Pergamon

Tetrahedron Letters, Vol. 38, No. 44, pp. 7657-7660, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10087-9

Efficient Resolution of Oxidized Cleland's Reagent by *C*2-Symmetric Boc-L-Phenylalanyl Esters

Colleen A. Evans, Louise Bernier, Josée Dugas and Tarek S. Mansour*

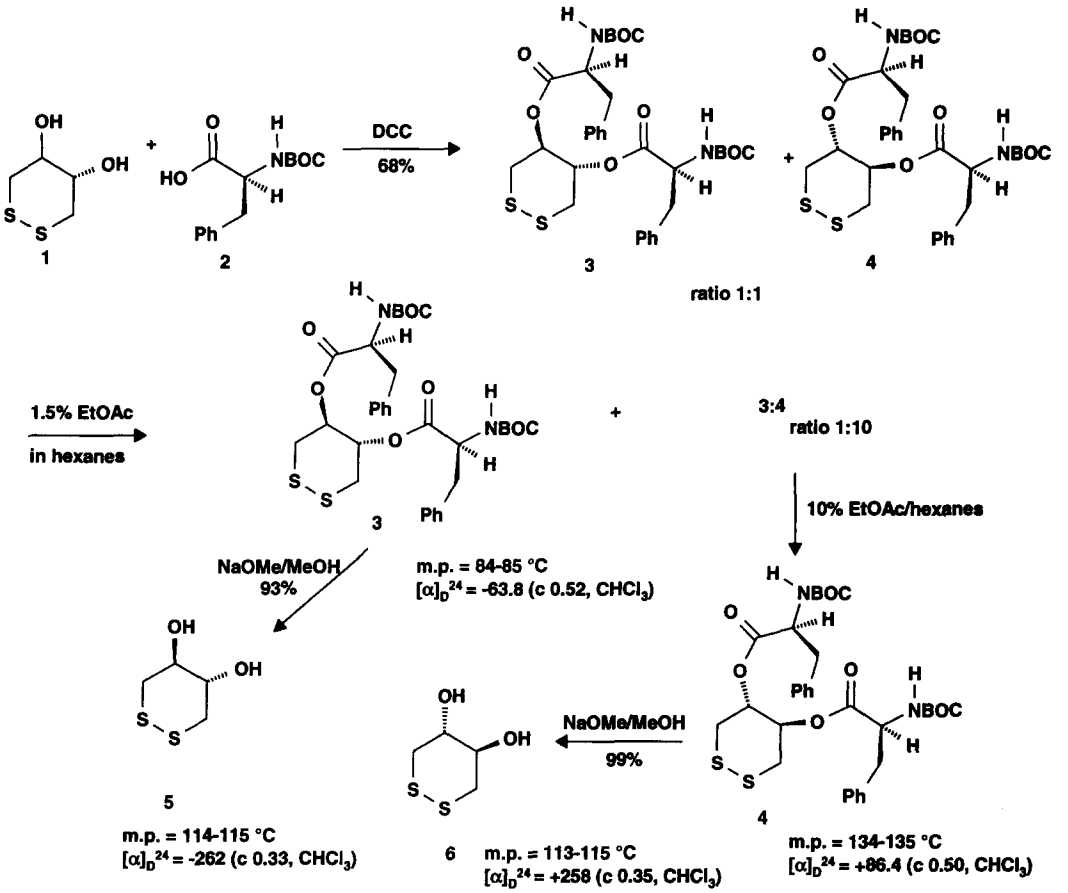
BioChem Therapeutic Inc., 275 Armand Frappier Blvd., Laval, Quebec, Canada H7V 4A7

Abstract: *Trans* 4,5-dihydroxy-1,2-dithiane (**1**,oxidized form of Cleland's reagent; dithiothreitol) is resolved efficiently in > 99% overall e.e. into its two enantiomers by fractional recrystallization of its BOC-L-phenylalanyl diesters. © 1997 Elsevier Science Ltd.

Optically active 1,2-diols are important building blocks in asymmetric synthesis.[1] Presently the most common method for the enantioselective synthesis of 1,2-diols is the asymmetric dihydroxylation of alkenes using osmium tetraoxide in the presence of a variety of chiral ligands or catalysts.[2] Variation utilizing simple ligands[3] or catalytic processes[4] are emerging. Despite that some limitations relating to the moderate enantiomeric excesses of anti 1,2-diols have been noted.[5] In such cases and in situations where the alkene is not readily available or possesses a potentially oxidizable functionality, one useful alternative is a resolution approach to access chiral materials of high enantiomeric excess.[6] In contrast to the resolution of primary and secondary alcohols by chemical and enzymatic methods,[7] few efficient methods of potential application to large scale have been reported for the resolution of vicinal diols. For example, enzyme-catalyzed hydrolysis methods[8] as well as chemical resolution protocols using *C*2-symmetric dihydropyrans[9] have been recently reported. The latter method effects essentially a thermodynamic resolution via the enantioselective formation of dispiroketals.

As part of an ongoing project, we required both enantiomers of *trans* 4,5-dihydroxy-1,2-dithiane (**1**) in multigram quantities. Here we report on the efficient resolution of **1** using amino acids.

Reaction of racemic **1** with N-t-butoxycarbonyl-L-phenylalanine (**2**) in methylene chloride in the presence of dicyclohexylcarbodiimide gave a diastereomeric mixture of esters **3** and **4** in equal amounts (Scheme 1). After removal of unreacted reagents by chromatography on silica gel, the mixture of **3** and **4** was obtained in 68% yield. Fractional crystallization with 1.5% ethyl acetate in hexanes provided the 4*S*,5*S* ester in 45% yield based on single isomer (90% theory) in one single crystallization step. Fractional recrystallization of the mother liquor containing **3** : **4** (1:10 ratio after removal of **3**) with 10% ethyl acetate in hexanes provided the 4*R*,5*R* ester **4** in 27% yield (54% based on theory). Hydrolysis of **3** or **4** was readily achieved by reaction with saturated K_2CO_3 or NaOMe in methanol in excellent yield to provide the desired diols **5** and **6** in > 99% e.e. as evidenced by comparison of the specific rotation of **6** with an authentic sample derived from L-tartaric acid.[10]



Scheme 1

An important aspect of all resolutions is to rely on efficient methods for the analysis of compounds immediately after the resolution step. In this regard, the % de of **3** and **4** was assessed by HPLC methods (Fig. 1) on C18 column using reverse phase conditions (experimental section). Despite the excellent agreement in the specific rotation values of **6** with the literature,[10] it was felt necessary to confirm this absolute value since the literature value was not supported by a chromatographic method. In this regard, the bisbenzoate derivative of **1** was resolved on chiralcel OD column using normal phase conditions (Fig. 2) with isopropanol/hexanes (1:9) as eluent. Analysis of **5** and **6** by this method established the % ee to be > 99% and > 97.5% respectively.

1,2-Dithiane-4,5-diol derivatives have recently been reported to inhibit the replication of HIV-1 and HIV-2 (the causative agents of AIDS) by mediating an electrophilic attack on the zinc finger region of the nucleocapsid p7 protein.[11] We believe that access to dithianes **5** and **6** in gram amounts will provide isomerically pure analogues with enhanced selectivity and therapeutic potential.[12]

Fig. 1
Resolution (R_s) = 3.74
Selectivity (α) = 1.10

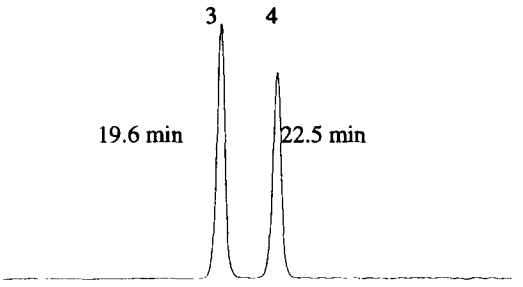
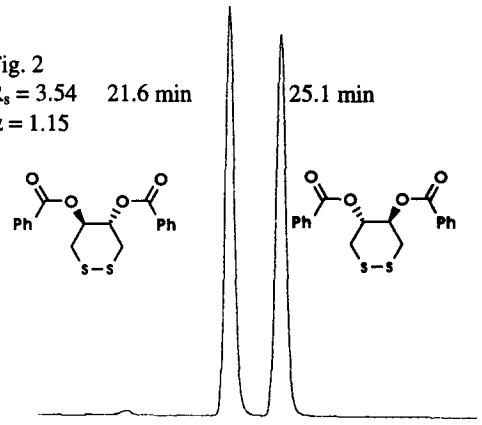


Fig. 2
R_s = 3.54 21.6 min 25.1 min
α = 1.15



In summary, we achieved an efficient resolution of both enantiomers of *trans* 4,5-dihydroxy-1,2-dithiane via their *C*2-symmetric Boc phenylalanyl esters and established the isomeric purity of the esters **3** and **4** and resolved enantiomers **5** and **6** by HPLC methods.[13,14]

EXPERIMENTAL SECTION

(4S,5S)-(-)-Bis-N-tert-butoxy-L-phenylalanyloxy-1,2-dithiane (**3**). To a solution of (±)-*trans*-4,5-dihydroxy-1,2-dithiane (4.76 g, 31.31 mmol), N-tert-butoxycarbonyl-L-phenylalanine (18.28 g, 69.0 mmol), 4-dimethylaminopyridine (10 mg) and methylene chloride (200 ml) at 0 °C under N_2 was added a solution of dicyclohexylcarbodiimide (14.2 g, 68.9 mmol) in methylene chloride (100 ml) over 5 min. during which time a white precipitant formed. The reaction was stirred at 0 °C for 1 hr and then at rt for 12 hrs at which times methanol (5 ml) and glacial acetic acid (0.2 ml) was added to quench the reaction. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated and purified by column chromatography eluting with 10% ethyl acetate/hexanes to give 13.84 g (68%) of a diastereomeric mixture (1/1 ratio). The diastereomeric mixture was dissolved with heating in 1L of 1.5% of ethyl acetate/hexanes. Immediately upon removal from heat crystallization began. While the solution was still warm, the white solid was removed twice by filtration to give 6.26 g of the desired product (4*S*,5*S*)-(-)-Bis-N-tert-butoxy-L-phenylalanyloxy-1,2-dithiane: $[\alpha]_D^{24}$ = -63.8 (c 0.52, $CHCl_3$); m.p. 84-85 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40 (s,18H), 2.8-3.04 (m,6H), 3.14 (dd,2H,J=5.9,14.0 Hz), 4.45 (q,2H,J=8.0 Hz), 5.09 (m,2H), 5.23 (d,2H,J=7.2 Hz), 7.20 (d,2H,J=6.5 Hz), 7.25-7.33 (m,6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3, 37.5, 38.2, 54.8, 72.8, 79.0, 127.0, 128.5, 129.2, 136.1, 155.6, 171.2; UV_{max} (MeOH) 210 nm; 100% de based on HPLC analysis: retention time = 19.63 min., column: YMC PVA-SIL 5μ 120 A, flow rate: 1.0 ml/min., eluent: 10-30% ethyl acetate/hexanes, detection: 270 nm; Anal. Calcd for $C_{32}H_{42}O_8N_2S$: C, 59.44; H, 6.50; N, 4.33; S, 9.91. Found: C, 59.38, H, 6.79; N, 4.32; S, 9.84.

(4R,5R)-(+)-Bis-N-tert-butoxy-L-phenylalanyloxy-1,2-dithiane (**4**). The mother liquor after removal of (**3**) was concentrated and repeatedly recrystallized from 10% ethyl acetate/hexanes to give 3.63 g (26.5%) of (4*R*,5*R*)-(+)-Bis-N-tert-butoxy-L-phenylalanyloxy-1,2-dithiane as a white solid: $[\alpha]_D^{24}$ = +86.4 (c 0.50, $CHCl_3$); m.p. 134-135 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40 (s,18H), 2.80-3.14 (m,8H), 4.51 (q,2H,J=5 Hz), 4.90-5.10 (m,4H), 7.11 (d,4H,J=6.2 Hz), 7.2-7.32 (m,6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3, 37.6, 38.0, 54.6, 72.4, 80.1, 127.1, 128.6, 129.2, 135.7, 155.0, 170.6; UV (MeOH) 210 nm; 100% de based on HPLC analysis retention time = 22.46 min., column: YMC PVA-SIL 5μ 120 A, flow rate: 1.0 ml/min., eluent: 10-30% ethyl acetate/hexanes, detection: 270 nm; Anal. Calcd for $C_{32}H_{42}O_8N_2S$: C, 59.44; H, 6.50; N, 4.33; S, 9.91. Found: C, 59.76, H, 6.94; N, 4.28; S, 9.95.

(4S,5S)-(-)-Dihydroxy-1,2-dithiane (5). To a slurry of (4*S*,5*S*)-(-)-Bis-N-tert-butoxycarbonyl-L-phenylalanyloxy-1,2-dithiane (2.50 g, 3.87 mmol) and MeOH (40 ml) was added a $NaOCH_3$/MeOH solution (4.37 mM, 1.9 ml, 8.51 mmol). The reaction was stirred at 0 °C for 15 min. and concentrated *in vacuo*. The resulting residue was dissolved in a minimum amount of ethyl acetate/hexanes (1/1) and purified by column chromatography eluting with 1/1 ethyl acetate/hexanes to yield 549 mg (93%) of the desired product as a white crystalline solid: m.p. 114-115 °C; $[\alpha]_D^{24}$ = -262 (c 0.33, $CHCl_3$), ^1H NMR ($CDCl_3$, 300 MHz) δ 2.59 (br s,2H), 2.93-3.20 (br m,4H), 2.70 (br s,2H); UV_{max} (H_2O), 282.8 nm. Anal. Calcd $C_4H_8O_2S_2$: C, 31.58; H, 5.30. Found: C, 31.68, H 5.50.

(4R,5R)-(+)-Dihydroxy-1,2-dithiane (6). Similar procedure to yield 583 mg (99%) of the desired product as a white crystalline solid: m.p. 113-115 °C; $[\alpha]_D^{24}$ = +258 (c 0.35,$CHCl_3$), lit. value[10] $[\alpha]_D$ = +260 (c 0.32,$CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.59 (br s,2H), 2.93-3.20 (br m,4H), 2.70 (br s,2H); UV_{max} (H_2O) 283.5 nm. Anal. Calcd $C_4H_8O_2S_2$: C, 31.58; H, 5.30. Found C, 31.73; H, 5.59.

REFERENCES AND NOTES

1. Fuhrhop, J.; Penzlia, G. *Organic Synthesis*; VCH Publisher: Weinheim, **1994**; pp. 171-192.
2. Becker, H.; King, S. B.; Tanniguchi, M.; Vanhessche, K. P. M.; Sharpless, K. B. *J. Org. Chem.* **1995**, *60*, 3940-3941 and references cited herein. For recent reviews see Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K.B. *Chem. Rev.* **1994**, *94*, 2483-2547. Balavoine, G. A.; Manoury, E. *Appl. Organomet. Chem.* **1995**, *9*, 199-225.
3. Hanessian, S.; Meffre, P.; Girard, M.; Beaudoin, S.; Sancéau, J. Y.; Bennani, Y. *J. Org. Chem.* **1993**, *58*, 1991-1993.
4. Oishi, T.; Hirama, M. *Tetrahedron Lett.* **1992**, *33*, 639-642. Imada, Y.; Saito, T.; Kawakami, T.; Murahashi, S.-I. *Tetrahedron Lett.* **1992**, *33*, 5081-5084. For processes involving kinetic resolution see Brimble, M. A.; Johnston, A. D. *Tetrahedron:Asymmetry* **1997**, *8*, 1661-1667.
5. For example see (a) Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568-7570 (b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768-2771.
6. Kawashima, M.; Hirayama, A. *Chem. Lett.* **1991**, *5*, 763-766.
7. Recent examples: Chemical methods (a) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492-1493 (b) Hasiguchi, S.; Fujii, A.; Haack, K. J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 288-290 (c) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809-1810. Recent examples: Enzymatic methods (a) Suginaka, K.; Yahashi, Y.; Yamamoto, Y. *Tetrahedron:Asymmetry* **1996**, *7*, 1153-1158 (b) Legros, J.-Y.; Toffano, M.; Drayton, S. K.; Rivard, M.; Fiaud, J.-C. *Tetrahedron Lett.* **1997**, *38*, 1915-1918.
8. Lipase-catalyzed transesterification. Kim, M.-J.; Choi, G.-B.; Kim, J.-Y.; Kim, H.-J. *Tetrahedron Lett.* **1995**, *36*, 6253-6256. For the use of other esterases see Barton, P.; Page, M. I. *Tetrahedron* **1992**, *48*, 7731-7734.
9. Edwards, P. J.; Ertwistle, D. A.; Ley, S. V.; Owen, D. R.; Perry, E. J. *Tetrahedron:Asymmetry* **1994**, *5*, 553-556. Ley, S. V.; Mio, S. *Synlett* **1996**, 789-790. Ley, S. V.; Mio, S.; Meseguer, B. *Synlett* **1996**, 791-792.
10. Carmack, M.; Kelly, C. J. *J. Org. Chem.* **1968**, *33*, 2171-2173.
11. Rice, W. O.; Baker, D. C.; Schaeffer, C. A.; Graham, L.; Bu, M.; Terpenin, S.; Clanton, D.; Schultz, R.; Bader, J. F.; Buckheit Jr., R. W.; Field, L.; Singh, P. K.; Turpin, J. A. *Antimicrob. Agents Chemother.* **1997**, *41*, 419-426 and references cited therein.
12. The enantiomers of **1** are not commercially available.
13. Attempted resolution with **1** with BocVal and BocAla were unsuccessful.

14. The authors thank Thérèse Godbout for the manuscript preparation and Nola Lee for helpful comments.

(*Received in USA* 13 *August* 1997; *revised* 29 *August* 1997; *accepted* 2 *September* 1997)