

THE OPENING OF *TRANS*-2-3-EPOXY-1-BUTANOL DERIVATIVES WITH ORGANOMETALLIC REAGENTS

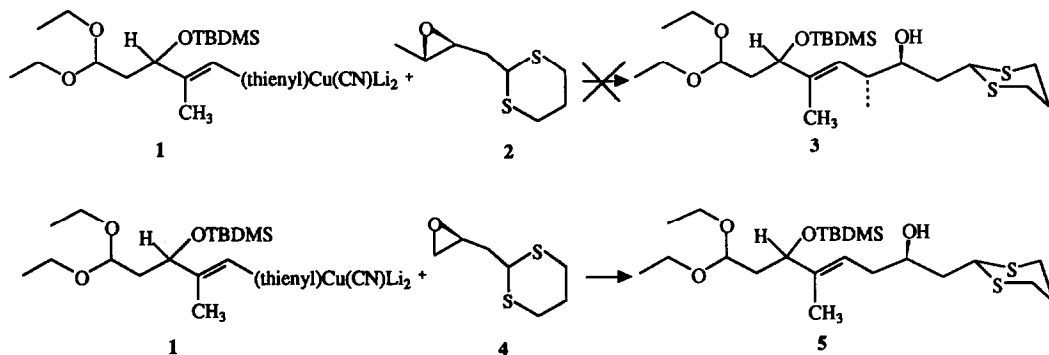
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Summary: The opening of *trans*-2-3-epoxy-butan-1-ol derivatives with various organometallic reagents was studied to find the best conditions necessary to obtain convenient yields and regioselectivities for their application in natural product synthesis.

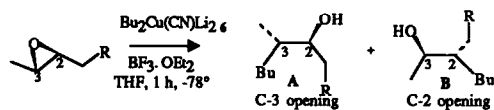
Chiral 2-3-epoxy-butan-1-ol derivatives of high enantiomeric excess are easily accessible by the Katsuki-Sharpless epoxidation of crotyl alcohol followed by derivatization.¹ Many natural products possess structural elements, R-CH(CH₃)-CH(OH)-R', R-CH=CH-CH(CH₃)-CH(OH)-R',² of which synthesis could be effected by opening these epoxides with organometallic reagents.

In our synthetic endeavours towards the C1-C9 North-Eastern segment of maytansin, compound 3, we found that the vinylcuprate **1** did not react ⁴ with the epoxide **2**,⁵ in the presence of BF₃.OEt₂,⁶ whereas with the primary epoxide **4**, it proceeded readily to give the coupled product **5**.⁷



In order to solve this problem, we were driven to investigate the reactivity of *trans*-2-3-epoxy-butan-1-ol derivatives⁸ towards organometallics to find the most effective reagents in terms of yields and regioselectivities. The results of this study are summarized in the following charts

Initial studies for the attempts of epoxide opening with vinyl cuprate **1**, showed that the high order homocuprate **6**,³ reacted in the presence of BF₃.OEt₂,⁷ with several disubstituted epoxides (chart 1).with preference for attack at C-3. However, only in the case where R=OBn **7** were the yield and regioselectivity of synthetic value.



R	A/B	Yield %	δ /epoxide	ref. & notes
	66/33	85	1.1	5
OBn	>95/<5	95	1.1	8
OTs	>90/10	50	1.1	8

Regioselectivity of the opening of *trans*-2,3-epoxy-butan-1-ol derivatives with higher order cuprate 6

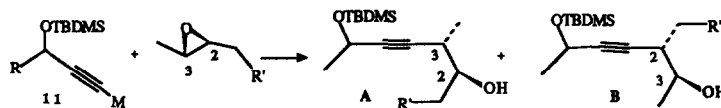
Chart 1

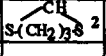
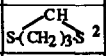
With the failure of vinyl cuprate 1 to open either epoxides 2 or 7, we resorted to the employment of vinyl alanes as a solution. However, in model studies, neither the mono nor the divinyl alanes 9 and 10 displayed any reactivity towards epoxide 7 (R=OBn) in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ according to Alexakis and Jachiet's procedure.⁹



Disappointed by these results, we next turned to the use of several alkyne reagents for the opening of the crotyl epoxide derivatives and initially exploited the conditions developed by Yamaguchi for the opening of primary epoxides by lithioalkynes in the presence of $\text{BF}_3 \cdot \text{OEt}_2$.¹⁰ But again, as seen in chart 2, little or no epoxide opening was obtained upon treating lithioalkyne 11 (M=Li) with various epoxides. On the other hand, when more than 2 equivalents of the alkynyl alane (M=AlEt₂), generated by the addition of AlEt₂Cl to 11 (M=Li),¹¹ was subjected to 1 equivalent of the individual epoxides, as seen in chart 2, *an acceptable yield and regioselectivity was only obtained for epoxide 7* (R=OBn). In the absence of neighbouring oxygen (ex.2) or in the use of bulkier protecting groups (12, 14), this led to no reaction or low yields, respectively, and thus underlines the importance of an accessible oxygen functionality in the proximity of the epoxide for coordination by the alane.¹³

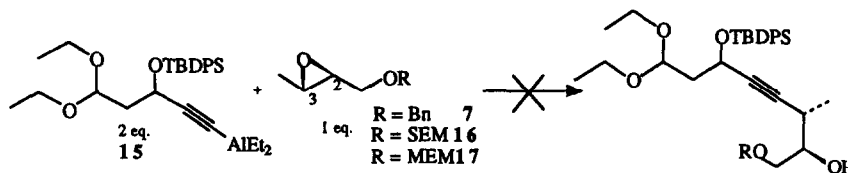
However, when the alane 15 was treated with epoxide 7 no opening was observed. Attributing the loss of reactivity displayed by alane 15, compared to 11 (M=AlEt₂), to the participation of the acetal moiety in 15 by complexation to the alane, attempts were also made to open epoxides 16 and 17 which themselves contain an acetal functionality in hope to disrupt the initial complexation, although in vain. Treatment of 2 equivalents of AlEt₂Cl with respect to the lithioalkyne followed by epoxide 7 led only to formation of the chlorhydrin.^{7b}



R	R'	M	A/B	yield %	1 I/ epoxide	ref. & notes
C ₃ H ₇	 2	Li/BF ₃	75/25	32	2	5, 15
C ₃ H ₇	OBn 7	Li/BF ₃	> 95/< 5	25	3	8, 15
C ₃ H ₇	OTs 8	Li/BF ₃	no reaction		1.5	8, 14, 15
C ₃ H ₇	OTBDPS 12	Li/BF ₃	no reaction		2	8, 14, 15
C ₃ H ₇	OBz 13	Li/BF ₃	no reaction		1.2	8, 14, 15
C ₃ H ₇	 2	AlEt ₂	no reaction		2.5	8, 14, 16
C ₃ H ₇	OBn 7	AlEt ₂	> 95/< 5	60-70	2.5	8, 16
C ₃ H ₇	OTs 8	AlEt ₂	complex mixture		2.5	8, 16
C ₃ H ₇	OTBDPS 12	AlEt ₂	no reaction		2.5	8, 14, 16
C ₃ H ₇	OTt 14	AlEt ₂	> 95/< 5	40	2.5	12, 16

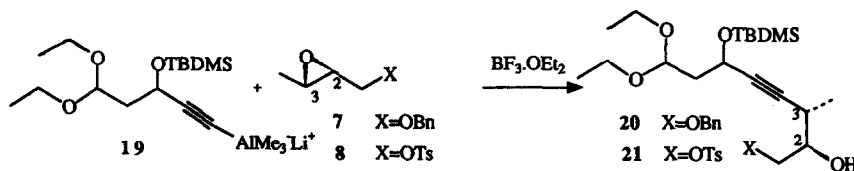
Regioselectivity of the opening of *trans*-2,3-epoxy-butan-1-ol with Alkynyl lithium and Aluminium Reagents

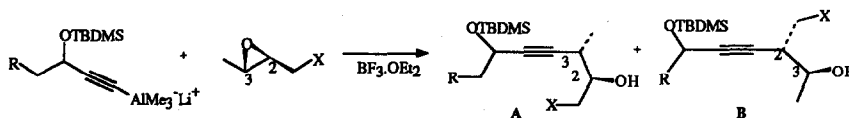
Chart 2



Finally, the reactivity of the corresponding alanates towards epoxides 7, 8 and 12 in the presence of BF₃.OEt₂⁹ was studied (chart 3).

Of particular interest was the fact that alanate 19 opened epoxides 7 and 8 with BF₃.OEt₂ to give 20 and 21¹⁸ in 85% and 65% yield respectively in contrast to that of alane 15. Further transformation of 20 to the north-eastern segment of maytansine will be published in due course.⁵





R	X	A/B	yield %	RM/epoxide/BF ₃	ref. & notes
C ₃ H ₇ 18	OBn 7	> 95/< 5	85	1.2/ 1/ 1	9, 17
C ₃ H ₇ 18	OTs 8	> 95/< 5	60-70	1.2/ 1/ 1	9, 17
C ₃ H ₇ 18	OTBDPS 12	> 95/< 5	60-70	1.2/ 1/ 1	9, 17
(EtO) ₂ CH-CH ₂ - 19	OBn 7	> 95/< 5	85	1.2/ 1/ 1	9, 17
(EtO) ₂ CH-CH ₂ - 19	OTs 8	> 95/< 5	60-70	1.2/ 1/ 1	9, 17

Regioselectivity of the opening of *trans*-2-3-epoxy-butan-1-ol with alkynyl alanates and BF₃.OEt₂

Chart 3

Acknowledgement- T. Skrydstrup was grateful for a Maxwell postdoctoral fellowship from the Académie des Sciences.

References and Notes

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- starting materials were recovered.
- Reactions of lithioalkynes in the presence of BF₃.OEt₂ were performed according to ref. 5.
- Epoxides in toluene were added to a solution of the alane in hexane at -40° C., warming slowly to 0° C and stirring for 2-3 h, see ref.11.
- reactions of alanates in presence of BF₃.OEt₂ were performed according to ref. 9.
- racemic 18 and 7 were used in this preliminary study giving 19 and 20 as mixture of diastereomers. Chiral compounds will be described elsewhere.cf. ref. 5

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