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FURTHER STUDIES ON CHROMIUM(II)-MEDIATED HOMOALLYLIC ALCOHOL SYNTHESES

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Summary: The stereochemical outcome of chromium(II)-mediated syntheses of homoallylic alcohols has been examined on 11 aldehydes, 3a - 13a.

Investigations in these laboratories have resulted in the successful syntheses of chiral building blocks found in a variety of polyether, macrolide, and ansamycin antibiotics.[1] There exists an ongoing need for new methods for the production of such building blocks with further improved flexibility and efficiency. Recently there has been interest in chromium(II)-mediated syntheses of homoallylic alcohols as an alternative to the use of aldol condensations. Observations by Hiyama and Nozaki[2] and by Heathcock[3] have demonstrated the feasibility of such an approach for the generation of threo stereochemistry at the 1,2-positions.[4] However, it has been noted that stereoselectivity with regard to the 2,3-positions was low and hence this reaction had seemed not particularly attractive from a synthetic point of view.

Encouraged by a successful application of this reaction to the synthesis of rifamycin precursers in which for all practical purposes only one product was obtained (10b and 13b in the table),[5] it was decided to investigate further those factors responsible for enhancing the 2,3-stereoselectivity. Thus, several aldehydes were reacted with $CrCl_2$ and crotyl bromide to produce a variety of homoallylic alcohols, the results of which are summarized in the table.

Operating under the assumption that the chelation involving β-oxygen was responsible for the enhancement of 2,3-stereoselectivity,[5] different protecting groups on β-hydroxyisobutyraldehyde were examined. From the data (3a, 4a, 5a), it is clear that this variation is of limited influence; moreover, the insensitivity of the product ratio to polarity of the reaction medium (3a) is also indicative of a lack of substrate chelation. Instead, it became apparent that the nature of the large substituent on the α-carbon of the aldehyde was the predominant factor. For those cases studied in which this substituent was a saturated cyclic ring, marked improvement of the 2,3-stereoselectivity was observed relative to the acyclic cases. The above results are consistent with a six-center transition state in which steric interactions are minimized, as depicted in Figure 1, with the orientation of the aldehyde α-carbon according to the Felkin modification[6] of Cram's rule. Although a conclusion as to the specific role of the cyclic acetal group in the observed increase of 2,3-stereoselectivity must await further experiments, one possible explanation might be that a favorable interaction of the lone pairs of cyclic acetal oxygens with the carbon atom of the aldehyde group makes one conformation preferred over the other two, resulting in pronounced steric discrimination of the two faces of the aldehyde group.[7]

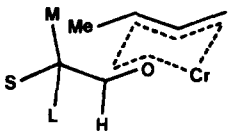
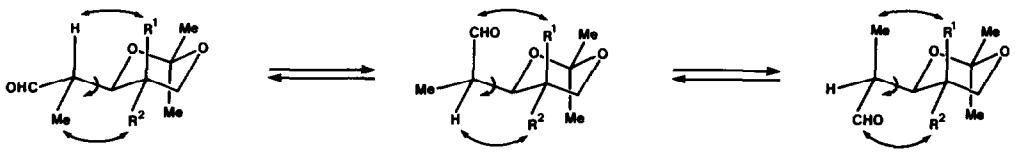
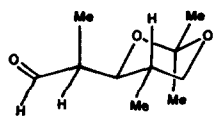


Figure 1

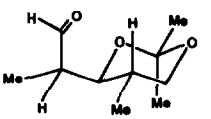
Regardless of the reasons behind it, the enhanced stereoselectivity makes practical the synthesis of those building blocks such as 6b in multi-gram quantities. Compound 6b can be converted to either of the more familiar aldehydes 9a or 11a in high yield by a short sequence of steps.[8] Thus, chromium aldols can be applied in the midst of a complex multi-step synthesis (eg. 10b, 13b) with excellent results.

One interesting observation is that in aldehydes with a syn dimethyl arrangement (10a, 12a, 13a) of the C.2 and C.4 positions, the diastereomeric ratio is enhanced relative to the anti case (9a, 11a). Three conformations, A, B, and C, should be considered for analysis of results. For each substrate there exists one conformation that is of lower energy due to the lack of steric interactions (see the two indicated arrows); for 9a and 11a this is conformation A, for 10a (similarly 13a) it is B, and for 12a it is C.[9] Each of 10a, 12a, and 13a has, in its most stable conformation, a hydrogen in a 1,3-diaxial relationship, which would effectively shield the approach of the reactant to one face of the aldehyde. In both 9a and 11a no such comparable phenomenon exists, which would explain the less pronounced 2,3-stereoselectivity.

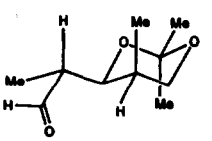




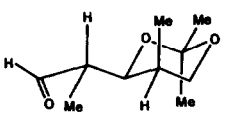
9a



10a

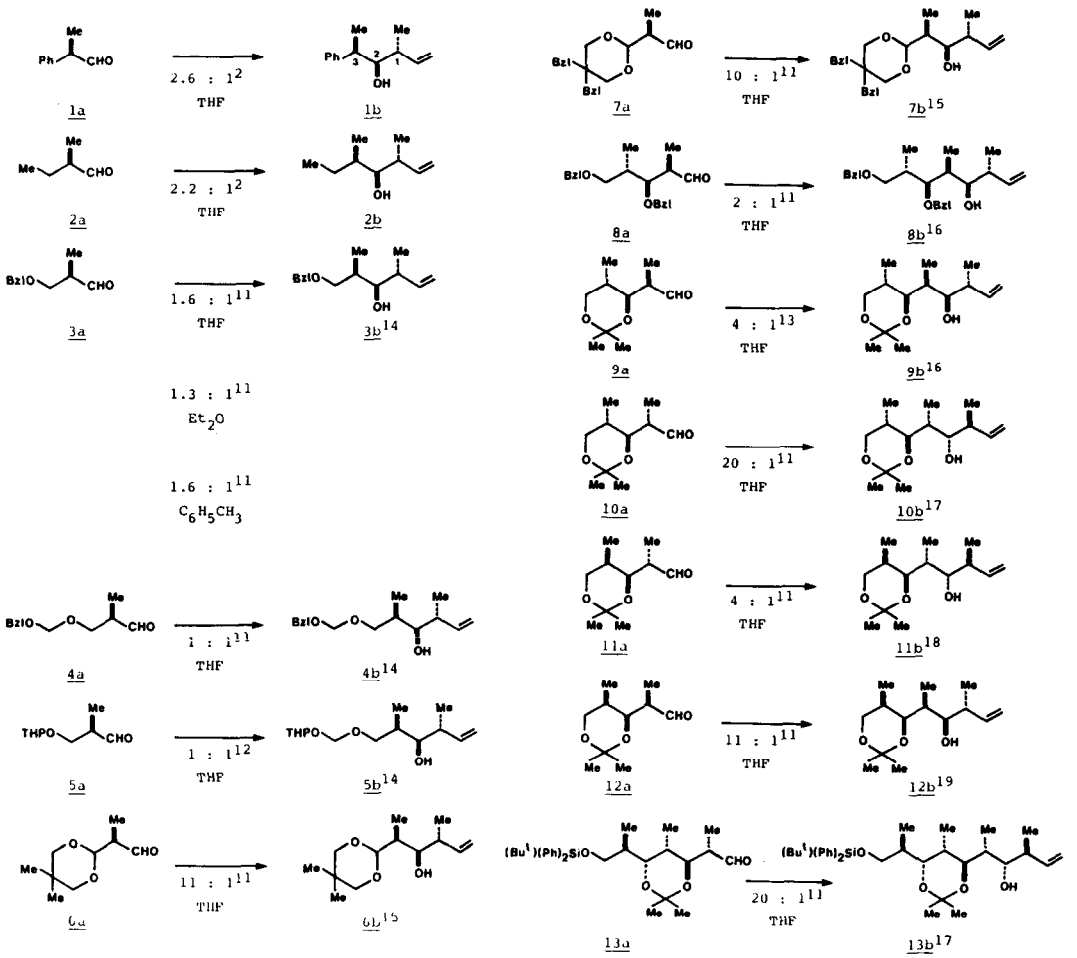


12a



11a

Table[10]



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References and Footnotes

1. Mark R. Johnson, Tadashi Nakata, and Yoshito Kishi, Tetrahedron Lett., 4343 (1979); Mark R. Johnson and Yoshito Kishi, ibid, 4347 (1979).

2. Yoshito Okude, Shigeo Hirano, Tamejiro Hiyama, and Hitosi Nozaki, J. Am. Chem. Soc., 99, 3179 (1977); Tamejiro Hiyama, Keizo Kimura, and Hitosi Nozaki, Tetrahedron Lett., 1037 (1981).

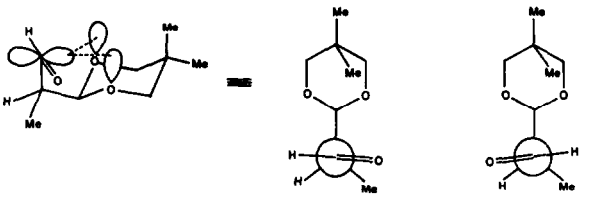
3. Charles T. Buse and Clayton H. Heathcock, Tetrahedron Lett., 1685 (1978).

4. The "threo" term is used to indicate the stereochemical relationship at the 1,2-position as in structure 1b; see H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, J. Am. Chem. Soc., 95, 3310 (1973). For numbering in this paper, see structure 1b.

5. Hiroto Nagaoka and Yoshito Kishi, Tetrahedron, 37, 5873 (1981).

6. M. Cherest, H. Felkin, and N. Prudent, Tetrahedron Lett., 2199 (1968).

7. The p-orbital of the aldehyde carbon seems to have favorable interaction with the two lone pairs of the cyclic acetal oxygens. Among the two possible modes, mode i follows Felkin's model, but mode ii does not. Preliminary experiments indicate that the ratio of alcohols obtained from the reaction of this aldehyde with methyllithium is somewhat greater than expected.



i ii

8. This transformation was possible in 4 or 5 steps, i.e. 1. O_3/CH_2Cl_2-MeOH/NaOAc/-78°C, followed by Me_2S treatment at -78°C → 0°C, then $NaBH_4$; 2. $MeSH/BF_3{\cdot}OEt_2/CH_2Cl_2$/RT; 3. 2,2-dimethoxypropane/acetone/camphorsulfonic acid (CSA)/RT; 4. NCS/ aq. MeCN/-12°C, or 1. $HS(CH_2)_3SH/BF_3{\cdot}OEt_2/CH_2Cl_2$/RT; 2. CuO/$CuCl_2$/aq. acetone/reflux; 3. $NaBH_4$/MeOH/0°C; 4. 2,2-dimethoxypropane/acetone/CSA/RT; 5. O_3/MeOH/NaOAc/-78°C, followed by Me_2S treatment at -78°C → RT.

9. An interaction involving one lone pair of an acetonide oxygen, similar to the one described in footnote 7, is possible for the conformations B and A, but not for C. For the cases of 9a - 12a, the steric interaction seems to be more important than the electronic interaction.

10. For a typical experimental procedure, see reference 5. Only the structure of the major stereoisomer produced in the reaction indicated is shown. The ratio appearing beneath the arrows represents that of the major to the next major stereoisomer.

11. Ratio determined by HPLC analysis of the crude reaction mixture or of its p-nitrobenzoate esters, if no UV chromaphore is present in the product.

12. Ratio determined by NMR.

13. Ratio determined by chromatographic isolation of diastereomers.

14. Structure of the major product determined by first ozonolysis, followed by sodium borohydride reduction and then comparison with the authentic material[5].

15. Structure of the major product determined by conversion to 11a (conditions in footnote 8) and comparison with the authentic material[5].

16. Structure assigned by its conversion to a symmetrical diacetonide in the following steps, 1.a. O_3/MeOH-CH_2Cl_2/NaOAc, followed by Me_2S treatment at -78°C → 0°C, b. $NaBH_4$/MeOH/0°C, 2. H_2/Pd-C/MeOH (for 8b only), 3. 2,2-dimethoxypropane/acetone/CSA/RT.

17. Structure of the major product determined by comparison with the authentic material.

18. Structure assigned based on successful conversion of 10b to a symmetrical diacetonide in 5 steps, i.e. 1. DMSO/$(COCl)_2/CH_2Cl_2$/-78°C followed by Et_3N treatment at -78°C → RT, 2. $LiAlH_4/Et_2O$/0°C, 3. chromatographic separation, 4.a. O_3/CH_2Cl_2-MeOH/NaOAc/-78°C, followed by Me_2S treatment at -78°C → 0°C, b. $NaBH_4$/MeOH/0°C, and 5. 2,2-dimethoxypropane/acetone/CSA/RT.

19. Structure implicated by inability to convert to a symmetrical derivative via schemes similar to references 16 and 18. Assuming threo aldol always predominates, the structure must be as depicted.

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