COMMUNICATION

Highly stereocontrolled reduction of an alkynyl ketone possessing a 1,3-dithianyl moiety using oxazaborolidine–BH_3

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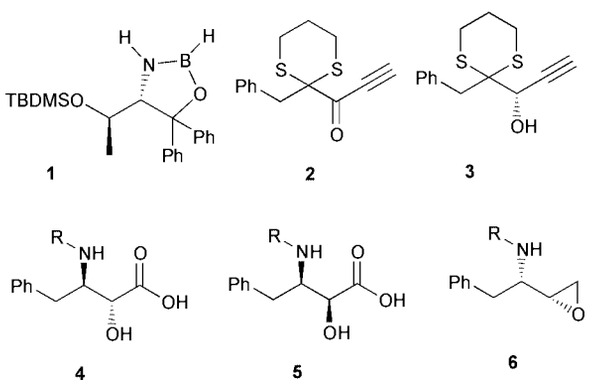
Highly enantioselective reduction of 2-benzyl-2-propioloyl-1,3-dithiane was conducted using oxazaborolidine derived from L-threonine and borane complex to give (*S*)-2-benzyl-2-(1-hydroxyprop-2-ynyl)-1,3-dithiane in high enantiomeric purity.

In conjugation with the exploration into new bioactive materials, an α-hydroxy ketone **3** possessing a latent carboxylic acid moiety is required. For the synthesis of HIV protease inhibitors, amino hydroxy alcohols **4**, **5**, and amino epoxide **6** are important synthetic units, and several approaches to their synthesis have been reported.[1] Our previous investigation has revealed that the oxazaborolidine-mediated reduction of 1,2-diimines[2] and 1,2-imino ketones[3] provides short efficient routes to homochiral 1,2-diphenylethylenediamines and *syn*- or *anti*-2-amino-1,2-diarylethanols in good overall yields. Oxazaborolidine **1** derived from L-threonine and borane has provided a convenient tool for the reduction of ketones and imines,[4] and therefore, application to multi-functionalized molecules has intrigued us, and may lead to a rapid access to a useful class of compounds. This paper describes an efficient approach to (*S*)-2-benzyl-2-(1-hydroxyprop-2-ynyl)-1,3-dithiane **3** in high enantiomeric excess.

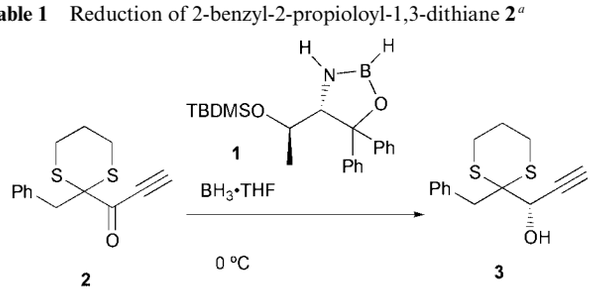


1 2 3 4 5 6

2-Benzyl-2-propioloyl-1,3-dithiane **2**, the starting material, was prepared from 2-ethoxycarbonyl-1,3-dithiane *via* the following sequences in good overall yield: benzylation (NaH, BnBr, DMF–PhH, 89%), saponification (LiOH, H_2O–THF, 73%), amide formation ($(COCl)_2$, DMF, then $HN(CH_3)$-OCH_3·HCl, CH_2Cl_2, 90%), and addition of acetylide (*n*-BuLi, TMSC≡CH, THF, 54%).[5] An initial examination was carried out in the presence of 1.0 eq. of the oxazaborolidine **1** using BH_3·THF as a stoichiometric reducing agent, and the results are summarized in Table 1.

First, the amount of BH_3·THF was examined. When the reduction was carried out with 1.0 equivalent of BH_3·THF, moderate enantioselectivity was obtained, whereas an enhanced selectivity was observed using 2.0 equivalents of the reductant. For the reaction solvent, use of aromatic solvents such as benzene, toluene, or chlorobenzene gave good enantioselectivities. Under the optimum reaction conditions the effects of

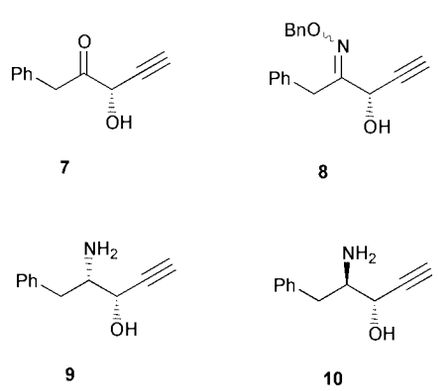
Table 1 Reduction of 2-benzyl-2-propioloyl-1,3-dithiane **2**[a]



2 3

Entry	BH_3·THF (eq.)	Solvent	Time/h	Yield (%)[b]	% ee[c]
1	1.0	THF	3.0	41	65
2	1.5	THF	3.0	40	68
3	2.0	THF	12.0	31	92
4	2.5	THF	16.5	61	83
5	3.0	THF	12.0	26	85
6	2.0	Et_2O	13.0	40	63
7	2.0	CH_2Cl_2	14.0	48	52
8	2.0	PhH	2.5	40	99
9	2.0	PhMe	3.0	64	89
10	2.0	PhCl	2.0	50	91

[a] The reaction was carried out according to the typical procedure. [b] Isolated yields. [c] Determined by HPLC using a chiral stationary phase column (Daicel OD).



7 8 9 10

reaction temperature and the amount of oxazaborolidine were examined, and Table 2 summarizes the results.

As shown in Table 2, the reduction in benzene at higher temperatures gave the reduction product **3** with decreased enantiomeric purities (entries 1 and 2), whereas at −15 or −30 °C in toluene, high enantioselectivities were observed. However, at −78 °C the reaction did not proceed enantioselectively. We next examined the amount of the oxazaborolidine **1**. When the reduction was carried out in the presence of 0.5 eq. of the catalyst **1**, both the product yield and the enantioselectivity were satisfactory. Even in the presence of 0.25 or 0.2 eq. of the catalyst **1**, the enantioselectivity was still very high.

Transformation into the benzyloxyimine **8**, a key intermediate for the synthesis of amino alcohols **9**, and **10** was

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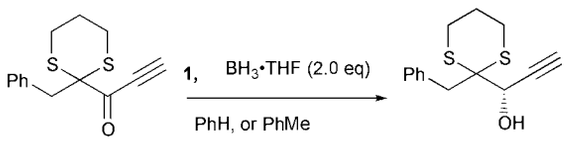
Table 2 Effects of the reaction temperature and the amount of **1** [a]



2 **3**

Entry	**1** (eq.)	Solvent	Temp. /°C	Time/h	Yield (%) [b]	% ee [c]
1	1.0	PhH	rt	2.0	34	80
2	1.0	PhH	50	20.0	20	21
3	1.0	PhMe	−15	6.0	58	98
4	1.0	PhMe	−30	6.0	71	93
5	1.0	PhMe	−50	6.0	49	76
6	1.0	PhMe	−78	5.0	30	32
7	0.5	PhMe	−15	5.5	65	97
8	0.25	PhMe	−15	8.5	49	99
9	0.2	PhMe	−15	7.0	31	96
10	0.1	PhMe	−15	8.0	12	76
11	0.05	PhMe	−15	8.0	7	5

[a] The reaction was carried out according to the typical procedure. [b] Isolated yields. [c] Determined by HPLC using a chiral stationary phase column (Daicel OD).

readily carried out *via* removal of the dithianyl moiety (NBS in acetone at −5 °C, 66%) followed by benzyloxyimination (BnONH·HCl, pyridine, MeOH, at 0 °C, 95%). Further reduction into *syn*- and *anti*-amino alcohols is under investigation using the methodologies previously reported from our laboratory.[3]

In conclusion, the present methodology using enantioselective reduction of 2-benzyl-2-propioloyl-1,3-dithiane **2**, demonstrates the power of the oxazaborolidine-mediated reduction of a functionalized molecule to give a very useful class of compounds with high enantiomeric excess in a short-step. Reduction of the compound **8** to both the *syn*- and *anti*-amino alcohols **9**, **10** as well as transformation into the hydroxy amino acids **4**, **5** will be reported in due course.

Experimental

A typical procedure for the reduction of 2-benzyl-2-propioloyl-1,3-dithiane is as follows: to a solution of (2*S*,3*R*)-2-amino-3-(*tert*-butyldimethylsiloxy)-1,1-diphenylbutanol (9.3 mg, 0.025 mmol) in toluene (1.0 mL) was added BH_3·THF complex (0.225 mL, 0.225 mmol), and the mixture was stirred for 1 h at 40 °C. After cooling the reaction mixture to −15 °C, a solution of 2-benzyl-2-propioloyl-1,3-dithiane **2** (26.2 mg, 0.1 mmol) in toluene (1.0 mL) was added dropwise during 2 h. The reaction mixture was quenched by addition of phosphate buffer, and the entire mixture was extracted with ethyl acetate. Drying and concentration of the combined extracts gave a crude oil, which was purified on preparative TLC (eluent: *n*-hexane–AcOEt = 4 : 1) to afford (*S*)-2-benzyl-2-(1-hydroxyprop-2-ynyl)-1,3-dithiane **3** as a colorless oil (13.0 mg, 49%). $[\alpha]_D^{23} = +37.6$ (*c* 0.25, $CHCl_3$). The enantiomeric purity was determined to be 99% ee by HPLC analysis using a chiral stationary phase column (Daicel OD, eluent: *n*-hexane–*i*-PrOH = 40 : 1). The absolute configuration of the product was determined by transformation into a known derivative and comparison with the authentic sample.[6]

Acknowledgements

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