alkylation with iodomethylbenzyl[27] ether as the electrophile proceeded rapidly at − 78 °C (entry 15).

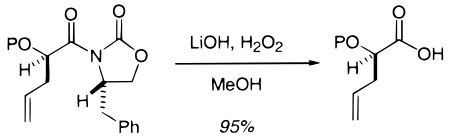
The auxiliary can be reductively removed by simple exposure to sodium borohydride in THF−H_2O to provide primary alcohol **7** in high yield (Scheme 3).[29] Lithium

Scheme 3



borohydride was used to reductively remove the auxiliary in the triethysilyl glycolate alkylation products to avoid silyl ether migration. Carboxylic acids **10** are available through the standard Evans hydrolysis procedure with lithium hydroxide and hydrogen peroxide (Scheme 4).[30]

Scheme 4



6, P = Bn, PMB **10**, P = Bn, PMB

In summary, the asymmetric glycolate alkylation of 4-substituted oxazolidinones can be used for the enantioselective preparation of highly useful α-alkoxy acids and 1,2-diols with the secondary hydroxyl selectively protected after removal of the auxiliary. Since the asymmetric glycolate alkylation with allyl iodides results in the production of protected homoallylic alcohols, this procedure also compliments existing methods for the enantioselective preparation of homoallylic alcohols.[31]

Acknowledgment. This work was supported by grants from the National Institutes of Health (GM38904, CA63572 and GM60567).

OL006091M

(17) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737−1739.
(18) Burke, S. D.; Quinn, K. J.; Chen, V. *J. Org. Chem.* **1998**, *63*, 8626−8627.
(19) During the preparation of this manuscript an additional example appeared. Chappell, M. D.; Stachel, S. J.; Lee, C. B.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 1633−1636.
(20) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835−875.
(21) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506−2526.
(22) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001−7031. Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5663−5660.
(23) Chakraborty, T. K.; Suresh, V. R. *Tetrahedron Lett.* **1998**, *39*, 7775−7778.
(24) **Typical procedure for the alkylaiton of oxazolidinone glycolates:** A solution of 5.0 mL (3 mmol) of sodium bistrimethylsilylamide (0.6 M in toluene) in 10 mL of THF was cooled to −78 °C. A solution of oxazolidinone glycolate (2 mmol) in 5 mL of THF was added dropwise over 5 min. The solution was stirred at −78 °C for 30 min. A solution of allyl iodide (10 mmol) in 5 mL of THF was added dropwise. The solution was stirred at −78 °C for 5 min and allowed to warm to −40 to −45 °C at which temperature it was stirred for 1−3 h. The reaction was monitored by TLC. After the reaction was deemed to be complete, saturated aqueous ammonium chloride was added and the mixture was warmed to room temperature. The mixture was partitioned between 1:1 ethyl acetate/hexanes and water. The organic layer was washed with saturated sodium chloride solution, dried, and concentrated. The residue was purified by flash chromatography to provide the pure alkylation product. Yields are for isolated, chromatographically purified products which were homogeneous by TLC and NMR.
(25) One example of an alkylation with methallyl bromide has appeared, see ref 18.
(26) The chlorotitanium enolate of the methyl glycolate oxazolidinone has been alkylated with BOMCl. Paterson, I.; Bower, S.; McLeod, M. D. *Tetrahedron Lett.* **1995**, *36*, 175−178.
(27) Ditrich, K.; Hoffmann, R. W. *Liebigs Ann. Chem.* **1990**, 15−21.
(28) Yields are for isolated, chromatographically purified material, homogeneous by TLC and NMR. Diastereomeric ratios were determined either by HPLC or by NMR (>98:2 indicates that the minor isomer could not be detected by NMR).
(29) Prashad, M.; Har, D.; Kim, H.-Y.; Repic, O. *Tetrahedron Lett.* **1998**, *39*, 7067−7070.
(30) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141−6144.
(31) Brown, H. C. Randad R. S.; Bhat K. S.; Zaidlewicz M.; Racherla U. S. *J. Am. Chem. Soc.* **1990**, *112*, 2389−2392. Roush W. R.; Walts A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186−8190.