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STEREOSELECTIVE SYNTHESIS OF CIS-α,β-EPOXYESTERS AND ALDEHYDES VIA DIVALENT TIN ENOLATE. A SYNTHESIS OF 2-AMINO-2-DEOXY-D-ARABINITOL

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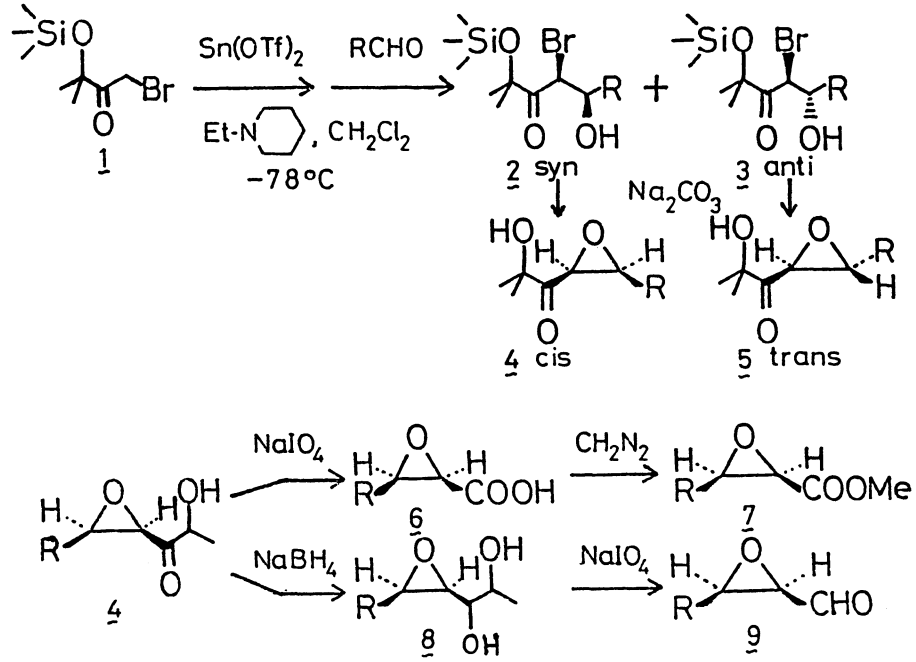
A convenient method for the stereoselective synthesis of cis-α,β-epoxyesters and aldehydes is established according to the $Sn(OTf)_2$ mediated cross aldol reaction between α-bromo-α'-silyloxyketone and aldehyde. The reaction is applied to the stereoselective synthesis of 2-amino-2-deoxy-D-arabinitol.

α,β-Epoxyesters and aldehydes are useful and versatile synthetic intermediates due to their multiple functionalities and also to the ease with which a wide range of functional groups are introduced into the molecule by nucleophilic opening of the epoxide. And it is expected that the stereoselective synthesis of these α,β-epoxy esters and aldehydes would furnish a new entry into the stereoselective construction of various polyoxygenated compounds.

α,β-Epoxyesters and aldehydes are most frequently prepared by the Darzens reaction[1] or by epoxidation of the corresponding α,β-unsaturated carbonyl compounds or esters.[2] However, the stereoselective synthesis of cis-β-substituted α,β-epoxyesters and aldehydes by these methods is, in general, not easily achieved due to the low stereoselectivity observed in the Darzens reaction or the difficulty in obtaining the starting material, Z-olefins. In a previous paper,[3] we reported a new method for the stereoselective synthesis of cis-β-substituted-α,β-epoxyketones, according to the stannous triflate mediated cross aldol reaction[4] between α-bromoketones and aldehydes. By treating the produced α-bromo-β-hydroxyketones with potassium fluoride/dicyclohexyl-18-crown-6, cis-α,β-epoxy ketones are obtained stereoselectively. High stereoselectivity (>95:5) was realized when a ketone having a bulky group attached to the carbonyl was used as starting material.

Based on these findings, we now wish to report in this communication, a convenient stereoselective synthesis of cis-α,β-epoxyesters and aldehydes, and also the application of this reaction to the stereoselective synthesis of 2-amino-2-deoxy-D-arabinitol. It was postulated that by using α-bromo-α'-silyloxyketone 1 as starting material, cis-α,β-epoxyketone 4 could be obtained with high stereoselectivity because of the bulkiness of the group adjacent to the carbonyl, and the obtained epoxyketone 4 could be easily converted to cis-α,β-epoxyesters and aldehydes by oxidative cleavage of the α-hydroxy ketone part.[5] The starting material, α-bromoketone 1, was easily prepared from 3-hydroxy-3-methyl-2-butanone via three steps; silylation of the hydroxy group with N,O-bis(trimethylsilyl)-

acetamide, followed by conversion to the corresponding silyl enol ether and then treatment with N-bromosuccinimide afforded the α-silyloxy-α'-bromoketone 1 in good yield.



The cross aldol product was yielded by the treatment of stannous triflate with α-bromoketone 1 in the presence of N-ethylpiperidine as a base, followed by addition of aldehyde. Without purification, the crude product in methanol solution was treated with sodium carbonate, an acid captor, to cause oxirane ring formation. It was found that cis-α,β-epoxyketone 4 was formed stereospecifically without detectable isomerization. Trans-α,β-epoxyketone 5 was prepared[6] for comparison and the diastereomer ratio of the products was determined by ^{1}H NMR. The results are summarized in Table 1. In all cases high stereoselectivity is achieved according to this procedure starting from α-bromoketone 1 and various aldehydes.

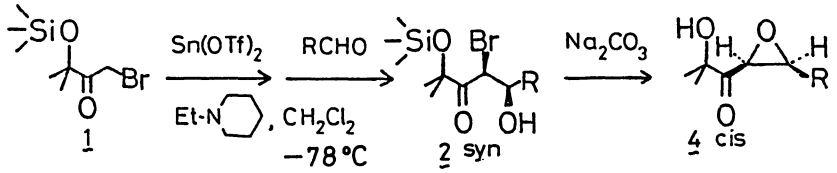


Table 1.

Aldehyde	Yield/%	cis:trans
PhCHO	70	>95:5
$PhCH_2CH_2CHO$	83	>95:5
n-$C_{11}H_{23}CHO$	79	>95:5

We found no difficulty in converting the obtained cis-α,β-epoxyketone 4 to cis-α,β-epoxyesters and aldehydes. Thus, according to the method of Heathcock,[5] the α-hydroxy ketone part of 4 was oxidatively cleaved by the addition of sodium metaperiodate to give an α,β-epoxycarboxylic acid 6, which was in turn converted to its methyl ester 7 with diazomethane. By reducing the carbonyl group of 4 to a hydroxy group with sodium borohydride prior to oxidative cleavage, the cis-α,β-epoxyketone 4 was easily converted to cis-α,β-epoxyaldehyde 9. By comparison with authentic trans-α,β-epoxyesters and aldehydes,[7] it was confirmed that in both cases oxidative cleavage had proceeded without isomerization to give the desired cis-isomers. In these ways, several cis-α,β-epoxyesters and aldehydes were prepared stereoselectively in good yields. (Table 2)

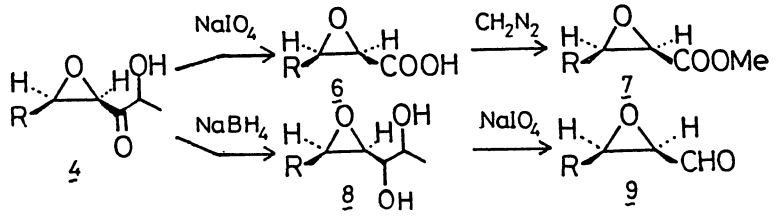
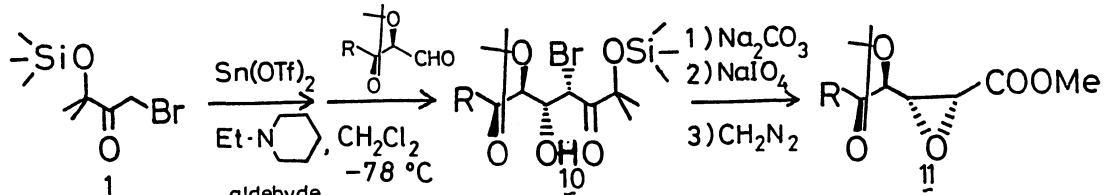


Table 2.

R	Yield of 7 /%	cis:trans	R	Yield of 9 /%	cis:trans
Ph	67	>95:5	Ph	65	>95:5
$PhCH_2CH_2$	73	>95:5	$PhCH_2CH_2$	75	>95:5
n-$C_{11}H_{23}$	79	>95:5	n-$C_{11}H_{23}$	77	>95:5

Having established a method for the stereoselective synthesis of α,β-epoxyesters and aldehydes, we next examined the reaction with chiral polyoxyaldehydes and the application of this reaction to the synthesis of amino deoxyalditols.

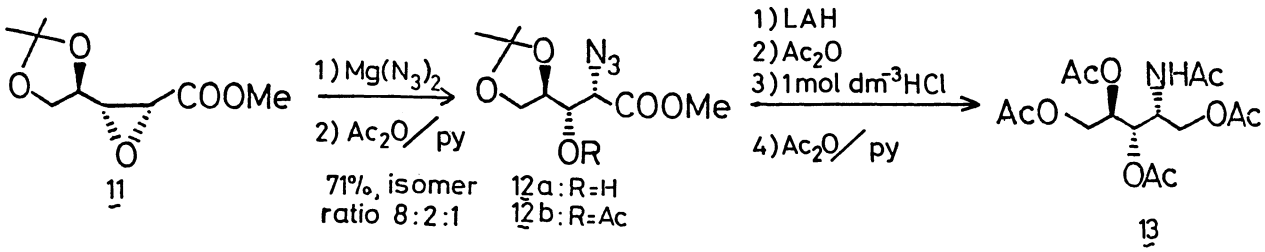
First, the aldol reactions between α-bromoketone 1 and both 2,3-O-isopropylidene-D-glyceraldehyde and 4-O-benzyl-2,3-O-isopropylidene-L-threose were examined and it was found that the reactions proceeded smoothly to give the cross aldol products in good yields. In these reactions, high level of stereocontrol was achieved and only one of the four possible stereoisomers was detected by ^{13}C NMR spectra in both cases. By the aforementioned procedures, these aldol products were converted to cis-α,β-epoxyesters 11. Next the stereoselective



aldehyde	10	11
2,3-O-isopropylidene-D-glyceraldehyde	78%	80%
4-O-benzyl-2 3-O-isopropylidene-L-threose	75%	77%

Scheme 1.

synthesis of 2-amino-2-deoxy-D-arabinitol was tried taking this cis-α,β-epoxyester as an intermediate. After screening of various nitrogen nucleophiles, it was found that magnesium azide reacted smoothly with epoxide 11 to afford the azido



Scheme 2.

alcohol 12a as the major product along with two other stereoisomers.[8] The major product, isolated as its acetate 12b, was transformed to 2-amino-2-deoxy-D-arabinitol pentaacetate by the routine procedures shown in Scheme 2. The pentaacetate 13 displayed identical optical rotation and ^{1}H NMR, ^{13}C NMR, and IR spectra with those of an authentic sample prepared from kanosamine,[9] unambiguously confirming the stereochemistry as illustrated in Scheme 2.

Thus, cis-α,β-epoxyesters and aldehydes can be stereoselectively obtained according to the stannous triflate mediated aldol reaction between α-bromo-α-silyloxyketone 1 and aldehyde. Also, a stereoselective synthesis of 2-amino-2-deoxy-D-arabinitol was achieved by application of this reaction.

References

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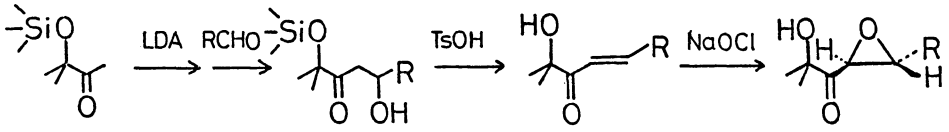
5) C. H. Heathcock, M. C. Pirrung, C. T. Buse, J. P. Hagen, S. D. Young, and J. E. Sohn, J. Am. Chem. Soc., 101, 7077 (1979).
6) Trans-α,β-epoxyketone 5 was prepared by the following route.



7) Trans-α,β-epoxyesters and aldehydes were prepared by oxidative cleavage of trans-α,β-epoxyketone 5.
8) The stereochemistry of the two minor products was not rigorously determined. However, we presume them to be the regioisomer and the α-epimer of 12a.
9) H. H. Baer and H. O. L. Fischer, J. Am. Chem. Soc., 82, 3709 (1960).

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