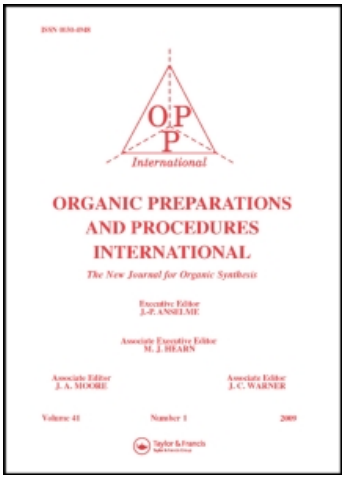


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF *R*-(+)-1,3-DITHIANE 1-OXIDE

P. C. Bulman Page[a]; R. D. Wilkes[a]; M. J. Witty[b]
[a] Robert Robinson Laboratories, Department of Chemistry, University of Liverpool, Liverpool, England
[b] Pfizer Central Research, Sandwich, Kent, England

To cite this Article Page, P. C. Bulman , Wilkes, R. D. and Witty, M. J.(1994) 'SYNTHESIS OF *R*-(+)-1,3-DITHIANE 1-OXIDE', Organic Preparations and Procedures International, 26: 6, 702 — 705
To link to this Article: DOI: 10.1080/00304949409458173
URL: http://dx.doi.org/10.1080/00304949409458173

SYNTHESIS OF *R*-(+)-1,3-DITHIANE 1-OXIDE

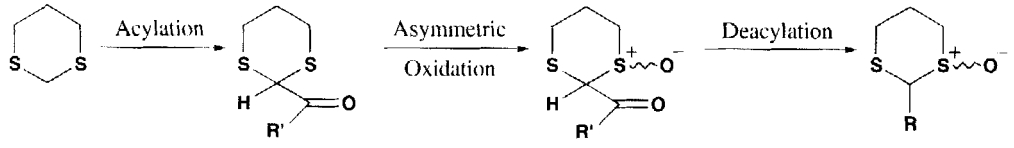
Submitted by (07/07/94)

P. C. Bulman Page*, R. D. Wilkes, and M. J. Witty†

Robert Robinson Laboratories, Department of Chemistry
University of Liverpool
Oxford Street, Liverpool L69 3BX, ENGLAND

† *Pfizer Central Research, Sandwich, Kent, CT13 9NJ, ENGLAND*

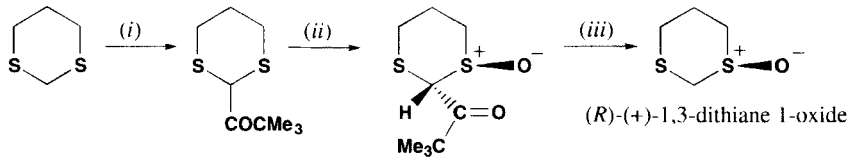
Non-racemic chiral sulfoxides have attained great significance as sources of chirality for asymmetric carbon-carbon bond formation. We have developed the 1,3-dithiane 1-oxide (DiTOX) units (**1**) as extremely effective moieties for the stereocontrol of a wide variety of synthetic transformations, mainly carbonyl group reactions.[1] We have been able to prepare efficiently several 2-monosubstituted[2] and 2,2-disubstituted-1,3-dithiane 1-oxides[3] in high enantiomeric excesses, indeed in some cases approaching optical purity; until recently, however, we had difficulty in preparing the parent compound, 1,3-dithiane 1-oxide (**1**, R = H), in reasonable quantities with very high e.e.[4] Enantiomerically pure 1,3-dithiane 1-oxide has previously only been prepared *via* adducts with (+)-camphor.[5] We now report a chemical synthesis of (*R*)-(+)-1,3-dithiane 1-oxide with very high e.e., effective for production of gram quantities of material.



1

We envisaged a three-step synthetic route, based upon an acylation-oxidation-deacylation sequence,[3,4] starting with the commercially available inexpensive 1,3-dithiane. 2-Acyl substituents have proved to be particularly effective for the modified Sharpless conditions generally employed by us for asymmetric sulfur oxidation of 1,3-dithiane substrates.[6] 2-Pivaloyl-1,3-dithiane (**2**) undergoes this asymmetric oxidation most efficiently (90% e.e.)[4] and was chosen as the intermediate in our scheme. Acylation of 1,3-dithiane was achieved using *ca.* two equivalents of base (1.1 equiv. sodium hexamethyldisilazide; 1.2 equiv. butyllithium) to induce complete deprotonation, conditions which we have previously shown to be optimal for the preparation of 2-acyl-1,3-dithiane 1-oxides.[7] Using this procedure we were able to prepare 2-pivaloyl-1,3-dithiane (**3**) in 25 gram quantities (77% yield). Deprotonation of the starting material, 1,3-dithiane, was carried out at 0°, and the mixture allowed to reach room temperature to ensure complete deprotonation.

The second step of the synthesis involves enantioselective sulfoxidation of 2-pivaloyl-1,3-dithiane using modified Sharpless conditions. Use of such a 'fourth generation' asymmetric synthesis[8] procedure has the advantage that either enantiomer of 1,3-dithiane 1-oxide may be synthesized by appropriate choice of chiral co-factor in the oxidation reaction. Hence, use of natural (+)-diethyl



2 3 1 (R=H)

i) $(Me_3Si)_2NNa$, THF, 0° to RT, 1 hr; BuLi, 0° to RT, 0.5 hr; Me_3CCO_2Et, RT, 2.5 hrs; H_2O
ii) (+)-DET, $Ti(OPr\text{-}i)_4$, H_2O, cumene hydroperoxide, CH_2Cl_2, -35°, 2 days *iii*) 5% NaOH, EtOH, Δ, 24 hrs

tartrate (DET) led to isolation of 2-pivaloyl-1,3-dithiane 1-oxide (**3**) with the (*R*)-absolute configuration at the sulfoxide sulfur atom; conversely, use of unnatural (–)-diethyl tartrate gave product with the (*S*)-absolute configuration at the sulfoxide sulfur atom.[4] The enantioselectivity is reasonably independent of temperature within the range -30° to -40°, and the reaction can be reliably performed within this temperature range to furnish **3** with *ca.* 90% e.e. 2-Pivaloyl-1,3-dithiane 1-oxide contains two asymmetric centers; diastereoselection in the oxidation is in favor of the *anti* diastereoisomer, with selectivities from 3:1 up to exclusive. In all cases where the reaction was performed on a 10 gram scale or greater, the *anti* diastereoisomer was isolated exclusively (63% yield). Typical conditions are shown in the Scheme, in which (+)-DET is employed to give the (*R*)-sulfoxide. A single recrystallization from either diethyl ether or ethanol furnished **3** in enantiomerically pure form.

The final step of the synthesis involved deacylation of **3** by heating under reflux in a 1:1 mixture of 5% aqueous sodium hydroxide and ethanol for approximately 15 hrs. No loss of stereochemical integrity is observed in this step, successfully performed on a 6 gram scale in 61% yield.

This three-step synthetic procedure, using commercially available 1,3-dithiane as starting material, furnishes either optical antipode of 1,3-dithiane 1-oxide in 30% overall yield in 90% e.e., or, with reduced yield, in up to optical purity. Below is given an experimental procedure for the preparation of (*R*)-(+)-1,3-dithiane 1-oxide with 90% e.e.

EXPERIMENTAL SECTION

Infrared spectra were recorded in the range 4000-600 cm^{-1} using a Perkin-Elmer 883 spectrophotometer, and were calibrated against the 1602 cm^{-1} absorption of polystyrene. Solid samples were run as Nujol mulls on sodium chloride plates. ^1H NMR spectra were recorded using a Bruker AMX400 instrument, using $CDCl_3$ solutions and TMS as an internal reference. Mass spectra were obtained on VG Micromass 7070E mass spectrometer. Microanalyses were performed using a Carlo Erba elemental analyzer at the University of Liverpool Department of Chemistry microanalytical laboratory. Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Optical rotations were measured on an Optical Activity AA-1000 polarimeter operating at 589 nm, corresponding to the sodium D line. Enantiomeric excesses were determined by ^1H NMR chiral shift reagent studies using 10 equivalents of (*R*)-(–)- or (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle reagent).

Butyllithium was purchased from the Aldrich Chemical Company in 800 mL bottles as a 2.5 M solution in hexanes. The molarity was determined by titration against a solution of diphenylacetic acid. Sodium hexamethyldisilazide was purchased from the Aldrich Chemical Company in 100 or

800 mL bottles as a 1 M solution in tetrahydrofuran (THF). 1,3-Dithiane was stored in a desiccator over self-indicating silica gel. (+)-Diethyl-(L)-tartrate (Aldrich) and titanium(IV) isopropoxide (Aldrich) were distilled under vacuum, and stored under nitrogen in the presence of molecular sieves. Cumene hydroperoxide (CHP) (80%) was purchased from the Aldrich Chemical Company and was used as supplied.

2-(2,2-Dimethylpropanoyl)-1,3-dithiane (2-pivaloyl-1,3-dithiane) (2).- To a solution of 1,3-dithiane (20.0 g, 166.3 mmol) in THF (350 mL) at 0° was added a 1 M solution of sodium hexamethyldisilazide in THF (1.1 eq., 183 mL, 183.0 mmol). The resulting yellow anion was allowed to reach room temperature and stirred at room temperature for 1 hr. The solution was cooled to 0°, and a 2.5 M solution of butyllithium in hexanes (1.2 eq., 80 mL, 199.6 mmol) added. The yellow solution was allowed to reach room temperature and stirred at room temperature for a further 30 minutes. Ethyl 2,2-dimethylpropanoate (1.1 eq., 23.82 g, 27.8 mL, 183.0 mmol) was added and the mixture stirred at room temperature for 2.5 hrs. A saturated aqueous solution of ammonium chloride was added, the aqueous phase extracted into dichloromethane, and the combined organic extracts were washed with water and dried over anhydrous magnesium sulfate. The solvents were removed *in vacuo* to give a yellow solid. Repeated trituration with petroleum ether followed by filtration gave **2** as a colorless needles (26.1 g, 77%), mp. 97-99°. IR: 2900 and 1673 cm^{-1}; ^1H NMR: δ 1.23 (9H, s), 1.89-2.07 (1H, m), 2.08-2.25 (1H, m), 2.50-2.59 (2H, m), 3.36-3.51 (2H, m), 4.51 (1H, s). MS: m/z (E.I.) 204.06445 (M^+); $C_9H_{16}OS_2$ requires 204.06426.

Anal. Calcd $C_9H_{16}OS_2$: C, 52.90; H, 7.89. Found: C, 52.73; H, 7.87

***anti*-2*R*-(2,2-Dimethylpropanoyl)-1,3-dithiane 1*R*-oxide (3).**- To a solution of (+)-diethyl-(L)-tartrate (2 eq., 20.18 g, 16.76 mL, 97.9 mmol) in dichloromethane (20 mL) under a nitrogen atmosphere was added titanium (IV) isopropoxide (1 eq., 13.91 g, 14.57 mL, 48.9 mmol). The resulting pale yellow solution was stirred at room temperature for 5 minutes. Water (1 eq., 0.88 mL, 48.9 mmol) was added carefully and the solution stirred for a further 30 minutes. 2-(2,2-Dimethylpropanoyl)-1,3-dithiane (10.0 g, 48.9 mmol), was dissolved in dichloromethane (200 mL) and added *via* cannula to the mixture. The solution was stirred at room temperature for 5 minutes and then at -35° for 30 minutes. Cumene hydroperoxide (1 eq., 9.32 g, 9.05 mL, 61.2 mmol) was added and the mixture stirred at -35° for 2 days. The orange solution was allowed to reach room temperature over 1 hr, and the dichloromethane removed *in vacuo*. Diethyl ether (350 mL) and a saturated aqueous solution of (+)-tartaric acid (150 mL) were added to the flask, and the mixture stirred at *ca.* -10° for 1.5 hrs. The resulting white suspension was allowed to reach room temperature over 10 minutes, the organic layer separated, and the aqueous layer extracted with diethyl ether. The combined organic extracts were washed with a saturated brine solution, dried over magnesium sulfate, and the solvents removed *in vacuo* to give a yellow oil. Dichloromethane (25 mL) was added, and the solution filtered to remove any titanium residues. The filtrate was reconcentrated to give a yellow oil. Flash column chromatography, using gradient elution from 100% dichloromethane to 100% ethyl acetate, furnished exclusively *anti*-2*R*-(2,2-dimethylpropanoyl)-1,3-dithiane 1*R*-oxide (**3**), as a colorless crystalline solid (6.81 g,

63%), mp. 103-105°. IR: 2923, 1707 and 1033 cm^{-1}; ^1H NMR: δ 1.26 (9H, s), 1.99-2.22 (1H, m), 2.41-2.70 (2H, m), 2.71-2.90 (2H, m), 3.42-3.58 (1H, m), 4.71 (1H, m). MS: m/z (E.I.) 220.05931 (M^+); $C_9H_{16}O_2S_2$ requires 220.05917; $[\alpha]_D^{20}$ = -20.5° (c = 0.10, EtOH); e.e. = 90% from ^1H NMR studies.

Anal. Calcd for $C_9H_{16}O_2S_2$: C, 49.06; H, 7.32. Found: C, 48.91; H, 7.35

(*R*)-(+)-1,3-dithiane 1-oxide (90% e.e.) (1, R = H).- To a stirred solution of *anti*-2-(2,2-dimethylpropanoyl)-1,3-dithiane 1-oxide (6.00g, 27.2 mmol) (**3**) in ethanol (120 mL) was added 5% aqueous sodium hydroxide solution (70 mL). The solution was refluxed overnight, and the organic layer separated. Further extraction of the aqueous layer with dichloromethane, followed by drying of the combined organic extracts over $MgSO_4$ and evaporation *in vacuo* gave a beige colored solid, which was purified by repeated trituration with diethyl ether, followed by recrystallization from dichloromethane to give (*R*)-(+)-1,3-dithiane 1-oxide, (**1**, R = H), as a pale yellow crystalline solid (2.26 g, 61%), mp. 106-107°. IR: 2927 and 1047 cm^{-1}; ^1H NMR: δ 2.19-2.32 (1H, m), 2.40-2.70 (4H, m), 3.25-3.38 (1H, m), 3.64 (1H, d, *J* = 12.8Hz), 3.98 (1H, dd, *J* = 2.8,12.7Hz). MS: m/z (E.I.) 136.00151(M^+); $C_4H_8OS_2$ requires 136.00166; $[\alpha]_D^{20}$ = +208.6° (c = 1.05, EtOH) (lit. +230° (c = 1.0, EtOH) for optically pure material; e.e. = 90% from ^1H NMR studies.

Anal. Calcd for $C_4H_8OS_2$: C, 35.27; H, 5.89. Found: C, 35.18; H, 5.93

Acknowledgment.- This investigation has enjoyed the support of the EPSRC and Pfizer Central Research (CASE award to RDW).

REFERENCES

1. P. C. B. Page, S. M. Allin, E. W. Collington and R. A. E. Carr, *J. Org. Chem*, **58**, 6902 (1993) and references therein.

2. P. C. B. Page, E. S. Namwindwa, S. S. Klair and D. Westwood, *Synlett*, 457 (**1990**); P. C. B. Page, R. D. Wilkes, J. V. Barkley and M. J. Witty, *ibid.*, 547 (**1994**).

3. P. C. B. Page and E. S. Namwindwa, *ibid.*, 80 (**1991**).

4. P. C. B. Page, M. T. Gareh and R. A. Porter, *Tetrahedron: Asymmetry*, **4**, 2139 (1993).

5. R. F. Bryan, F. A. Carey, O. D. Dailey, R. J. Maher and R. Miller, *J. Org. Chem.*, **43**, 90 (1978).

6. H. B. Kagan and F. Rebiere, *Synlett*, 643 (**1990**) and references therein.

7. P. C. B. Page, M. T. Gareh and R. A. Porter, *Tetrahedron Lett.*, **34**, 5159 (1993).

8. S. N. Kilenyi and R. A. Aitken in "*Asymmetric Synthesis*," Chapman & Hall, London, 1992.

****