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ALDOL METHODOLOGY: SYNTHESIS OF SYN-3-HYDROXY-2-VINYLCARBONYL COMPOUNDS

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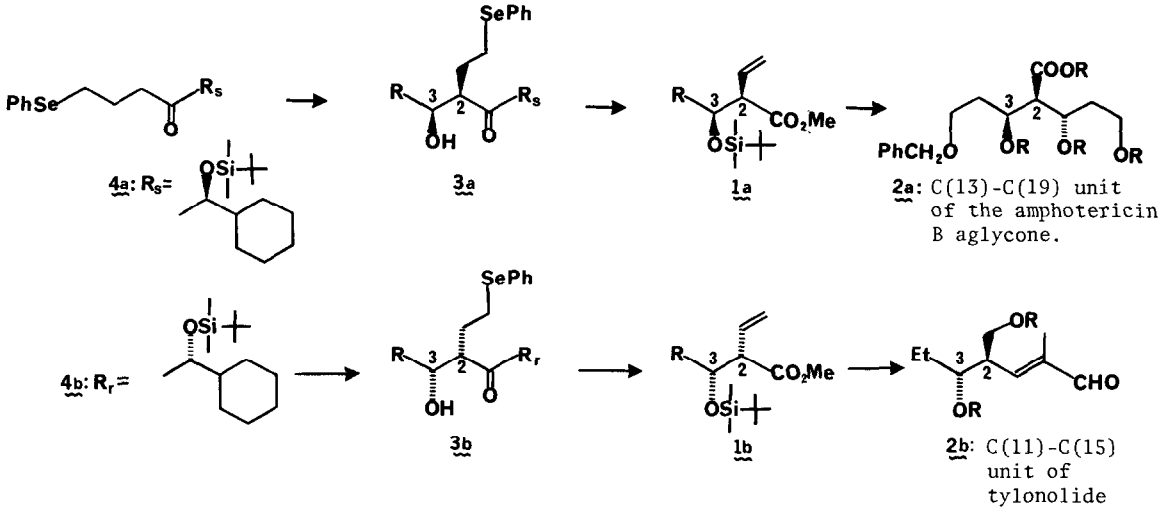
Summary: A direct approach to syn-3-hydroxy-2-vinylcarbonyl compounds via a boron-mediated aldol reaction with (S)-1-cyclohexyl-1-triethylsilyloxypenta-3(Z)-en-2-one (6c) is described.

The titled compounds (1a, 1b) are versatile synthons for the synthesis of macrolides as exemplified by the construction of the C(13)-C(19) unit (2a) of the amphotericin B aglycone and also the C(11)-C(15) unit (2b) of tylonolide (Scheme 1).[1] The syn stereochemistry at the 2,3-positions of 1a and 1b is either retained in the target molecule (see 2,3-positions of 2a) or can be transformed into the anti-configuration (see 2,3-positions of 2b).† In our earlier report both 1a and 1b were derived from the corresponding benzeneselenoethyl compounds 3a and 3b which were in turn prepared via a boron-mediated aldol reaction using chiral selenoketones 4a and 4b, respectively. In those cases where the benzeneselenoethyl group is not required to be present as

Scheme 1

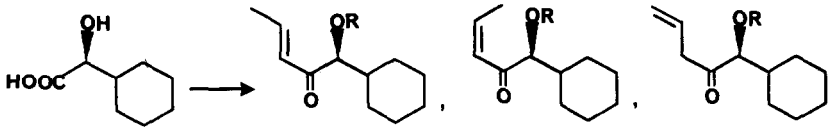


a latent double bond in subsequent synthetic transformations,[2] 3a and 3b may be bypassed. The synthesis of 1a directly from one of the unsaturated ketones (5b, 6b,c, and 7b) shown in Scheme 2 is readily envisioned and offers an obvious synthetic advantage. This note describes such a direct approach and also the intriguing stereochemical outcome of the aldol reactions involving these unsaturated ketones.[3]

† The numbering used in this note is arbitrary.

The preparation of 5a and 6a from (S)-hexahydromandelic acid (8) follows the earlier procedure[4] with some modification (see the caption of Scheme 2), using (E)-and (Z)-propenyllithium, respectively.[5] Silylation of 5a to 5b and of 6a to 6b and 6c proceeded in the usual fashion with with the corresponding silyl chloride (diisopropylethylamine) or silyl triflate (2,6-di-t-butyl-4-methylpyridine).[6b] Treatment of the dilithium salt of 8 with allylmagnesium bromide followed by 15% phosphoric acid workup[7] provided 7a in 51% yield, contaminated with the double addition product (6 %) and 5a (9%). Compound 7a is acid- and base-sensitive and silylation of 7a was carried out with extreme care to minimize the undesired double bond isomerization to an extent of 3%.

Scheme 2



8

5a: R=H
5b: R=t-BuMe$_2$Si

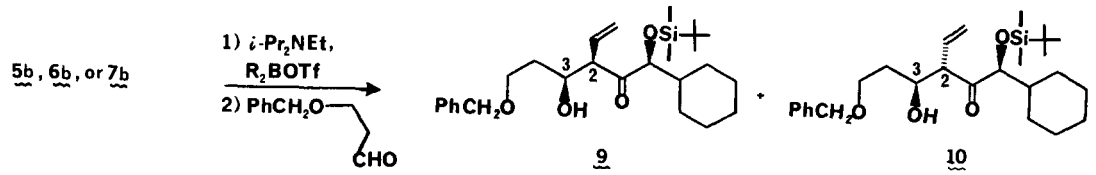
6a: R=H
6b: R=t-BuMe$_2$Si
6c: R=Et$_3$Si

7a: R=H
7b: R=t-BuMe$_2$Si

8→5a. 3.5 equiv (E)-CH_3CH=CHLi (Et_2O), -78°C→r.t.; 5a→5b. t-BuMe_2SiOTf, 2,6-di-t-butyl-4-methylpyridine (CH_2Cl_2), 0°C; 8→6a. 1.9 equiv n-BuLi, 1.6 equiv Z-CH_3CH=CHLi(Et_2O), -78°C→r.t.; 6a→6b. t-BuMe_2SiOTF, 2,6-di-t-butyl-4-methylpyridine (CH_2Cl_2), 0°C; 6a→6c. Et_3SiCl, iPr_2NEt (DMF) r.t.; 8→7a. 1.9 equiv n-BuLi, 1.6 equiv CH_2=CH-CH_2MgBr (Et_2O), -78°C→r.t.; 7a→7b. t-BuMe_2SiOTf, 2,6-di-t-butyl-4-methylpyridine (CH_2Cl_2), 0°C.

Our initial studies of the aldol reaction were undertaken with 3-benzyloxypropanal and the three t-butyldimethylsilyloxyketones (5b, 6b and 7b). The reactions proceeded smoothly under the standard conditions (boron enolate formation with 2.0 equiv of a boron triflate and 2.5 equiv of diisopropylethylamine, followed by addition of the aldehyde), but the stereoselectivity was unexpectedly low as revealed in Table 1. While the (Z)-α,β-unsaturated ketone 6b provided

Table 1. Aldol reaction of 5b, 6b, and 7b with 3-benzyloxypropanal



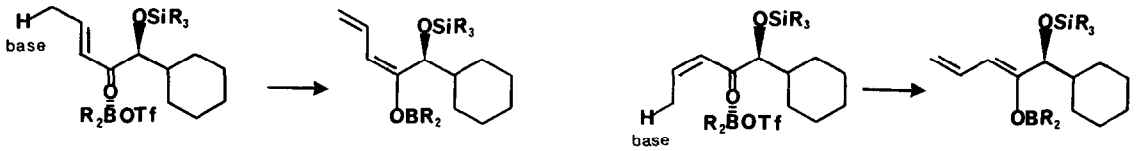
9 10

Ketone	R_2BOTf	9 : 10	Yield
5b	R = cyclopentyl	1:3.5	89%
	R = n-Bu	1:1.6	70%
	R_2 = 9-BBN	1:2	96%
6b	R = cyclopentyl	10:1	80%
	R = n-Bu	4:1	47%
	R_2 = 9-BBN	3:1	87%
7b	R = cyclopentyl	20:1	71%

mainly the corresponding syn-3-hydroxy-2-methyl ketone 9 (3:1 to 10:1), the 2,3-anti diastereomer 10 predominated in the products obtained from the (E)-isomer 5b.[8] With the β,γ-unsaturated ketone 7b which was expected to form a highly diastereoface-selective boron enolate, the formation of the syn-isomer 9 was not exclusive (20:1), since 7b apparently underwent partial isomerization to 5b under the conditions used.[8]

It is now well established that the Z- and E-boron enolates react with aldehydes to provide mutually exclusively the corresponding 2,3-syn- and 2,3-anti products, respectively.[1b] Since the preferred conformations of 5b and 6b are in all likelihood s-trans (5b′) and s-cis (6b′), it is not surprising that these conformations respond to kinetic deprotection in the process of the enolate formation to form mainly 11 and 12, respectively (Scheme 3). Thus, further attempts to modify 6b were warranted in order to further enhance the 2,3-syn:anti ratio in the aldol reaction.

Scheme 3



The triethylsilyloxyl derivative 6c indeed achieved our present goal. Table 2 summarizes the results obtained from the aldol reaction of several representative aldehydes with the dicyclopentylboron enolate derived from 6c. Those obtained from 6b are also included for comparison. Clearly all the reactions using 6c proceeded smoothly with satisfactory stereoselection and establish the general synthetic utility of this chiral reagent.[8,9]

Table 2. Aldol reaction of representative aldehydes with the dicyclopentyl boron enolates derived from 6b and 6c.

Ketone	Aldehyde	2,3 syn: 2,3 anti	Yield
6b	3-benzyloxypropanal	10:1	80%
6c		>100:1	93%
6b	CH_3CHO	13:1	70%
6c		>100:1	85%
6b	CH_3CH_2CHO	14:1	78%
6c		>100:1	81%
6b	PhCHO	13:1	82%
6c		>100:1	83%
6b	i-PrCHO	>50:1	21%[a]
6c		>100:1	77%

[a] 65% based on recovered starting material.

Preparation of 6a, 6c, and 9:

To a cold (-78°C) suspension of S-hexahydromandelic acid (16.56 g, 0.105 mol) in 250 mL of dry ether was slowly added n-butyllithium (83.0 mL of a 2.39 M solution in hexane, 1.9 equiv). The thick mixture was allowed to warm to -30°C and stirred at this temperature for 30 min. Z-propenyllithium (258.0 mL of a 0.65 M solution in ether) was introduced over 1.5 h, and the mixture was slowly warmed to r.t. After 1 h at r.t. the now clear solution was added via cannula to the vortex of a rapidly stirring 0°C solution of 700 mL of 1/2 saturated ammonium chloride. Usual workup followed by flash chromatography (hexane:ether, 6:1) provided 6a (11.33 g, 59.6%). This alcohol (430.9 mg, 2.36 mmol) was dissolved in 6 mL of dry dimethylformamide and treated with diisopropylethylamine (1.25 mL, 3.0 equiv) followed by triethylsilyl chloride (600 µl, 1.5 equiv). After 15 min, 20 ml of saturated sodium bicarbonate was added. Extractive workup followed by flash chromatography (hexane:ether, 20:1) gave 6c (660.0 mg, 95.0%). [^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.58 (q, J=8 Hz, 6H), 0.93 (t, J=8 Hz, 9H), 1.00-1.32 (complex m, 5H), 1.41-1.80 (complex m, 6H), 2.11 (d, J=7 Hz, 3H), 3.68 (d, J=6 Hz, 1H), 6.27 (dq, J=11, 7 Hz, 1H), 6.48 (d, J=11 Hz, 1H) $[\alpha]_D^{25}$= -49.50° (c 1.39, $CHCl_3$)]. To a -78°C solution of 6c (150.0 mg, 0.506 mmol) in 10 ml of dry dichloromethane was added diisopropylethylamine (224 µl, 2.54 equiv) followed by dicyclopentylborinyl trifluoromethanesulfonate (256 µl, 2.04 equiv). After stirring at 0°C for 2.5 h, 3-benzyloxypropanal (2.5 equiv) was added and the reaction mixture stirred for 2.5 h. Methanol (3 mL), pH 7 phosphate buffer (3 ml) and 30% hydrogen peroxide (0.5 mL) were added and stirring was continued for 1 h. Usual workup followed by flash chromatography (hexane:ether, 6:1) yielded 9 (215 mg, 93.0%) [NMR ($CDCl_3$, 250 MHz) δ 0.58 (q, J=8 Hz, 6H), 0.94 (t, J=8 Hz, 9H), 0.83-1.30 (complex m, 5H) 1.41-1.97 (complex m, 8H), 3.52-3.72 (complex m, 4H, 1H, D_2O ex), 3.96 (d, J=5 Hz, 1H), 4.15 (m, 1H), 4.51 (s, 2H), 5.26 (d, J=18 Hz, 1H), 5.32 (d, J=10 Hz, 1H), 5.84 (ddd, J=18, 10, 9 Hz, 1H), 7.32 (m, 5H), $[\alpha]_D^{25}$ = +118.32° (c .497, $CHCl_3$)].

References and Footnotes

1. (a) Masamune, S.; Kaiho, T.; Garvey, D.S. J. Am. Chem. Soc. 1982, 104, 5521. Also see (b) Masamune, S.; Choy, W. Aldrichimica Acta 1982, 15, 47.
2. In some cases the seleno group rather than an olefin is preferred during the multistep transformation of other functional groups. For instance, base treatment of 1a induces double bond migration.
3. Compare the results described in this note with a report on a similar aldol reaction employing a chiral crotonate imide: Evans, D. Aldrichimica Acta 1982, 15, 23.
4. Masamune, S.; Choy, W.; Kerdesky, F.A.J.; Imperiali, B. J. Am. Chem. Soc. 1981, 103, 1566.
5. Linstrumelle, G.; Krieger, J.K.; Whitesides, G.M. Org. Syn. 1976, 55, 103.
6. Attempted silylation employing imidazole as the base in conjunction with triethylsilyl chloride resulted in low yields of the desired product. The more hindered base, diisopropylethylamine greatly increased the yield (90~95%). This was also the case with tBDMSiOTf where the more hindered base 2,6-di-t-butyl-4-methylpyridine gave better yields than lutidine. (a) Corey, E.J.; Cho, H.; Rucker, C.; Hua, D.H. Tetrahedron Lett. 1981, 22, 3455. (b) Choy, W.; Reed, III, L.A.; Masamune, S. J. Org. Chem. 1983, 48, 1137.
7. Knudsen, C.G.; Rapoport, H. J. Org. Chem. 1983, 48, 2260.
8. In each of these reactions only one 2,3-syn and one 2,3-anti aldol diastereoisomer as shown in 9 and 10 were obtained. The stereochemistry of these compounds were established by converting them to the compounds of known stereochemistry previously obtained (ref. 1a).

9. We thank the National Institutes of Health (AI15403) and Kao Corporation for financial support. D.B. is a National Cancer Institute Trainee (NCI Grant 5-T32-CA-09112).

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