Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 24 Sep 2006.

SYNTHETIC COMMUNICATIONS, 21(17), 1797-1802 (1991)

SYNTHESIS OF NONRACEMIC 2-VINYL-MONOPROTECTED 1,3-DIOLS FROM THE REACTIONS OF CHIRAL ALLYLSTANNANES WITH ALDEHYDES

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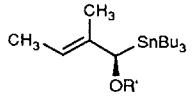
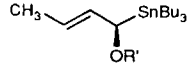
Abstract: A new approach for the synthesis of 2-vinyl monoprotected 1,3-diols has been developed. By employing different Lewis acid, either anti-anti or anti-syn stereoisomer can be selectively prepared.

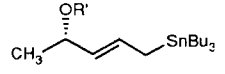
The synthetic utilities of chiral allylstannanes have been demonstrated by Marshall et al.[1] Our recent studies have involved variations in the structures of the allylstannanes, and the influence of such variations on diastereoselectivity of additions to aldehydes.[2] It was discovered that allylstannane I gives much better diastereofacial selectivity than the crotylstannane II. The fact that such a subtle change in the structure of the allylstannane led to a dramatic increase in diastereofacial selectivity suggested to us that an allylstannane of type III might



I

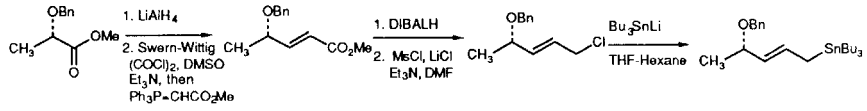


II

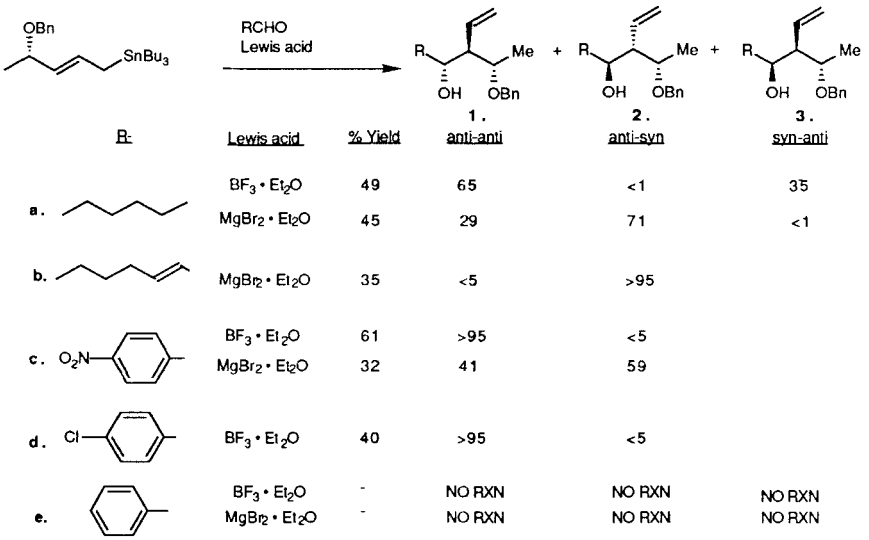


III

provide good diastereoselectivity. The chiral center of allylstannane III is closer to the reacting sp^2 carbon than the corresponding stereogenic center in stannane I and II, which may enhance the stereoselectivity. Furthermore, the products from the reactions of III with aldehydes are 2-vinyl-1,3-diols, valuable intermediates in natural product synthesis.[3] Now we wish to report our preliminary results from this study.



Scheme I



Scheme II

The preparation of allylstannane III is depicted in Scheme I. Starting from (S)-lactate, conventional methods were used to prepare the precursor allyl chloride. The displacement of the chloride with the tributyltin anion was accomplished in about 50% yield following a recent report.[4]

The reactions of allylstannane III with various aldehydes in the presence of Lewis acids were studied in dichloromethane at -78 °C (BF_3•Et_2O) and 0 °C ($MgBr_2$). The results are summarized in Scheme II.[5]

The stereochemistry of the products was determined by conversion of the stereoisomers into their acetonides, then the measurements of the relevant proton coupling constants.[6] An added proof for the product stereorelationship comes from the large difference in the chemical shift of the vinyl proton H_a,

Table Representative ^{1}H NMR data ($CDCl_3$, TMS), δ, J (Hz)

Product	H_a ($J_{a,b}$)	H_b ($J_{a,b}$ $J_{b,c}$ $J_{b,d}$)	H_c ($J_{c,b}$)	H_d ($J_{d,b}$)
1a.	5.30, (8.4)	2.24, (8.4, 8.4, 8.4)	3.67, (8.4)	3.74, (overlap)
1c.	5.23, (9.1)	2.49, (9.1, 9.1, 9.1)	3.76, (9.1)	4.68, (5.3)
1d.	5.24, (8.9)	2.50, (8.9, 8.9, 8.9)	3.71, (8.9)	4.40, (8.9)
2a.	5.74, (9.5)	2.11, (9.5, 6.8, 2.3)	3.78, (6.8)	3.95, (overlap)
2b.	5.69, (10.3)	2.33, (10.3, 3.0, 6.2)	3.74, (3.0)	4.22, (6.2)
2c.	5.85, (9.5)	2.45, (9.5, 2.4, 4.9)	3.81, (2.4)	4.22, (4.9)
3a.	5.75, (8.8)	2.21, (8.8, 8.8, 2.6)	3.78, (8.8)	3.89, (2.6)

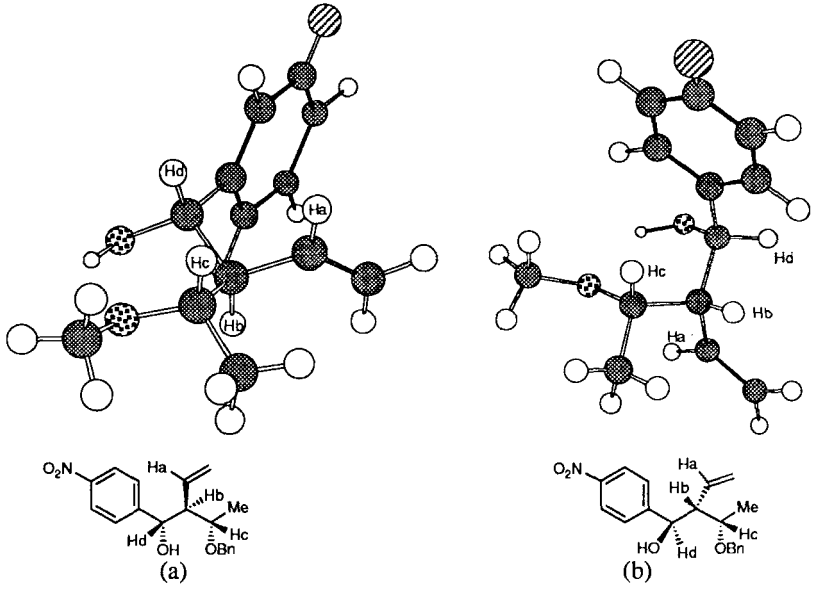


Figure 1. (a) lowest energy conformer of the anti-anti isomer (**1c**) by MacroModel, observed: δ Ha = 5.23 ppm, calculated coupling constants: $J_{a,b}$ = 11.5 Hz, $J_{b,c}$ = 10.7 Hz, $J_{b,d}$ = 9.8 Hz, observed: $J_{a,b}$ = 9.1 Hz, $J_{b,c}$ = 9.1 Hz, $J_{b,d}$ = 5.3 Hz; (b) anti-syn isomer (**2c**), observed: δ Ha = 5.85 ppm, calculated coupling constants: $J_{a,b}$ = 11.3 Hz, $J_{b,c}$ = 2.2 Hz, $J_{b,d}$ = 2.3 Hz, observed: $J_{a,b}$ = 9.5 Hz, $J_{b,c}$ = 2.4 Hz, $J_{b,d}$ = 4.9 Hz.

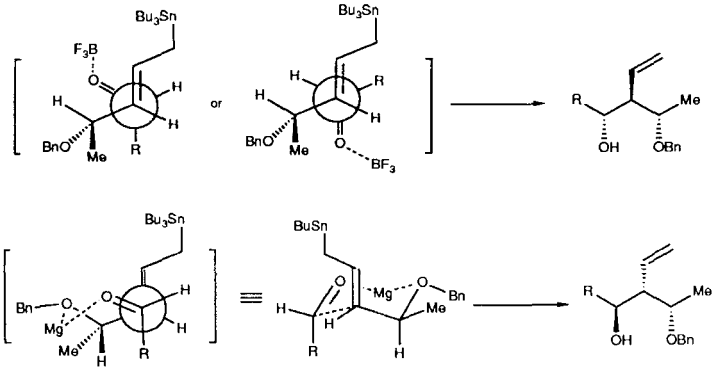


Figure 2. Possible transition state arrangements leading to anti-anti and anti-syn isomers.

Table and Fig. 1. Perhaps due to intramolecular hydrogen bonding, these mono-protected 1,3-diols have relatively rigid conformations. This is shown by the dramatic difference in the chemical shifts of the vinyl proton H_a between the anti-anti and the anti-syn isomers.[9] The two structures in Fig. 1 are the lowest energy conformations for each isomer found by the multiconformer submode of the MacroModel program (MM2).[7] Both structures show intramolecular hydrogen bonding. In the anti-anti isomer, the vinyl group is shielded by the phenyl ring and thereby exhibits a much higher field shift of the vinyl protons.[10] In the anti-syn isomer, the vinyl group is anti to the phenyl group and therefore free from the shielding effect.

Although the chemical yields are modest, several interesting features have emerged. The preferential formation of either anti-anti isomers by BF_3•Et_2O or anti-syn products by $MgBr_2$ can be rationalized by the depicted transition states in Fig. 2.

For the reactions catalyzed by BF_3•Et_2O, attacks by aldehydes on the allylstannane occurs in the re-face with C-H eclipsing C=C bond. Whereas in the reactions catalyzed by $MgBr_2$, attacks occur in the si-face with C-O eclipsing C=C bond. This can be explained in terms of the electronic effects in electrophilic additions to chiral alkenes. When $MgBr_2$ is used as catalyst, chelation of the benzyloxy group

of the allylstannane III is possible. Consequently, the $BnOMg^+$ group becomes more electron-withdrawing. Thus the "inside alkoxy" arrangement becomes more favorable because this conformation is least efficient for electron-withdrawing from the already electron-poor transition state.[8] When $BF_3 \cdot Et_2O$ is used as catalyst, no chelation occurs. The C-H eclipsed arrangement is preferred on steric grounds. The electrophile attacks from the position anti to the methyl group, which is a better electron donor than the benzyloxy group.

The allylstannane III is less reactive than either I or II as evidenced by its failure to react with benzaldehyde and the generally lower chemical yields. The reduced reactivity perhaps is due to a combination of both steric and electronic effects. Introduction of a chiral center next to the reacting carbon increases steric hindrance. The benzyloxy group is electron-withdrawing, thus reducing the π electron density of the double bond. Currently, we are trying to overcome this negative effect by varying the protecting group.

Acknowledgement: This research is supported in part by a grant from the National Institute of Health (1-R15-GM44260-01A1). AJP thanks the R. W. Johnson Pharmaceutical Research Institute for a travel award to the National American Chemical Society Meeting in Atlanta.

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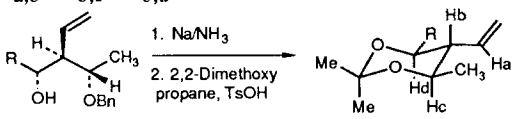
3. Versatility of 2-vinyl aldols in macrolides synthesis, see: (a) Boschelli, D.; Ellingboe, J. W.; Masamune, S. *Tetrahedron Lett.* **1984,** *25*, 3395. (b) In the synthesis of avenaciolide and iso avenaciolide, see: Suzuki, K.; Mayazawa, M.; Shimazaki, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1986,** *27*, 6233, 6237.

4. Hull, C.; Mortlock, S. V.; Thomas, E. J. *Tetrahedron*, **1989**, *45*, 1007. Although a 70% yield was reported for this step, we could obtain a maximum 50% yield with the allyl chloride after several trials.

5. These were results presented at the 201st American Chemical Society National Meeting, April 14-19, 1991, Atlanta, GA. A typical reaction procedure follows.
1-(p-nitrophenyl)-2-vinyl-3-benzyloxybutan-1-ol, 1C: To a solution of (0.16 g, 0.34 mmol) allylstannane III and (0.12 g, 0.81mmol) p-nitrobenzaldehyde in 3 ml CH_2Cl_2 at -78 °C was added (0.10 ml, 0.81 mmol) BF_3•Et_2O. The solution was allowed to stir for 1.5 hr at -78 °C, then ether was added, and the reaction was quenched with sat. $NaHCO_3$ solution. The organic layer was washed with sat. NaCl solution and dried over $MgSO_4$. The crude product was purified by column chromatography (10% EtOAc/Hex) to give (0.068 g, 0.21 mmol) the title compound as a colorless oil (61% yield). $[\alpha]_D^{20}$ = +4.2° (EtOH, c=0.1). IR (neat): 3400, 3080, 2956, 2854, 1457, 1344, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.11 (d, J = 8.7 Hz, 2H), 7.36 (s, 5 Hz), 7.36 (m, 2H), 5.23-4.80 (m, 2H), 5.23 (ddd, J = 9.1, 9.5, 17.1 Hz, 1H), 4.76 (d, J = 11.3 Hz, 1H), 4.68 (d, J = 5.3 Hz, 1H), 4.49 (d, J = 11.3 Hz, 1H), 3.76 (dq, J = 6.1, 9.1 Hz, 1H), 2.49 (ddd, J = 9.1, 9.1, 9.1 Hz, 1H), 1.26 (d, J = 6.1 Hz, 3H).

6. $J_{a,b} \approx J_{b,c} \approx J_{b,d} \approx 9.1$ Hz



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9. The anti-anti stereochemistry of the products is not to be confused with the syn (erythro)-selective process of the reactions between allylstannanes and aldehydes in the presence of Lewis acid. In fact, both anti-anti and anti-syn isomers are from syn-selective process, which is in accord with literature precedents.[1,2]

10. For similar shielding effect in the determination of the optical purity of secondary chiral alcohols using O-methyl mandelate, see: Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balhovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.

(Received in USA 13 May, 1991)