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Efficient enantio- and diastereoselective synthesis of enantiopure *syn*-α-bromo-β-hydroxy-α-methylpropionate esters and their *cis*-α,β-epoxy derivatives based on a chiral oxazaborolidinone-promoted asymmetric aldol reaction

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Abstract

syn-α-Bromo-β-hydroxy-α-methylpropionate esters were prepared in high diastereoselectivity with essentially enantiopure state by employing the chiral oxazaborolidinone-promoted asymmetric aldol reaction with β-bromo-β-methylketene silyl acetal. The subsequent subjection of the α-bromo-β-hydroxy esters to basic conditions led to the quantitative transformation to the corresponding enantiopure *cis*-α,β-epoxy derivatives.

1. Introduction

Development of versatile syntheses of enantiopure α-bromo-β-hydroxy esters is required in order to extend their availability as precursors to α,β-epoxy esters, α-amino-β-hydroxy esters, β-amino-α-hydroxy esters and so on.[1] These studies are, however, limited to *anti* isomers without an alkyl substituent at the α-position of the α-bromo-β-hydroxy esters.[2] Effective preparation of enantiopure α-bromo-β-hydroxy-α-methyl esters is being intensively studied to provide α,α-disubstituted α-amino acids with a methyl group at the α-position as constituents of biologically active compounds.[3] We disclose herein a highly enantio- and diastereoselective general synthesis of such α-bromo-β-hydroxy-α-methyl esters realized by using the stereoselective oxazaborolidinone-promoted asymmetric aldol reaction with β-bromo-β-methylketene silyl acetal.

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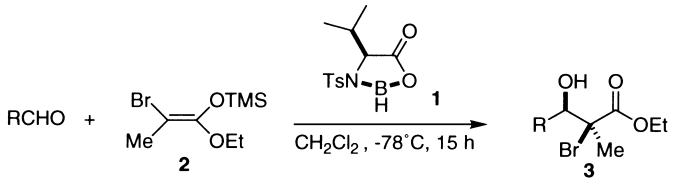
2. Results and discussion

We were aware that considerably large substituents at the β-position of ketene silyl acetals brings about the high enantioselectivity (almost >98% ee) in asymmetric aldol reactions in the presence of chiral oxazaborolidinone **1**, prepared in situ from L-Ts-Val and BH_3·THF.[4]

According to the strategy, β-bromo-β-methylketene silyl acetal **2** (bp 73–74°C/0.1 mmHg, *E*:*Z* = 1: 2) was chosen as an appropriate silyl nucleophile available for the topic under study. The reaction of a variety of aldehydes with the silyl nucleophile **2** proceeded in good yields under standard conditions (CH_2Cl_2, –78°C, 15 h, in the presence of a stoichiometric amount of chiral borane **1**) and the results are summarized in Table 1. Very high enantioselectivities were observed as expected. The considerably high diastereoselection observed is particularly intriguing beyond the scope of the asymmetric aldol reaction which proceeds independent of the geometry of the silyl nucleophiles used.[4,5] The following transformation (DIBALH reduction and acetalization) was carried out with respect to *syn*-**3a** and then the structure of the acetonide was confirmed (Scheme 1). When **3a** was first reported as an intermediate for radical reactions in a previous paper,[6] the configuration was assigned as *anti* from the misinterpretation of three singlet methyls in the acetonide derivative. The detailed NOE experiments allowed revision of the structure as *syn* after reassignment of the methyls using H–H COSY with $Eu(fod)_3$ shift reagent.

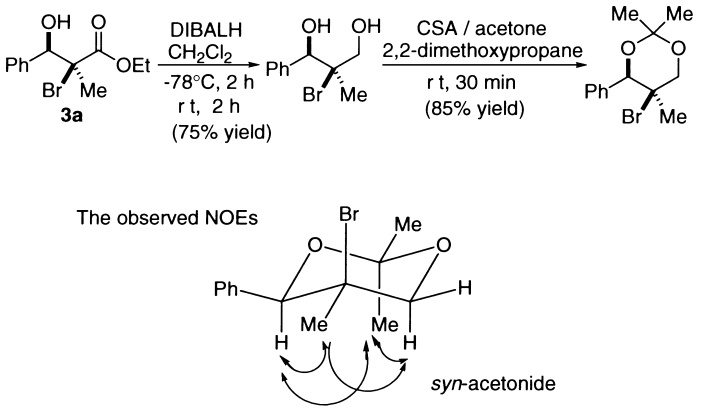
Table 1
Preparation of enantiopure *syn*-α-bromo-β-hydroxy-α-methylpropionate esters by chiral oxazaborolidinone-promoted aldol reactions



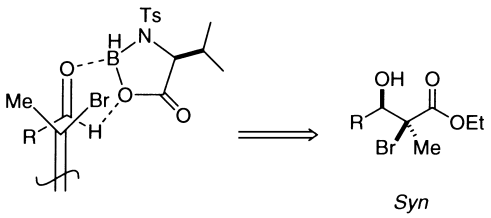
Entry	R (RCHO)	Yield (%)[a]	*syn* / *anti*[b]	% ee (*syn*)[c]
1	C_6H_5	82 (**3a**)	7 : 1	95
2	$(CH_3)_2CH$	68 (**3b**)	16 : 1	97
3	$C_6H_5CH_2CH_2$	80 (**3c**)	9 : 1	96
4	$CH_3CH_2CH_2$	85 (**3d**)	10 : 1	98
5	$TBSOCH_2CH_2$	87 (**3e**)	15 : 1	95

a Isolated yields.
b Diastereomeric ratios were determined from their ^1H NMR data.
c Enantiomeric excess was determined by HPLC analysis with a chiral column: DAICEL CHIRALPAK-AD with 0.2-3% isopropanol in hexane.

For a rationale to explain the *syn* selectivity, a predominant arrangement of the aldehyde carbonyl and the silyl nucleophile should be indispensable to a transition state assembly, as depicted in Scheme 2. Electronic effects might be presumably requisite to the arrangement because the steric



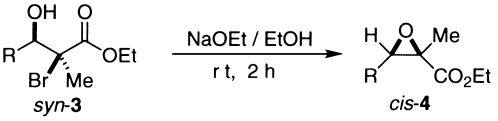
Scheme 1.



Scheme 2. A transition state assembly to *syn*

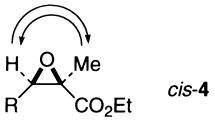
bulkiness of bromo and methyl substituents (van der Waals radii) is nearly the same.[7] This reaction is unexpectedly useful for the synthesis of such enantiopure compounds. In addition, it is practically useful that the major *syn* isomers can be easily purified by simple flash column chromatography on silica gel.

Table 2
Stereospecific transformation of *syn*-α-bromo-β-hydroxy esters to tri-substituted *cis*-α,β-epoxy esters[a]



Entry	R	Yield (%)[b]
1	C_6H_5	87 (**4a**)
2	$(CH_3)_2CH$	74 (**4b**)
3	$C_6H_5CH_2CH_2$	81 (**4c**)
4	$CH_3CH_2CH_2$	78 (**4d**)
5	$TBSOCH_2CH_2$	93 (**4e**)

a Reaction conditions: A solution of *syn*-**3** in Et_2O was stirred with NaOEt (1.1 equiv) at rt for 2 h (entry 2 for 15 h).
b Isolated yields after flash column chromatography (SiO_2).



cis-**4**

Scheme 3. The observed NOEs

We can, furthermore, demonstrate a facile utility of the enantiopure *syn*-**3** compounds by transformation of them to tri-substituted *cis*-epoxy esters, which are also versatile synthetic intermediates. By treatment of sodium ethoxide in ethanol, *syn*-**3** was converted to the corresponding tri-substituted *cis*-epoxy ester **4** in good yields, as shown in Table 2. The reaction takes place in a stereospecific manner so that a single product is produced. All stereochemistries in this paper were reconfirmed by NOEs between the hydrogen and the methyl in all *cis*-epoxides (Scheme 3).

3. Conclusion

An efficient enantio- and diastereoselective synthesis of enantiopure *syn*-α-bromo-β-hydroxy-α-methylpropionate esters was conveniently realized and the following transformation also proceeded to the corresponding enantiopure tri-substituted *cis*-α,β-epoxy esters in high yields.

4. Experimental

4.1. General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. All reactions involving organometallic reagents were conducted under an argon atmosphere. IR spectra were determined with a JASCO FT/IR-5300 Fourier transform infrared recording spectrophotometer. ^{1}H NMR spectra were determined on a JEOL JNM-LA 400 (a superconducting, 400 MHz, FT instrument) spectrometer. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Significant ^{1}H NMR data are tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant(s) in hertz, number of protons. ^{13}C NMR spectra were measured at 100 MHz with a JOEL JNM-LA 400 spectrometer. High-pressure liquid chromatography (HPLC) was done with a JASCO Model PU-980 liquid chromatograph.

4.2. A typical procedure of chiral oxazaborolidinone-promoted asymmetric aldol reactions with β-bromo-β-methylketene silyl acetal **2**

To a solution of *N*-(*p*-toluenesulfonyl)-*S*-valine (1.5 g, 5.5 mmol) in dry CH_2Cl_2 (25 mL) at 0°C was added BH_3·THF (5.0 mL, 5.0 mmol, 1 M in THF). The solution was stirred for 30 min at 0°C, then additionally for 30 min at rt. The solution was cooled to –78°C and benzaldehyde (0.5 mL, 5.0 mmol) in CH_2Cl_2 (1 mL) was added slowly over 5 min. After stirring for 5 min, **2** (1.77 g, 7.0 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 5 min, the reaction mixture was stirred for

15 h at –78°C, and 10% hydrochloric acid (5 mL) was added to quench the reaction. The reaction mixture was allowed to warm to rt and evaporated to a concentrated residue. The residue was diluted with ether and the phases were separated. The organic phase was washed with satd $NaHCO_3$ aq. solution and brine, dried over $MgSO_4$, and evaporated in vacuo. Flash column chromatography (7% ethyl acetate/hexane) provided separately the pure aldols of *syn*-**3a** and *anti*-**3a** with a ratio of 7:1 (R_f values 0.4 and 0.3, respectively, on silica gel TLC with 20% ethyl acetate in hexane) (1.18 g, 82%).

Compound *syn*-**3a**: $[\alpha]_D^{22}$ +10.1 (*c* 1.48, $CHCl_3$). IR (film) 3508, 1734 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.30 (t, $J=7.07$, 3H), 1.75 (s, 3H), 3.27 (d, $J=3.16$, 1H), 4.24 (q, $J=7.07$, 2H), 5.23 (d, $J=2.92$, 1H), 7.25–7.51 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.79, 22.55, 62.40, 67.67, 77.16, 127.90, 128.00, 128.51, 136.86, 170.46. Anal. calcd for $C_{12}H_{15}O_3Br$: C, 50.19; H, 5.27. Found: C, 50.21; H, 5.31.

Compound *syn*-**3b**: $[\alpha]_D^{22}$ –10.7 (*c* 3.66, $CHCl_3$). IR (film) 3506, 1735 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88 (d, $J=6.8$, 3H), 1.06 (d, $J=6.60$, 3H), 1.32 (t, $J=7.07$, 3H), 1.76 (septet, $J=6.84$, 1H), 1.88 (s, 3H), 2.52 (br.s, 1H), 3.94 (d, $J=6.09$, 1H), 4.25 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.72, 19.22, 20.41, 21.83, 30.95, 62.08, 69.37, 78.99, 170.62. Anal. calcd for $C_9H_{17}O_3Br$: C, 42.70; H, 6.77. Found: C, 42.77; H, 6.64.

Compound *syn*-**3c**: $[\alpha]_D^{22}$ +45.0 (*c* 0.77, $CHCl_3$). IR (film) 3508, 1732 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.24 (t, $J=7.07$, 3H), 1.62–1.85 (m, 2H), 1.82 (s, 3H), 2.73 (d, $J=4.64$, 1H), 2.66–2.73 (m, 1H), 2.96 (ddd, $J=9.52$, 4.88, 14.16, 1H), 4.01 (ddd, $J=4.16$, 1.96, 10.04, 1H), 4.20 (q, $J=7.07$, 2H), 7.17–7.38 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.76, 22.45, 32.53, 32.54, 62.24, 67.71, 74.86, 126.00, 128.41, 128.46, 141.40, 170.57. Anal. calcd for $C_{14}H_{19}O_3Br$: C, 53.34; H, 6.08. Found: C, 54.00; H, 6.13.

Compound *syn*-**3d**: $[\alpha]_D^{22}$ +21.5 (*c* 1.81, $CHCl_3$). IR (film) 3504, 1736 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.84 (t, $J=7.07$, 3H), 1.22 (t, $J=7.07$, 3H), 1.12–1.28 (m, 1H), 1.30–1.42 (m, 2H), 1.49–1.61 (m, 1H), 1.72 (s, 3H), 2.51 (d, $J=4.40$, 1H), 3.94 (dd, $J=4.40$, 9.52, 1H), 4.17 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.75, 13.79, 19.68, 22.26, 33.86, 62.15, 68.17, 75.38, 170.59. Anal. calcd for $C_9H_{17}O_3Br$: C, 42.70; H, 6.77. Found: C, 43.21; H, 6.55.

Compound *syn*-**3e**: $[\alpha]_D^{22}$ +2.3 (*c* 3.49, $CHCl_3$). IR (film) 3462, 1736 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.0 (s, 6H), 0.82 (s, 9H), 1.23 (t, $J=7.07$, 3H), 1.54–1.67 (m, 2H), 1.78 (s, 3H), 3.35 (d, $J=2.93$, 1H), 3.71–3.82 (m, 2H), 4.15 (dt, $J=2.88$, 9.28, 1H), 4.18 (q, $J=7.07$, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ –5.54, –5.50, 13.83, 18.16, 23.00, 25.83, 34.35, 61.19, 62.19, 66.57, 74.55, 170.51. Anal. calcd for $C_{14}H_{29}O_4BrSi$: C, 45.52; H, 7.91. Found: C, 45.86; H, 7.73.

4.3. A typical procedure of stereospecific transformation of syn-α-*bromo*-β-*hydroxy esters to* cis-α,β-*epoxy esters*

To a solution of *syn*-**3a** (574 mg, 2.0 mmol) in EtOH (10 mL) was added sodium ethoxide (1 M soln in EtOH) and the reaction mixture was stirred for 2 h at rt. The reaction mixture was evaporated in vacuo. The resulting residue was dissolved in ether, washed with water, and dried over $MgSO_4$. After evaporation of the solvent, the crude material was purified by flash column chromatography (4% ethyl acetate/hexane) to provide *cis*-**4a** (358.4 mg, 87%) as a colorless oil.

Compound *cis*-**4a**: $[\alpha]_D^{22}$ +34.4 (*c* 1.01, $CHCl_3$). IR (film) 1749 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.92 (t, $J=7.07$, 3H), 1.72 (s, 3H), 3.93 (m, 2H), 4.02 (s, 1H), 7.10–7.39 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.70, 19.41, 61.01, 62.85, 63.69, 126.26, 127.90, 128.12, 133.68, 168.45. Anal. calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.02; H, 6.69.

Compound **4b**: $[\alpha]_D^{22}$ +23.8 (*c* 1.30, $CHCl_3$). IR (film) 1749 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.86 (d, $J=6.84$, 3H), 1.03 (d, $J=6.60$, 3H), 1.23 (t, $J=7.07$, 3H), 1.33–1.46 (m, 1H), 1.50 (s, 3H), 2.55 (d, $J=9.52$, 1H), 4.18 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.15, 18.25, 19.45, 19.96, 27.85, 60.01, 61.27, 69.62, 170.02. Anal. calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.34; H, 9.57.

Compound **4c**: $[\alpha]_D^{22}$ +32.9 (*c* 0.42, $CHCl_3$). IR (film) 1745 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.27 (t, $J=7.07$, 3H), 1.54 (s, 3H), 1.90 (m, 2H), 2.73 (dt, $J=8.04$, 13.88, 1H), 2.84 (ddd, $J=8.76$, 6.08, 14.16, 1H), 2.95 (t, $J=6.22$, 1H), 4.18 (q, $J=7.07$, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.24, 19.34, 29.87, 32.36, 59.72, 61.49, 63.53, 126.15, 128.37, 128.50, 140.75, 169.93. Anal. calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.84; H, 7.81.

Compound **4d**: $[\alpha]_D^{22}$ +35.8 (*c* 0.61, $CHCl_3$). IR (film) 1746 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.94 (t, $J=7.07$, 3H), 1.30 (t, $J=7.07$, 3H), 1.40–1.61 (m, 4H), 1.56 (s, 3H), 2.92 (t, $J=5.86$, 1H), 4.24 (q, $J=7.07$, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.75, 14.21, 19.33, 19.44, 30.03, 59.51, 61.33, 64.08, 170.11. Anal. calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 63.10; H, 9.29.

Compound **4e**: $[\alpha]_D^{22}$ +12.9 (*c* 2.80, $CHCl_3$). IR (film) 1749 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.0 (s, 6H), 0.83 (s, 9H), 1.23 (t, $J=7.07$, 3H), 1.51 (s, 3H), 1.65–1.79 (m, 2H), 3.04 (dd, $J=6.12$, 6.12, 1H), 3.70 (m, 2H), 4.17 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ –5.34, 14.15, 18.19, 19.28, 25.79, 31.31, 59.28, 59.92, 61.31, 61.85, 169.96. Anal. calcd for $C_{14}H_{28}O_4Si$: C, 50.30; H, 9.79. Found: C, 49.97; H, 9.83.

Acknowledgements

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