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ACYCLIC STEREOSELECTION. III.

SYNTHESIS OF *THREO*-3-HYDROXY-2-METHYLCARBOXYLIC ACIDS[1]

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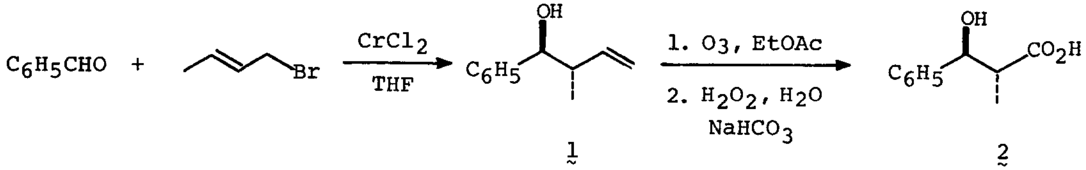
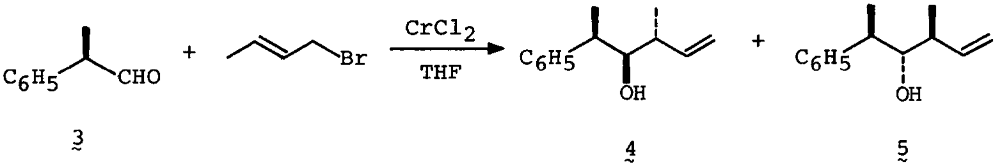
We have been interested in developing highly stereoselective syntheses of β-hydroxycarbonyl compounds which may be applicable to the total synthesis of macrolides, and have recently reported an effective route to *erythro*-3-hydroxy-2-methylcarboxylic acids.[1] Although the corresponding *threo* stereoisomers also may be prepared by the aldol condensation,[2] the general unavailability of the requisite (E)-enolates poses a problem which we have not solved satisfactorily.

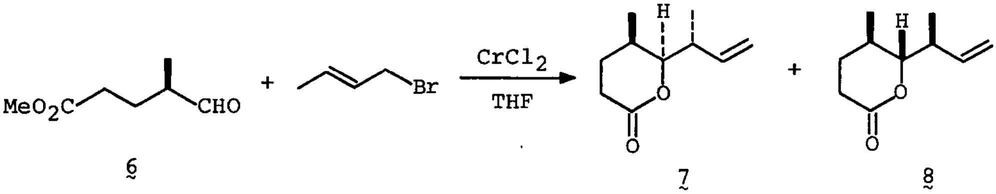
In a recent article, Hiyama and co-workers reported that aldehydes and ketones react with allyl halides in the presence of Cr(II) to give homoallylic alcohols.[3] It was noted that the reaction between benzaldehyde and crotyl bromide gives only one stereoisomer, but the stereostructure of this adduct was not ascertained.[3] On the basis of a cyclic transition state hypothesis which we have previously used to explain the stereoselectivity observed in aldol condensations,[2] it seemed to us that the Hiyama condensation might provide a route to *threo*-3-hydroxy-2-methylcarboxylic acids.

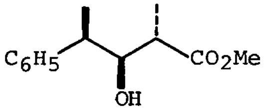
We have repeated the Hiyama condensation of benzaldehyde with crotyl bromide and find that the product is indeed the (SR,SR)-diastereomer **1**. Ozonolysis of **1**, followed by oxidative work-up, affords the *threo*-β-hydroxy acid **2**, which was identified by direct comparison with an authentic sample.[4]



The condensation has also been carried out with aldehydes 3 and 6, each of which has a chiral center adjacent to the carbonyl group. In each case, only two of the four possible diastereomers are obtained.[6] Isomers 4 and 5 were separated (preparative GLPC) and subjected to the sequence: (1) bis-trimethylsilylacetamide; (2) $NaIO_4$, $KMnO_4$, *t*-BuOH, H_2O; (3) CH_2N_2, ether; the known[7] *threo*-β-hydroxy esters 9 and 10, respectively, were produced. Thus, again we observed high *threo* selectivity, although the α-asymmetric induction is disappointingly low (4/5 = 2.6:1).[8] An attractive mechanism for the







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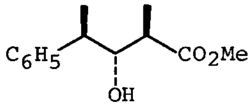

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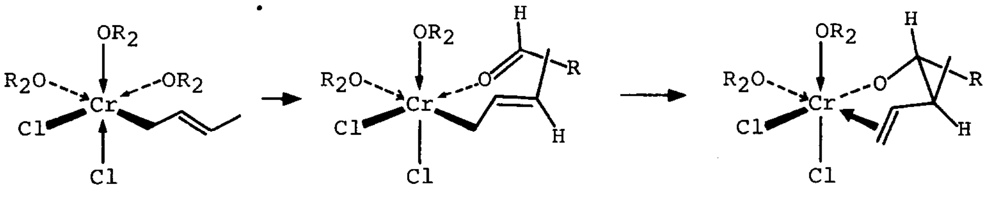
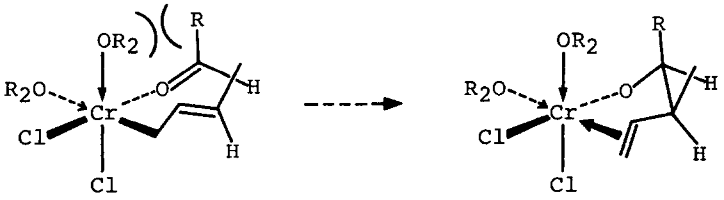
condensation involves the intermediate crotylchromium(III) chloride (**11**), which is presumably octahedrally coordinated with three THF molecules. Replacement of one ligand by the aldehyde oxygen would give a reactive complex (**12**), which can undergo electronic reorganization to **13**, the chromium(III) salt of the observed product. The high stereoselectivity observed in this reaction may



11 **12** **13**

be due to the severe non-bonded interactions present in the alternative rotomer **12'**, which would afford the other diastereomer (**13'**).[9] The application of these ideas to aldol condensations utilizing chromium(III) enolates is under investigation.[10]



12' **13'**

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REFERENCES AND NOTES

1. For paper II, see C.T. Buse and C.H. Heathcock, J. Am. Chem. Soc., 99, 8109 (1977).
2. W.A. Kleschick, C.T. Buse, and C.H. Heathcock, ibid., 99, 247 (1977).
3. Y. Okude, S. Hirano, T. Hiyama, and H. Nozaki, ibid., 99, 3179 (1977).
4. Hydroxy acid 2 is most easily obtained by condensing the enolate of methyl propionate with benzaldehyde. The resulting mixture of hydroxy esters (*erythro/threo* ≈ 1.5:1) is then hydrolyzed[5] with KOH in methanol, whereupon the less soluble *threo* salt crystallizes. This salt is collected, neutralized, and recrystallized to afford nearly pure 2.
5. A modification of the procedure described by: J. Canciell, J. Gasard, and J. Jacques, Bull. Soc. Chim. France, 2653 (1966).
6. Although only one enantiomer is depicted for each compound, all are racemates.
7. T. Matsumoto, Y. Hosada, K. Mori, and K. Fukui, Bull. Chem. Soc. Japan, 45, 3516 (1972).
8. Although no proof has been adduced, we believe that lactones 7 and 8 also have the configurations (RS,SR,RS) and (RS,RS,SR), on the basis of analogy. The "Cram's-rule selectivity in this case is nil (7/8 = 1:1).
9. This argument presumes that the crotyl group retains the (E)-configuration throughout its transfer from chromium to carbon.
10. After this manuscript was submitted, a paper appeared (J. Mulzer, J. Segner, and G. Bruntrup, Tetrahedron Letters, 4651 (1977)) which described the stereoselective synthesis of *threo*-3-hydroxycarboxylic acids by the condensation of carboxylic acid dianions with aldehydes. In some cases, excellent stereoselectivity was achieved under conditions of thermodynamic control (three days at 25° C). However, even under the best conditions, hydroxy acid 2 was produced in only 10% diastereomeric excess over the corresponding *erythro* isomer. Although the Hiyama method requires two steps rather than one, the excellent stereoselectivity observed in the formation of simple two-chiral center β-hydroxy acids such as 2 may render it the synthetic method of choice in these cases.