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STEREOSELECTIVE SYNTHESIS OF β-HYDROXY-α-METHYLKETONES VIA Z- AND E-VINYLOXYBORANES GENERATED DIRECTLY FROM CYCLOHEXYL ETHYL KETONE

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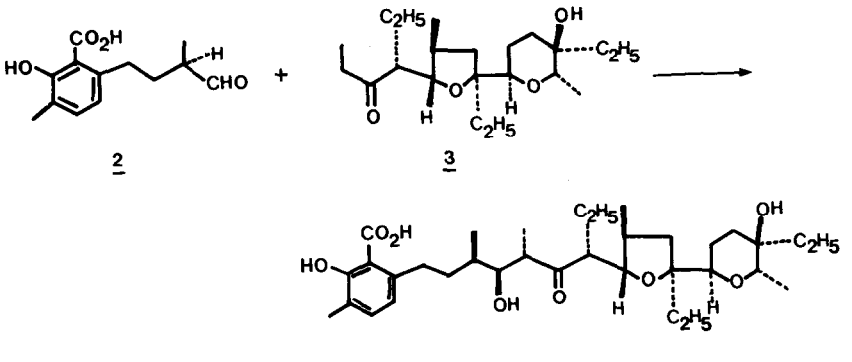
E- and Z-dialkylvinyloxyboranes, prepared directly from cyclohexyl ethyl ketone, undergo stereoselective aldol condensations to provide threo- and erythro-β-hydroxy-α-methylketones, respectively.

The preceding note describes the stereoselective preparation of β-hydroxy-α-methylcarboxylic acid thiol esters.[1] In addition to this two-carbon chain extension, one logical retrosynthetic analysis of macrolide antibiotics,[2] such as erythronolide, and ionophoric metabolites,[3] such as lasalocid A (1), poses a problem of uniting two major, sensitive fragments of a target molecule through a stereoselective, directed aldol condensation in order to construct a new β-hydroxy-α-methylketone moiety. An example is a crucial step (2 + 3 → 1) incorporated in Kishi's brilliant synthesis of 1.[4] The requirements for this type of operation are indeed demanding, and despite the extensive study of this reaction over the years [5-8] further improvement is still necessary. The highly stereoselective approach to this synthetic problem described herein, which seems superior, in an overall sense, to known related metal enolate approaches, involves the generation and use of vinyloxyboranes directly from ketones.



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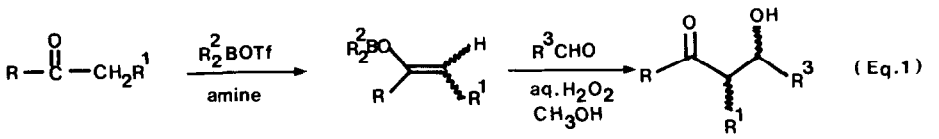
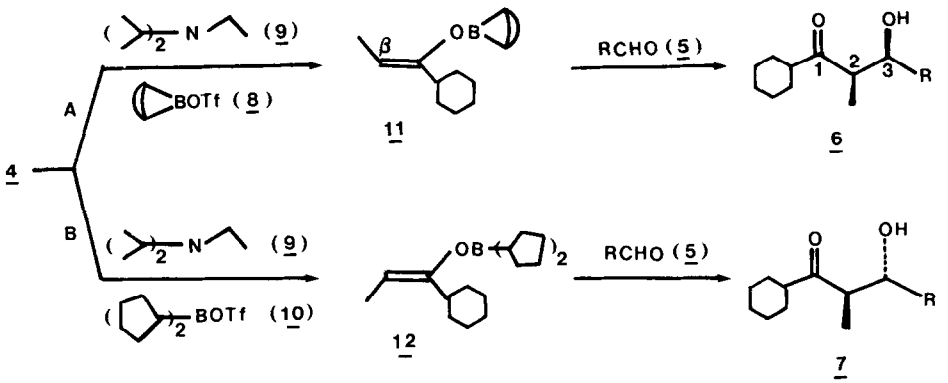
After considering several known preparative routes to vinyloxyboranes,[9-12] Mukaiyama's method,[12] utilizing the combination of a ketone, dialkylboron trifluoromethanesulfonate (triflate) and hindered amine (Eq.1), appeared to be very mild and potentially applicable to the synthesis



(Eq.1)

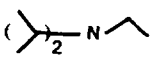
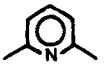
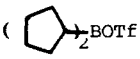
of antibiotics. Cyclohexyl ethyl ketone (4), selected as a suitable model substrate (cf., structure 3), was first converted into the corresponding vinyloxyboranes at -78→0°C by the use of all possible combinations of three representative dialkylboron triflates (di-n-butyl, dicyclopentyl, or 9-borabicyclo[3.3.1]non-9-yl (9-BBN) triflate) and two representative hindered amines (N,N-diisopropylethylamine or 2,6-lutidine) and then condensed with an aldehyde (5) to provide excellent yields of the cross-aldol products. The Table summarizes the yields and erythro/threo ratios of the aldol products (6 and 7) and reveals the following four notable features: (1) In no case was a significant amount (>5%) of the β,β-disubstituted regioisomer detected, either via the vinyloxyborane intermediates or via the aldol products. (2) The variation in the erythro/threo ratio from one case to another is dramatic. (3) Combination A, 9-BBN triflate (8) and N,N-diisopropylethylamine (9), provides almost exclusively the erythro aldol products (erythro/threo ratios ≥97/≤3 with three selected aldehydes).[13, 14] (4) Combination B, involving dicyclopentylboron triflate (10) and N,N-diisopropylethylamine, reverses the ratio to 15/85-12/88, giving predominantly the threo-isomers (Eq 2).[14] Thus, by proper selection of reagents, a means is now available for the generation of either erythro or threo aldol products in a highly stereoselective manner starting from the same ketone (4).



(Eq.2)

For the two most stereoselective sequences, involving Combinations A and B, the vinyloxyborane intermediates were examined by ^{1}H NMR spectroscopy.[16] The ratio of the Z- and E-stereoisomers (11-12) was >95:<5 for Combination A and 12:88 for Combination B, the yields in both cases being 85-95%. These ratios correspond almost exactly to the erythro/threo distribution of the aldol products, and therefore it can be concluded that the stereochemical information embodied in the vinyloxyboranes is preserved during the process of aldol condensation, 11 and 12 providing exclusively the erythro and threo products (6 and 7), respectively.

Table 1. The Effects of Dialkylboron Triflate and Hindered Amine Upon the Stereoselectivity of the Aldol Condensation via Cyclohexyl Ethyl Ketone.

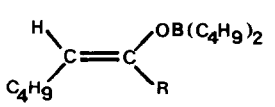
						
	aldehyde[a]	isomer ratio[b]	yield[c]	aldehyde[a]	isomer ratio[b]	yield[c]
n-Bu_2-BOTf	5a	43:57	--	5a	82:18	82
	5a	14:86	88	5a	54:46	79
	5b	12:88	86			
	5c	15:85	88			
	5a	>97:<3	79[15]	5a	91:9	84
	5b	>97:<3	87			
	5c	>97:<3	82			

[a] 5a, R=C_6H_5; 5b, R=2-C_3H_7; 5c, R=$CH_2CH_2C_6H_5$.

[b] Erythro (6): threo (7). $J_{2,3}$ (Hz): 6a, 5.6; 6b, 3.5; 6c, 4.2; 7a, 8.5; 7b, 7.0; 7c, 6.5. The stereochemistry of these isomers was assigned in a manner similar to that described in the preceding note.

[c] Combined isolated yield based on ketone.

We earlier reported that pure E- (but not Z-) vinyloxyboranes (13) derived from α-diazoketones and tributylborane provided the threo aldol products rather selectively (erythro/threo ratio = 1:3-4) but not exclusively.[10] Also, Heathcock's extensive investigation[6] on lithium enolates of type 14 revealed that with very bulky R substituents aldol stereoselectivity was excellent, but "diminished or disappeared" with smaller R substituents such as secondary or primary alkyl groups. Thus, certain vinyloxyborane systems exhibit unique advantages over these and others in controlling the stereochemistry of the aldol condensation. With judicious choice of R^1 in 15 R may be secondary, as shown above, or even tert-butylthio, as described in the preceding note,[1] and the problem associated with the stereochemical control of the aldol condensation is, in a way, reduced to the development of methods for the mild, stereoselective preparation of appropriate vinyloxyboranes. The dramatic effects of the R^1 group of 15 upon both the stereoselective formation of vinyloxyboranes and the subsequent aldol condensations are indeed remarkable and are of considerable significance in terms of the mechanistic interpretation of these reactions.



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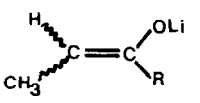

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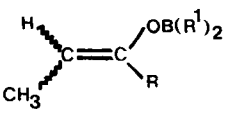

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References and Footnotes

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12. (a) T. Mukaiyama and T. Inoue, Chem. Lett., 559 (1976); (b) T. Inoue, T. Uchimaru and T. Mukaiyama, ibid., 153 (1977).
13. With S-t-butyl propanethioate we were not able to selectively obtain erythro aldol products via this type of procedure.[1]
14. Where applicable the ratios were determined by ^{1}H NMR and in other cases (involving 5b) the erythro and threo isomers were isolated separately by TLC (SiO_2).
15. This experiment was performed by Mr. David Garvey.
16. The ratios were determined by comparison of the vinyl proton signals.

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