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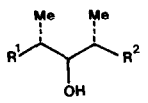
STEREO- AND REGIOSELECTIVE METHODS FOR THE SYNTHESIS OF THREE CONSECUTIVE ASYMMETRIC UNITS FOUND IN MANY NATURAL PRODUCTS

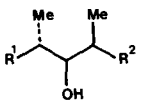
Mark R. Johnson, Tadashi Nakata, and Yoshito Kishi*
Department of Chemistry, Harvard University
12 Oxford Street, Cambridge, MA 02138

Abstract: Regio- and stereoselective methods are described for the synthesis of compounds possessing the stereochemistry of type 1a, 1b, 1c, and 1d from the aldehyde 2.

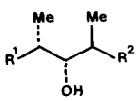
The partial structural unit, R-CH(CH_3)CH(OH)CH(CH_3)-R', is often found in important natural products. Three asymmetric centers of this unit give rise to four possible diastereomers represented as 1a-d; all of which are known as partial structures of polyether,[1] ansamycin,[2] or macrolide[3] antibiotics. We have been interested in developing stereo- and regioselective methods for synthesizing the structural units 1a-d from the aldehyde 2, which is readily available in racemic and optically active forms.[4, 5]



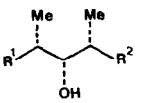
1a



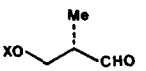
1b



1c



1d



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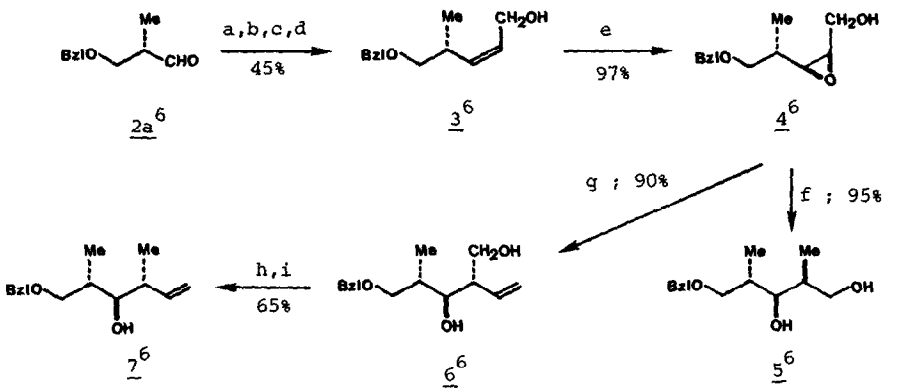
(X = a protecting group)

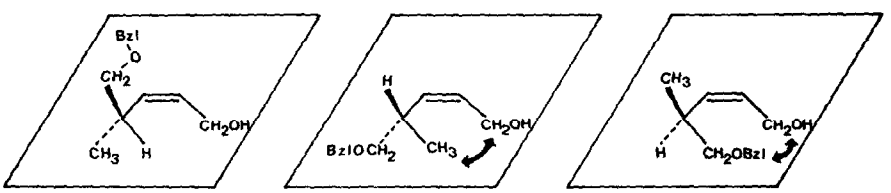
As a possibile method to prepare diastereomers 1a and 1b, we examined the sequence of reactions shown in Scheme 1. The cis-allylic alcohol 3[6] was synthesized from 2a[6] via an acetylenic compound in 45% overall yield. It was anticipated that epoxidation of 3 should give the desired epoxide 4 as the major product, because (1) A is the expected preferred conformation of 3 (note the steric compression indicated by arrow in the alternative eclipsed conformations B and C,[7] and (2) the cooperative effect of the hydroxy group and ether oxygen would be expected to direct the course of the epoxidizing reagent.[8] Thus, epoxidation (MCPBA/CH_2Cl_2/0°C) of 3 yielded only one epoxide [PMR ($CDCl_3$) δ 1.03 ppm (3H, d, J = 7 Hz)],[6] to which the structure 4 was tentatively assigned. It was assumed that the opening of the epoxide ring of 4 by an equivalent of a "methyl anion" would take place regiospecifically at the desired position because of steric hindrance due to the methyl group for the incoming nucleophile at the undesired position.[9]

Scheme 1



Reagents: a. $CBr_4/(C_6H_5)_3P/CH_2Cl_2/0^oC$, b. 1. CH_3Li (2 eq.)/THF/-78°C, 2. $ClCO_2Me$/THF/-78°C → RT, c. H_2/Pd-$CaCO_3$/quinoline/hexane, d. DIBAL/CH_2Cl_2-$C_6H_5CH_3$/-78°C, e. MCPBA/CH_2Cl_2/0°C, f. $LiCu(CH_3)_2/Et_2O$/-20°C, g. CH_2=CHMgBr/CuI/Et_2O/-20°C, h. MsCl/Py/0°C, i. $LiAlH_4/Et_2O$/0°C.

The ring opening of 4 with lithium dimethylcuprate (Et_2O/-20°C) was found to be regio- and stereoselective giving exclusively the alcohol 5 [PMR ($CDCl_3$) δ 0.78 ppm (3H, d, J = 7 Hz), 0.97 (3H, d, J = 7 Hz)][6] in 95% yield. Similarly, the ring opening of 4 with divinylcuprate (Et_2O/-20°C) afforded exclusively the alcohol 6[6] in 90% yield, which was efficiently converted to the alcohol 7 [PMR ($CDCl_3$) δ 0.88 (3H, d, J = 7 Hz), 1.09 (3H, d, J = 7 Hz)][6] in a 2-step procedure in 65% yield. The structures of 7, and consequently 4 and 5, were established by comparison of spectroscopic data of 7 with those of the authentic substance prepared from *cis*, *cis*-3,5-dimethyl-4-hydroxycyclohexanone.[10]

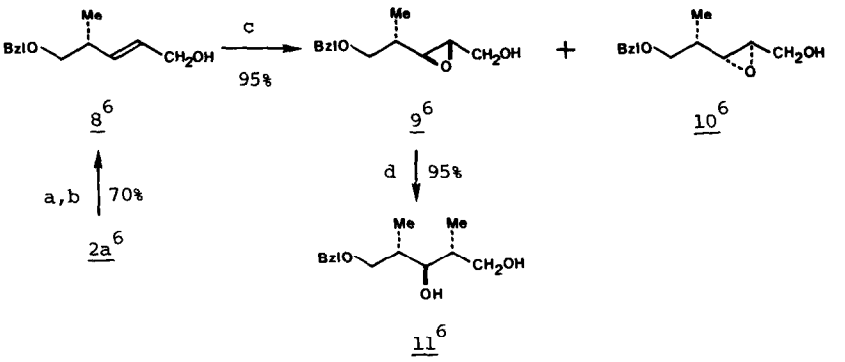


A B C

Scheme 2 summarizes the same sequence of reactions in the trans series. Epoxidation of the trans-allylic alcohol 8,[6] synthesized from 2a in 2 steps, was examined; m-chloroperbenzoic acid (CH_2Cl_2/0°C) gave about a 3:2 mixture of the epoxides 9[6] and 10.[6, 11] The structure 9 was assigned to the major epoxide, since its ring opening with lithium dimethylcuprate (Et_2O/-20°C) gave exclusively the alcohol 11 [PMR ($CDCl_3$) δ 0.88 ppm (3H, d, J = 7 Hz), 1.01 (3H, d, J = 7 Hz)],[6] the structure of which was established, in turn, by comparison of spectroscopic data with the authentic substance.[10] The lower stereoselectivity of epoxidation for the trans-allylic alcohol

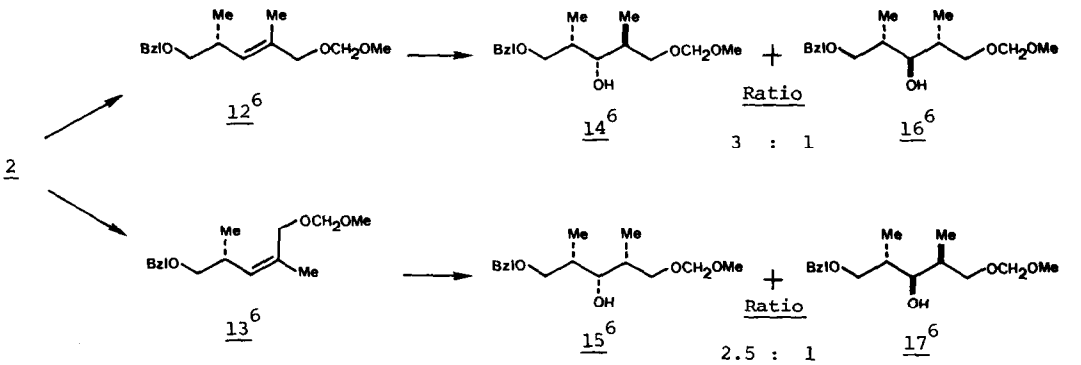
8 than for the cis-allylic alcohol 3 might be attributed to the different degree of preference of one conformation over the others; namely, the steric compression indicated by an arrow in conformation B and C of 3 would be less in the case of the trans-allylic alcohol 8.[7]

Scheme 2



Reagents: a. $(C_6H_5)_3P{=}CHCO_2Et/C_6H_6$/reflux, b. DIBAL/$CH_2Cl_2$-$C_6H_5CH_3$/-78°C, c. MCPBA/$CH_2Cl_2$/0°C, d. $LiCu(CH_3)_2/Et_2O$/-20°C.

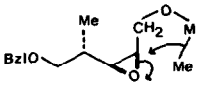
We have previously recognized that hydroboration is efficient in controlling the three asymmetric centers of 1c and 1d. Two olefins, 12[6] and 13[6], both of which were stereoselectively synthesized from 2,[8] were found to yield the expected alcohols 14[6] and 15[6] as major products on hydroboration (1. B_2H_6/THF/0°C, 2. aq. NaOH/H_2O_2/RT). Although the degree of stereoselectivity is considerably lower than that observed in the examples in the monensin synthesis,[7] it is still competitive with a method using a crossed Aldol reaction.[12, 13]



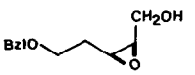
Acknowledgment Financial assistance from the National Institutes of Health, National Science Foundation, and the Hoffmann-La Roche Company is gratefully acknowledged.

References and Footnotes

1. Reviews on polyether antibiotics: J. W. Westley, Adv. Appl. Microbiol., 22, 177 (1977); B. C. Pressman, Annu. Rev. Biochem., 45, 510 (1976); J. W. Westley, Annu. Rep. Med. Chem., 10, 246 (1975).
2. Reviews on ansamycin antibiotics: K. L. Rinehart, Jr., and L. S. Shield, Prog. Chem. Org. Nat. Prod., 33, 231 (1976); W. Wehrli, Top. Current Chem., 72, 21 (1977).
3. Reviews on macrolide antibiotics: W. Keller-Schierlein, Prog. Chem. Org. Nat. Prod., 30, 313 (1973); W. D. Celmer, Pure Appl. Chem., 28, 413 (1971); S. Masamune, G. S. Bates, and J. W. Corcoran, Angew. Chem. Intern. Ed., 16, 585 (1977).
4. See footnote 5 in the following paper.
5. We consider this a case where it would be feasible to extend the chain of 1a-d from left to right but not from right to left; thus, 1b is not enantiomeric, but diastereomeric with 1c in this sense.
6. Satisfactory spectroscopic data (ms, nmr, ir) were obtained for this substance.
7. G. Schmid, T. Fukuyama, K. Akasaka, and Y. Kishi, J. Am. Chem. Soc., 101 259 (1979).
8. M. R. Johnson and Y. Kishi, Tetrahedron Lett., 4347 (1979)
9. It was also expected that initial formation of an intermediate like i (M = metal) might enhance the regioselectivity; J. E. Baldwin, J. C. S. Chem. Comm., 734 (1976). However, it seems, at least in the case of $LiCu(CH_3)_2$, that the steric hindrance mentioned plays a major role for observed regioselectivity, since the ring opening of ii under the same conditions yielded about a 1:1 mixture of two possible alcohols (C.-L. J. Wang and Y. Kishi, unpublished results).



i



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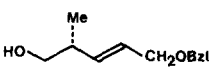
10. The synthesis of cis, cis-3,5-dimethyl-4-hydroxycyclohexanone and its transformation to 7 and then to 11 were carried out by Dr. W. Rutsch in our laboratories.
11. The Sharpless procedure (tert.-BuOOH/$VO(acac)_2$/C_6H_6/RT gave a 1:1 ratio. Epoxidation of iii under both conditions also afforded a 3:2 isomer ratio.



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12. For the method using a crossed Aldol reaction, see: H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, J. Am. Chem. Soc., 95, 3310 (1973); C. T. Buse and C. H. Heathcock, J. Am. Chem. Soc., 99, 8109 (1977); T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smith-Palmer, and Y. Kishi, J. Am. Chem. Soc., 100, 2933 (1978).
13. We studied hydroboration of the compounds bearing the OH, OMe, SMe, or $N(Me)_2$ group instead of the $C_6H_5CH_2$ in 12 and 13 with the hope that these polar groups might change the steric course of the reaction and give the products belonging to the type 1a or 1b. However, we found that the major product in all cases studied was the 1c or 1d type (C.-L. J. Wang and Y. Kishi, unpublished results).

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