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An efficient method for the synthesis of enantiopure 2,3-*anti*-propionate aldols involving a 3,5-*syn*- or *anti*-diol subunit through chiral borane-mediated enantioselective aldol reaction coupled with radical reduction

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Abstract

2,3-*anti*-Propionate aldols involving a 3,5-*syn*- or *anti*-diol subunit, versatile enantiopure segments available for macrolide synthesis, were prepared by a chiral oxazaborolidinone-promoted asymmetric aldol reaction with 2-bromo-1-ethoxy-2-methyl-1-trimethylsiloxyethene and the following highly *anti*-preferential radical debromination.

Keywords: asymmetric aldol reaction; chiral borane; anti-propionate aldol; radical reduction.

There is currently a demand for an efficient means of preparing enantiopure 2,3-*anti*-propionate aldols involving a 3,5-*syn*- or *anti*-diol which appear in the C16–C19 segment of scytophycin C,[1] the C4–C7 segment of discodermolide,[2] the C32–C35 subunit of the synthetic intermediate directed to rapamycin,[3] the C20–C23 segment of ionomycin,[4] which is shown as an example in Fig. 1, and so on.

We have previously reported that 1,3-*syn*- or *anti*-diol can be stereoselectively provided by applying a chiral oxazaborolidinone (**1** or **2**)-promoted asymmetric aldol reaction to ketene silyl acetal **3**.[5] Further, radical reduction of 2-bromo-3-hydroxy-2-methylpropionate derivatives with Bu_3SnH was also reported to give *syn*-propionate aldols via chelation control in the presence of $MgBr_2 \cdot OEt_2$.[6] Guindon et al. have already reported that the reverse *anti*-propionate aldols are surely obtained from the radical reduction of the acetals of 2-methyl-2-phenylseleno-3,5-dihydroxypentanoate derivatives with Bu_3SnH via non-chelation control with respect to exocyclic effect.[7] The above information persuaded us to investigate the following reactions: after acetalization of the diols derived from successive aldol reactions of an aldehyde with ketene silyl acetals, **3** and **4**, the subunits above might be prepared by debromination according to the radical reduction. We disclose herein a versatile solution toward the targets.

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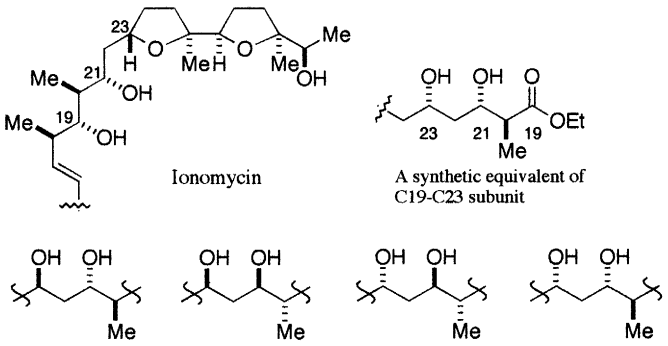
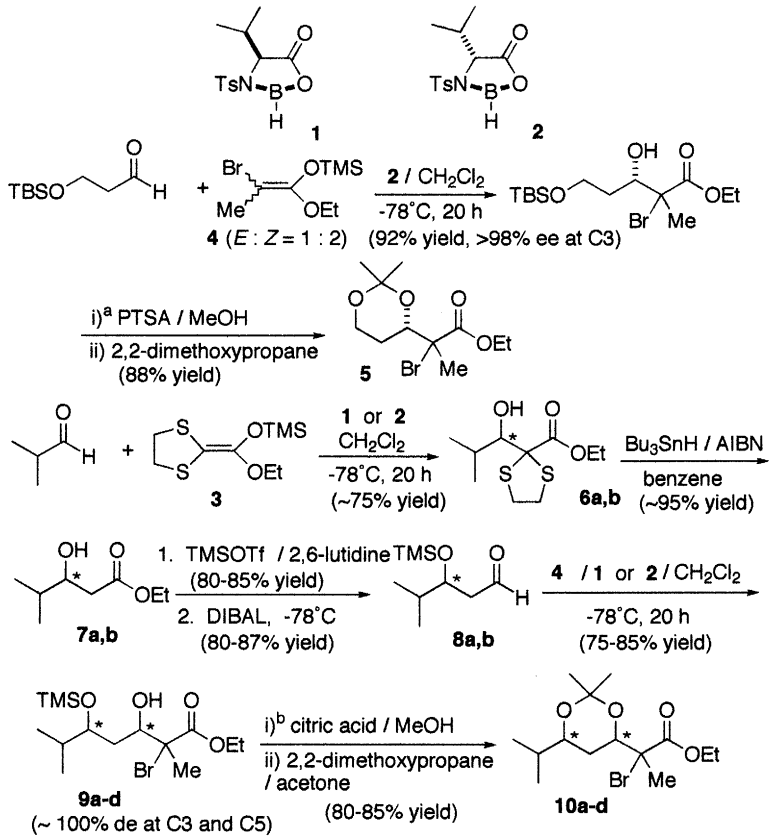


Fig. 1. Synthetic targets as enantiopure subunit

A preliminary trial was done with the corresponding epimeric bromide **5**. The bromide **5** was prepared by the chiral oxazaborolidinone-promoted asymmetric aldol reaction of 3-*tert*-butyldimethylsiloxypropanal with 2-bromo-1-ethoxy-2-methyl-1-trimethylsiloxyethene **4** (74–75°C/15 mmHg; *E*:*Z*=1:2) in a stoichiometric amount of chiral borane **2** to give the α-bromo aldol in 92% yield with >98% ee at C3, followed by treatment with 2,2-dimethoxypropane (88% yield). The bromide **5** was then subjected to a hydrogen transfer reaction with Bu_3SnH with a catalytic amount of Et_3B in toluene at −78°C with stirring overnight. Ethyl (2*S*,3*S*)-3,5-dihydroxy-3,5-isopropylidene-2-methylpentanoate

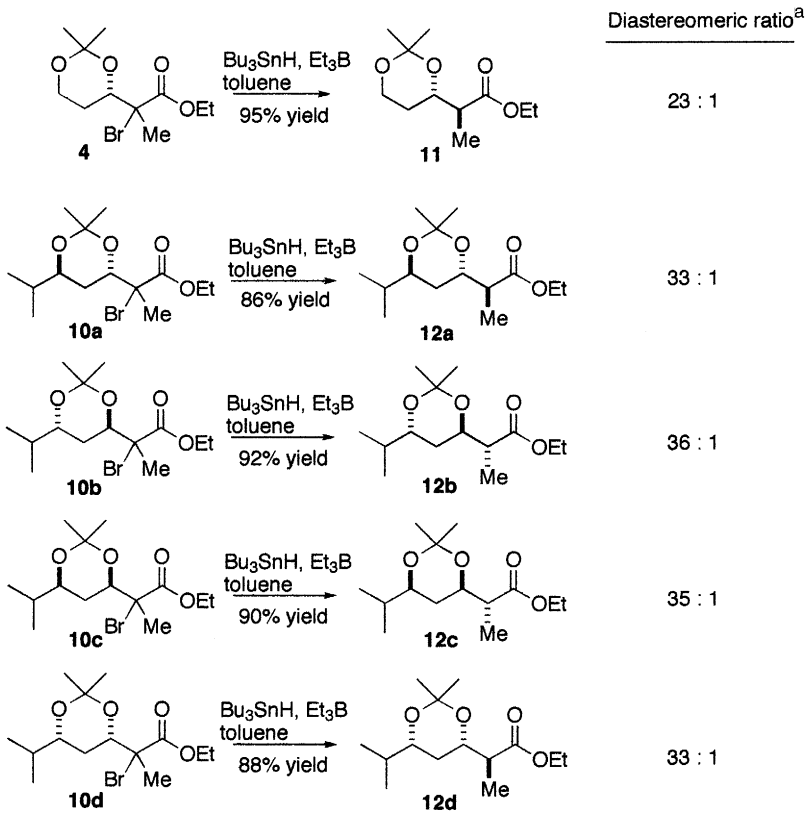


Scheme 1. [a]One-pot reaction: (i) 10 min stirring; (ii) addition of excess 2,2-dimethoxypropane. [b]One-pot reaction: (i) 20 min stirring; (ii) evaporation of MeOH and addition of excess 2,2-dimethoxypropane with acetone

11, $[\alpha]_D^{22}$ +20.1 (*c* 1.49, $CHCl_3$), was preferentially obtained in a ratio of 23:1 in 95% yield; the relative *anti* configuration was confirmed on the basis of NMR experiments of its lactone derivative. The *anti* selectivity has proved to be undoubtedly high in the α-bromo system bearing an isopropylidene acetal moiety in the radical reductions.

The epimeric bromides **10a**–**d** involving the enantiopure 1,3-diol unit required for the synthesis of the targets under consideration were prepared as follows (Scheme 1). Reaction of isobutanal with silyl nucleophile **3** smoothly proceeded in a stoichiometric amount of chiral borane **1** or **2** to afford the corresponding dithiolane aldols in an essentially enantiopure state. The sequential procedure for desulfurization was carried out under the conditions of Bu_3SnH with AIBN,[8] instead of Ni_2B–H_2,[5a] to give the enantiopure aldols **7a**,**b** in almost quantitative yields. TMS protection of the hydroxyl group in **7a**,**b** was achieved with TMSOTf and 2,6-lutidine, and the ethoxycarbonyl function in the resulting TMS protected aldols was directly converted to the corresponding aldehydes to give **8a**,**b** on treatment of DIBAL at −78°C.

The second asymmetric aldol reaction of **8a**,**b**, in this sequence to **10a**–**d**, with silyl nucleophile **4** in the presence of chiral borane **1** or **2** furnished aldol **9a**–**d** (~100% de at C3 and C5) in good yields. The stereochemistry at the stereogenic center (C3) is completely controlled by only the stereochemistry of the chiral borane used [‘promoter (catalyst) control’ on enantioselective acyclic stereoselection][5] so that each 3,5-*syn* or *anti*-diol unit is readily available in a pure state of relative configuration. After deprotection



Scheme 2. All reactions were performed at a substrate concentration of 0.1 M using 2.0 equiv. of Bu_3SnH with a catalytic amount of Et_3B. [a]Diastereomeric ratio was determined from their ^1H NMR spectra

of the TMS function in **9a**–**d**, subjecting the resulting diol to acetalization afforded **10a**–**d** which are epimeric only at C2.

The arranged epimeric bromides **10a**–**d** underwent the debromination radical reaction under the conditions of Bu_3SnH and Et_3B in toluene, similar to the reaction applied to **4**, to afford the corresponding target compounds **12a**–**d** in high yields (86–92%) with excellent *anti*-diastereoselectivity (33–36:1), as shown in Scheme 2. By using silica gel flash column chromatography, the target molecules were easily purified to enantiopure 2,3-*anti*-propionate aldols involving a 3,5-*syn*- or *anti*-diol subunit:[9,10] **12a** $[\alpha]_D^{24}$ −37.09 (*c* 0.62, $CHCl_3$); **12b** (the enantiomer of **12a**) $[\alpha]_D^{24}$ +37.0 (*c* 0.50, $CHCl_3$); **12c** $[\alpha]_D^{24}$ −14.2 (*c* 0.42, $CHCl_3$); and **12d** (the enantiomer of **12c**) $[\alpha]_D^{24}$ −13.9 (*c* 0.62, $CHCl_3$).

In conclusion, we have achieved an effective access to the preparation of essentially enantiopure 2,3-*anti*-propionate aldols involving a 3,5-*syn*- or *anti*-diol subunit, available for the enantioselective synthesis of appropriate fragments of several complex macrolides, by using chiral oxazaborolidinone-promoted asymmetric aldol reactions coupled with *anti*-diastereoselective radical reduction.

Acknowledgements

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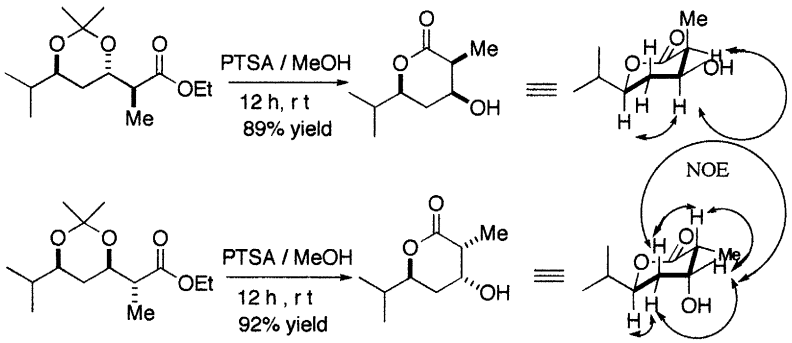
9. The relative configurations of **12a** and **12c** were confirmed by NOE experiments after H–H COSY experiments of their lactone derivatives.



10. Selected spectroscopic data [^{1}H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz)]. Compound **11**: ^{1}H NMR δ (ppm): 1.10 (d, *J*=7.07, 3H), 1.25 (t, *J*=7.07, 3H), 1.34 (s, 3H), 1.43 (s, 3H), 1.48 (m, 1H), 1.59 (ddd, *J*=5.64, 11.70, 11.96, 1H), 2.48 (dq, *J*=7.07, 7.84, 1H), 3.86 (ddd, *J*=1.72, 5.40, 11.72, 1H), 3.97 (dt, *J*=3.2, 11.68, 1H), 4.08 (ddd, *J*=2.72, 8.32, 11.24, 1H), 4.16 (dq, *J*=0.96, 7.07, 2H); ^{13}C NMR δ (ppm): 12.27, 14.22, 19.06, 27.93, 29.67, 45.56, 59.72, 60.22, 70.59, 98.39, 174.66. Compound **12a**: ^{1}H NMR δ (ppm): 0.86 (d, *J*=6.84, 3H), 0.92 (d, *J*=6.76, 3H), 1.10 (d, *J*=7.07, 3H), 1.25 (t, *J*=7.07, 3H), 1.29 (s, 3H), 1.30 (s, 3H), 1.52–1.69 (m, 3H), 2.48 (dq, *J*=7.07, 8.80, 1H), 3.41 (ddd, 6.56, 7.00, 9.52, 1H), 3.94 (ddd, *J*=5.52, 6.08, 9.48, 1H), 4.08–4.20 (m, 2H); ^{13}C NMR δ (ppm): 12.47, 14.22, 17.58, 18.71, 24.10, 24.24, 32.91, 33.92, 45.59, 60.23, 68.46, 71.57, 100.48, 174.77. Compound **12c**: ^{1}H NMR δ (ppm): 0.77 (d, *J*=6.84, 3H), 0.81 (d, *J*=7.08, 3H), 1.01 (d, *J*=7.08, 3H), 1.15 (t, *J*=7.07, 3H), 1.24 (s, 3H), 1.29 (s, 3H), 1.50–1.61 (m, 3H), 2.48 (dq, *J*=7.07, 7.84, 1H), 3.40 (ddd, *J*=2.16, 6.60, 11.44, 1H), 3.90 (ddd, 2.44, 8.32, 11.48, 1H), 4.15 (q, *J*=7.07, 2H); ^{13}C NMR δ (ppm): 12.32, 14.23, 17.66, 18.32, 19.59, 29.99, 30.13, 33.05, 45.61, 60.18, 70.90, 73.77, 98.37, 174.81.