Highly Regioselective Nucleophilic Substitution of Cyclic Carbonates of *threo*-2,3-Dihydroxy Esters: Synthesis of Optically Pure β-Hydroxy Esters

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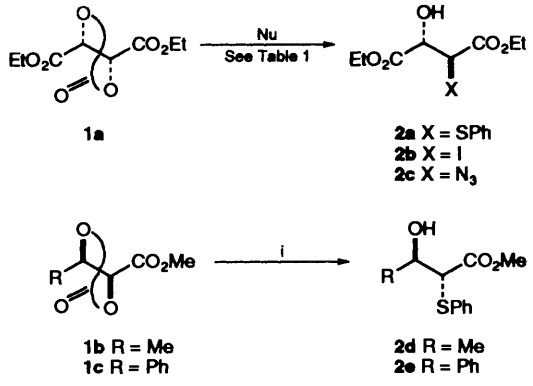
The nucleophilic ring opening of the cyclic carbonates of optically active *threo*-2,3-dihydroxy esters **1** afforded the α-substituted β-hydroxy esters **2** with highly regio- and stereo-selectivity under mild conditions. The α-sulfanyl or α-iodo β-hydroxy esters **2** thus obtained were transformed to the β-hydroxy esters **3**, which are useful chiral synthons for natural product synthesis.

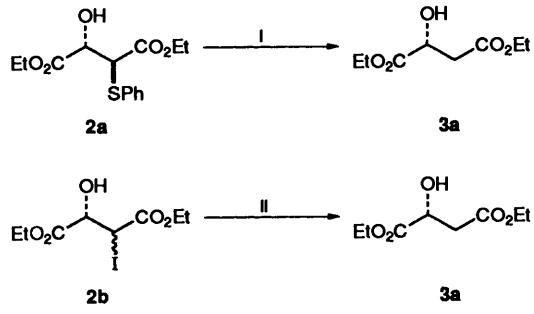
Optically active α-substituted β-hydroxy esters are useful intermediates in the synthesis of natural products. They are usually prepared by regioselective ring opening of epoxides,[1] cyclic sulfates[2] and cyclic sulfinates.[3] Now, we wish to report that the cyclic carbonates of optically active *threo*-2,3-dihydroxy esters are good substrates for nucleophilic substitution under mild conditions (Scheme 1). Optically active *threo*-2,3-dihydroxy esters can be readily prepared from (*E*)-α,β-unsaturated esters by Sharpless asymmetric dihydroxylation (AD).[4]



Scheme 1 *Reagents and conditions:* i, PhSH (2 equiv.), Et_3N (2 equiv.), THF, 0 °C

Diethyl L-tartrate was transformed to the cyclic carbonate **1a** by reaction with triphosgene.[5] The cyclic carbonate **1a** was treated with 2 equiv. of benzenethiol and triethylamine in THF at 0 °C for 30 min to afford (2*S*,3*S*)-α-sulfanyl β-hydroxy diester **2a** † in 95% yield (Table 1, entry 1). When the carbonate **1a** was treated with lithium iodide in DMF at room temperature for 2 h, a *ca.* 1:1 mixture of the epimeric α-iodo β-hydroxy ester **2b**[3b] was obtained (entry 2).‡ Alternatively, reaction of the carbonate **1a** with sodium azide in DMF at room temperature for 4 h afforded the azido ester **2c**[6] $[\alpha]_D^{25}$ +16.4 (*c* 0.20, $CHCl_3$) [lit.,[6] $[\alpha]_D^{25}$ +17.5 (*c* 1.48, CH_2Cl_2)] in 88% yield (entry 3). For the carbonate of the monoester **1b**, the α-sulfanyl β-hydroxy ester **2d**[7] $[\alpha]_D^{25}$ +138 (*c* 0.95, $CHCl_3$) [lit.,[7] $[\alpha]_D^{25}$ −133 (*c* 1.0, $CHCl_3$) for the enantiomer] was obtained (entry 4). These procedures seem to be mild in comparison with the reactions of LiBr or NaN_3 with cyclic sulfinates under reflux conditions.[3] Asymmetric dihydroxylation[8] of the *trans*-methyl cinnamate with the AD-mix-β followed by treatment with triphosgene gave the cyclic carbonate **1c**. Treatment of compound **1c** with benzenethiol (2 equiv.) and triethylamine (2 equiv.) afforded the (2*R*,3*R*)-α-sulfanyl β-hydroxy ester **2e**, where the nucleophile attack had occurred exclusively at position C(2) (entry 5). This is in contrast to the regioselective opening of a cyclic sulfate with sodium azide at C(3), where the phenyl group acts as an activating substituent.[2f,9]

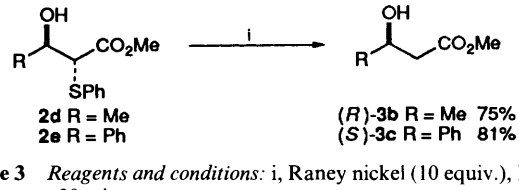
The α-phenylsulfanyl and the α-iodo esters **2a** and **2b** can serve as useful intermediates for the synthesis of unnatural diethyl (*R*)-malate **3a**.[3b,10] Desulfanylation[11] of the α-phenylsulfanyl group in the diester **2a** with Raney nickel provided compound **3a**[3b,10] $[\alpha]_D^{25}$ +9.7 (*c* 1.25, EtOH) [lit.,[3b] +10.5 (*c* 2.05, EtOH)] in 70% yield. Alternatively, epimeric iodo alcohol **2b** was also readily reduced[12] to compound **3a** $[\alpha]_D^{25}$ +10.1 (*c* 0.12, EtOH) with Zn in EtOH (Scheme 2).



Scheme 2 *Reagents and conditions:* i, Raney Nickel (10 equiv.), EtOH, room temp., 30 min (70%); ii, Zn (3 equiv.), EtOH, reflux, 1 h (72%)

Optically active β-hydroxy esters are useful chiral synthons in the synthesis of various natural products. They are usually prepared by the enantioselective microbial reduction[13] of β-keto esters, from the biopolymer PHB,[14] or Ru- (*R*)- or (*S*)-BINAP catalysed asymmetric hydrogenation[15] of the corresponding β-keto esters.

The α-sulfanyl β-hydroxy monoesters **2d** and **2e** can be transformed to the optically active β-hydroxy esters. Reductive cleavage of compounds **2d** and **2e** with Raney nickel afforded the optically active β-hydroxy esters (*R*)-**3b** $[\alpha]_D^{25}$ −45.4 (*c* 0.27, $CHCl_3$) (lit.,[16] $[\alpha]_D$ −47) and (*S*)-**3c**,[17] $[\alpha]_D^{25}$ −17.5 (*c* 0.46, EtOH) [lit.,[17a] $[\alpha]_D^{22}$ −18.3 (EtOH)], respectively (Scheme 3).



Scheme 3 *Reagents and conditions:* i, Raney nickel (10 equiv.), EtOH, room temp., 30 min

† **2a**: TLC: SiO_2, EtOAc–hexanes 1:1, R_f = 0.56; $[\alpha]_D^{25}$ −28.2 (*c* 2.0, $CHCl_3$); δ_H(300 MHz, $CDCl_3$) 1.21 (6 H, m), 3.43 (1 H, d, *J* 6.2), 4.10–4.30 (5 H, m), 4.53 (1 H, m), 7.29 (3 H, m) and 7.50 (2 H, m); ν_{max}(neat)/cm^{-1} 3500 and 1736; *m/z* 298 (M^+), 121 (base peak), 109 and 45 (Found: C, 55.9; H, 6.2; S, 10.75. $C_{14}H_{18}SO_5$ requires: C, 56.36; H, 6.08; S, 10.75%).

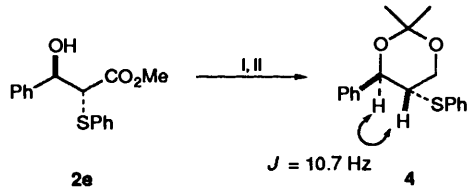
‡ The ratio was determined by 300 MHz ^1H NMR.

Table 1 Regioselective ring opening of the cyclic carbonates (**1–2**)

Entry	Substrate	Nucleophiles	Solvent	Conditions		Product[a]	Yield[b]
				Temp. (°C)	Time (h)		
1	**1a**	$PhSH–Et_3N$	THF	0	0.5	**2a**	95
2	**1a**	LiI	DMF	25	2	**2b**	85
3	**1a**	NaN_3	DMF	25	4	**2c**	88
4	**1b**	$PhSH–Et_3N$	THF	0	1	**2d**	89
5	**1c**	$PhSH–Et_3N$	THF	0	0.5	**2e**	91

[a] $[\alpha]_D^{25}$ Values in $CHCl_3$. **2a**: −28.2 (*c* 2.0); **2c**: +16.4 (*c* 0.20); **2d**: +138 (*c* 0.95); **2e**: +68.8 (*c* 0.85). [b] Isolated yield.

To establish the relative stereochemistry of the newly introduced C–S bond in compound **2e**, the α-sulfanyl β-hydroxy ester **2e** was converted into the cyclic ketal **4** and the stereochemistry was deduced from the coupling constant (*J* 10.7 Hz, *trans* coupling) in the ^1H NMR (200 MHz) spectrum (Scheme 4).



2e **4**

Scheme 4 *Reagents and conditions:* i, $LiAlH_4$, THF, reflux; ii, 2,2-dimethoxypropane, *p*-TsOH (67% overall)

In summary, nucleophilic ring opening of the cyclic carbonates of optically active *threo*-2,3-dihydroxy esters afforded α-substituted β-hydroxy esters with high regio- and stereoselectivity, which can be transformed to β-hydroxy esters, useful chiral synthons in organic synthesis.

Experimental

Methyl(2R,3R)-3-*Hydroxy*-3-*phenyl*-2-(*phenylsulfanyl*)*propionate* **2e**.—A solution of the carbonate **1c** (160 mg, 0.72 mmol) in anhydrous THF (2 cm^3) at 0 °C under N_2 was added benzenethiol (158 mg, 1.44 mmol) and triethylamine (145 mg, 1.44 mmol). The reaction mixture was stirred for 30 min at 0 °C. The solvent was then evaporated and the residue was diluted with water and extracted with diethyl ether (30 cm^3). The diethyl ether layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was separated by silica gel column chromatography (EtOAc–hexanes 1:1, R_f = 0.57) to afford compound **2e** (188 mg, 91%); $[\alpha]_D^{25}$ +68.8 (*c* 0.85, $CHCl_3$); δ_H(300 MHz, $CDCl_3$) 3.12 (1 H, d, *J* 5.5), 3.65 (3 H, s), 3.91 (1 H, d, *J* 7.8), 5.00 (1 H, dd, *J* 7.8 and 5.5), 7.20 (5 H, m) and 7.35 (5 H, m); ν_{max}(neat)/cm^{-1} 3500 and 1737; *m*/*z* 288 (M^+), 229, 109 and 91 (base peak) (Found: C, 66.5; H, 6.1; S, 10.9. $C_{16}H_{16}SO_3$ requires: C, 66.64; H, 5.59; S, 11.12%).

Acknowledgements

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References

1 (*a*) R. O. Duthaler, *Tetrahedron*, 1994, **50**, 1539; (*b*) R. M. Nanson, *Chem. Rev.*, 1991, **91**, 437.
2 (*a*) Y. Gao and K. B. Sharpless, *J. Am. Chem. Soc.*, 1988, **110**, 7538; (*b*) B. M. Kim and K. B. Sharpless, *Tetrahedron Lett.*, 1989, **30**, 655; (*c*) B. B. Lohray, Y. Gao and K. B. Sharpless, *Tetrahedron Lett.*, 1989, **30**, 2623; (*d*) R. Oi, K. B. Sharpless, *Tetrahedron Lett.*, 1991, **32**, 999; (*e*) N. Machinaga, C. Kibayashi, *Tetrahedron Lett.*, 1990, **31**, 3637; (*f*) A. M. P. Koskinen, E. K. Karvinen and J. P. Siirila, *J. Chem. Soc., Chem. Commun.*, 1994, 21.
3 (*a*) B. B. Lohray and J. R. Ahuja, *J. Chem. Soc., Chem. Commun.*, 1991, 95; (*b*) Y. Gao and C. M. Zepp, *Tetrahedron Lett.*, 1991, **32**, 3155.
4 *Catalytic Asymmetric Synthesis*, ed. I. Ojima, VCH Publishers, Inc., New York, 1993, pp. 227–272.
5 (*a*) R. M. Burk and M. B. Roof, *Tetrahedron Lett.*, 1993, **34**, 395; (*b*) S.-K. Kang, J.-H. Jeon, K.-S. Nam, C.-H. Park and H.-W. Lee, *Synth. Commun.*, 1994, **24**, 305.
6 J. Legters, L. Thijs and B. Zwanenburg, *Tetrahedron*, 1991, **47**, 5287.
7 The enantiomer of compound **2d** was prepared by baker's yeast reduction of α-sulfanyl β-keto esters: T. Fujisawa, T. Itoh and T. Sato, *Tetrahedron Lett.*, 1984, **25**, 5083.
8 K. B. Sharpless, W. Anberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu and X.-L. Zhang, *J. Org. Chem.*, 1992, **57**, 2768.
9 In the reaction of 2,3-epoxycarboxylic acid methyl ester with sodium azide, two regioisomeric products were obtained; J. Legters, L. Thijs and B. Zwanenburg, *Tetrahedron Lett.*, 1989, **30**, 4881.
10 Preparation of D-malates: (*a*) H. Wynberg and E. G. Staring, *J. Am. Chem. Soc.*, 1982, **104**, 166; (*b*) I. Chibata, *Pure Appl. Chem.*, 1978, **50**, 667; (*c*) S. Hemrot, M. Larchevegue and Y. Petit, *Synth. Commun.*, 1986, **106**, 183; (*d*) E. Hungerbuhler, D. Seebach, D. Wasmuth, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 958; (*e*) M. Alpegiani, S. Hanessian, *J. Org. Chem.*, 1987, **52**, 278; (*f*) K. Kusuta, J. Inanaga and M. Yamaguchi, *Tetrahedron Lett.*, 1989, **30**, 2945.
11 (*a*) W. A. Bonner and R. A. Grimm, in *The Chemistry of Organic Sulfur Compounds*, eds. N. Kharasch and C. Y. Meyers, vol. 2, Pergamon Press, Oxford, 1966, p. 35; (*b*) J. T. B. Ferreira, J. A. Marques and J. P. Marino, *Tetrahedron: Asymmetry*, 1994, **5**, 641.
12 For a review of the reduction of organic halides, see: A. R. Pind, *Synthesis*, 1980, 425.
13 (*a*) K. Mori, in *Studies in Natural Products Chemistry*, ed. A.-U. Rahman, vol. 1, Stereoselective Synthesis, Elsevier, 1988, pp. 677–712; (*b*) K. Mori, in *Organic Synthesis: Modern Trends*, ed. O. Chizhov, Blackwell, 1987, pp. 293–304; (*c*) E. Santaniello, P. Ferraboschi, P. Grisenti and A. Manzocchi, *Chem. Rev.*, 1992, **92**, 1071; (*d*) D. Seebach, M. A. Satter, R. H. Weber and M. F. Zuger, *Org. Synth.*, 1984, **63**, 1.
14 (*a*) G. Hungerbuhler, D. Seebach and D. Wasmuth, *Helv. Chim. Acta.*, 1981, **64**, 1467; (*b*) D. Seebach, M. F. Zuger, *Helv. Chim. Acta.*, 1982, **65**, 495; (*c*) D. Seebach and M. F. Zuger, *Tetrahedron Lett.*, 1985, **25**, 271; (*d*) T. Sugai, M. Fujita and K. Mori, *Nippon Kagaku Kuishi* (*J. Chem. Soc. Jpn.*), 1983, 1315.
15 R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi and S. Akutagawa, *J. Am. Chem. Soc.*, 1987, **107**, 5856.
16 G. Solladie and A. Almario, *Tetrahedron Lett.*, 1992, **33**, 2477.
17 (*a*) K. Kishikawa, M. Yamamoto, S. Kohmmoto and K. Yamada, *Chem. Lett.*, 1989, 787; (*b*) K. Soai, T. Yamanoi, H. Hikima and H. Oyamada, *J. Chem. Soc., Chem. Commun.*, 1985, 138; (*c*) C. Mioskowski and G. Solladie, *Tetrahedron*, 1980, **36**, 227.

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