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DIRECTED METHALLYLATIONS AS A SYNTHETIC ROUTE TO 1,3-POLYOLS

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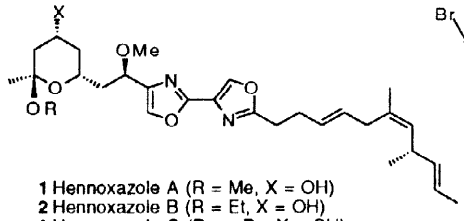
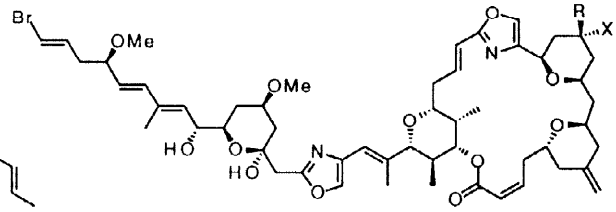
Abstract: The directed methallylation of β-hydroxyaldehydes and ketones with methallylboronic acid is examined. The reaction proceeds with good to excellent selectivity with ketones.

One of the most common functional group arrays in natural products is the 1,3-diol.[1] The presence of alternating oxygens on a contiguous carbon chain can be found in a variety of bioactive organic compounds such as the hennoxazoles (**1** – **7**, Scheme I)[2] and the phorboxazoles (**8**, **9**),[3] and natural products such as tetracycline (**10**) are derived biosynthetically from 1,3-oxygenated precursors.[4]

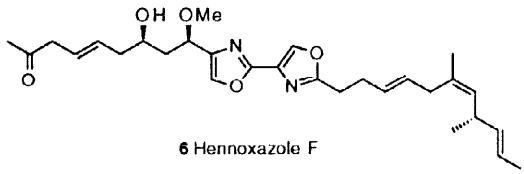
Scheme I



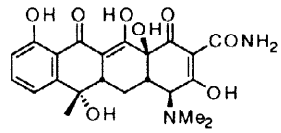
1 Hennoxazole A (R = Me, X = OH)
2 Hennoxazole B (R = Et, X = OH)
3 Hennoxazole C (R = *n*-Bu, X = OH)
4 Hennoxazole D (R = Me, X = H)
5 Hennoxazole E (R = H, X = OH)
7 Hennoxazole G (R = Me, X = OAc)



8 Phorboxazole A (R = H, X = OH)
9 Phorboxazole B (R = OH, X = H)



6 Hennoxazole F



10 Tetracycline

A majority of natural products that possess 1,3-diols are derived via polyacetate and polypropionate biogenetic pathways.[5] Since these are so prevalent in natural products, it is not surprising that considerable efforts have been expended toward the selective synthesis of 1,3-diols.[6] Ideally, the stereochemistry present in a given molecule can be used to control the formation of additional stereocenters in subsequent synthetic steps. We were therefore interested in the possibility of performing a stereocontrolled methallylation of carbonyls via resident β-oxidation. The lack of an α-substituent in these carbonyl compounds typically leads to poor selectivity, regargless of whether chelation or standard Felkin-Ahn conditions are the primary criterion for stereocontrol.[7] We therefore were interested in performing a directed addition to these carbonyls via the β-alcohols. Previously, Kabalka examined directed allylations and crotylations of α-hydroxyketones and α-

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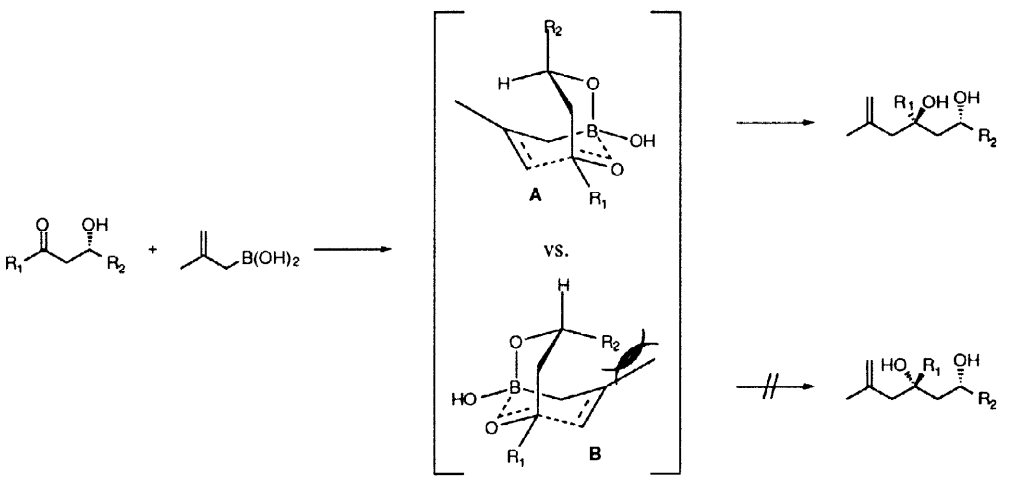
ketoacids with the corresponding boronic acids and found that these underwent accelerated and highly selective additions.[8]

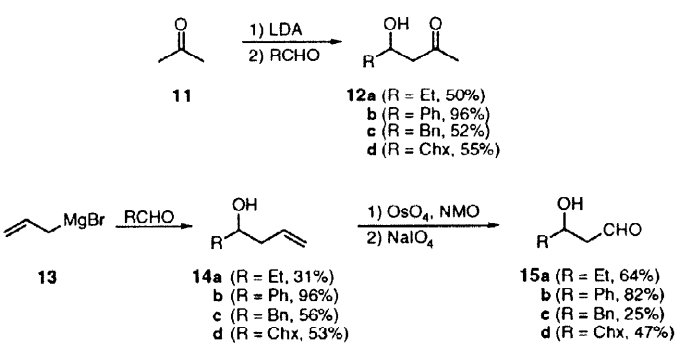
More recently, Kabalka studied the directed allylation of β-hydroxyaldehydes and ketones and found that the ketones gave the corresponding anti 1,3-diols with good selectivity while the aldehydes were less selective.[9] Concurrent with this work, we had become interested in the possibility of performing directed methallylations on β-hydroxycarbonyls as part of our efforts toward the total synthesis of the hennoxazoles and the phorboxazoles.[3b] We reasoned that a directed methallylation would proceed with high selectivity independent of the presence of any α substitution. This rationalization arose from the expectation that methallylboronic acid would, through formation of the boronic ester, undergo directed addition through one of two possible orientations (Scheme II). While purported transition state **A** (which directs the β-alkyl substituent into a pseudoequatorial position) would be expected to proceed uneventfully, the corresponding transition state **B** would be disfavored due to the projection of the β-alkyl substituent (R_2) into the methallyl group. Based on this analysis, the anti 1,3-diol would be expected to be formed as the major or only product.

Scheme II



The requisite β-hydroxycarbonyl compounds were prepared in standard fashion. Addition of the lithium enolate of acetone to several representative aldehydes led directly to the corresponding ketones in fair to good yields (**12**, Scheme III).[10] Alternatively, the aldehydes could be treated with allylmagnesium bromide to generate homoallylic alcohols **14**.[10] Direct ozonolysis of these double bonds proved difficult, but the requisite β-hydroxyaldehydes (**15**) could be prepared via the osmylation/periodate cleavage alternative.[10] The latter compounds were exceedingly capricious and had to be used immediately.

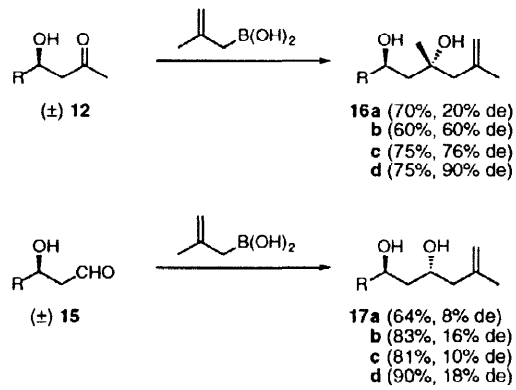
Scheme III



We were pleased to find that directed methallylation of the β-hydroxyketones with methallylboronic acid[11] typically proceeded with reasonable to good selectivity (Scheme IV).[10] We observed the greatest

selectivity when the β-alkyl group was cyclohexyl (**16d**), although similar selectivity was observed with the corresponding phenyl and benzyl products.[10] The only case where selectivity was poor was with the relatively small ethyl group (**16a**).[10]

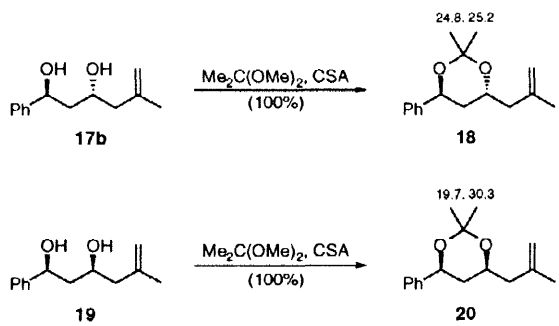
Scheme IV



Unlike the aforementioned ketones, the β-hydroxyaldehydes studied did not display useful selectivity. Addition to aldehydes **15** afforded nearly a 1:1 mixture of syn and anti 1,3-diols.[10] The lack of selectivity in this addition is almost certainly indicative of the reaction proceeding without preassociation of the boronic acid with the alcohol, presumably due to the increased electrophilicity of the aldehydes.

The stereochemical outcome of these methallylations was confirmed via conversion to the corresponding acetonides.[12,13] For example, treatment of **17b** and **19** with 2,2-dimethoxypropane gave the desired acetonides (Scheme V).[10] Examination of their respective ^{13}C NMR spectra revealed that **18** was in a twist-boat conformation (δ 25.2 and 24.8 ppm) while **20** was clearly in a chair conformation (δ 30.3 and 19.7 ppm).[12]

Scheme V



Based on these observations, it seems clear that directed methallylations are viable with β-hydroxyketones, and that reasonable selectivity can be expected from these transformations. Alternatively, β-hydroxyaldehydes do not appear to be amenable to directed additions, at least with boronic acids.

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REFERENCES AND NOTES

1. See: Faulkner, D. J. *Nat. Prod. Rep.* **1997**, *14*, 259 and previous articles in this series.
2. Hennoxazole isolation: a) Ichiba, T.; Yoshida, W. Y.; Scheuer, P. J.; Higa, T.; Gravalos, D. G. J. Am. Chem. Soc. 1991, 113, 3173. b) Higa, T.; Tanaka, J.; Kitamura, A.; Koyama, T.; Takahashi, M.; Uchida, T.

Pure Appl. Chem. **1994**, *66*, 2227. The structure of the hennoxazoles was determined via the total synthesis of *ent*-hennoxazole A, see: Wipf, P.; Lim, S. *Chimia* **1996**, *50*, 157.

3. a) Molinski, T. F. *Tetrahedron Lett.* **1996**, *37*, 7879. b) Searle, P. A.; Molinski, T. F.; Brzezinski, L. J. Leahy, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 9422. c) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126.
4. See: Thomas, R.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1984**, 443 and references cited within.
5. For an excellent discussion of these biosynthetic studies, see: O'Hagan, D. *The Polyketide Metabolites*, Horwood: New York, 1991.
6. For a recent example, see: Brückner, R.; Weigand, S. *Synlett* **1997**, 225. For a thorough treatise that details a number of methods, see: Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021 and references cited within.
7. For a recent discussion on Felkin-Ahn vs. chelation control in additions to carbonyls, see: Nógrádi, M. in *Stereoselective Synthesis, A Practical Approach*, VCH: Weinheim, 1995, pp. 139-154.
8. a) Wang, Z.; Meng, X.-J.; Kabalka, G. W. *Tetrahedron Lett.* **1991**, *32*, 5677. b) Wang, Z.; Meng, X.-J.; Kabalka, G. W. *Tetrahedron Lett.* **1991**, *32*, 4619. c) Wang, Z.; Meng, X.-J.; Kabalka, G. W. *Tetrahedron Lett.* **1991**, *32*, 1945.
9. Kabalka, G. W.; Narayana, C.; Reddy, N. K. *Tetrahedron Lett.* **1996**, *37*, 2181.
10. The structures assigned to each new compound were determined by their characteristic ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra. Diastereomeric ratios were determined via analysis of the NMR spectra of the mixtures after chromatographic purification.
11. A solution of methallylboronic acid in THF was typically prepared as follows: a suspension of KOtBu (10.0 g, 82 mmol) in THF (60 mL) was cooled to –78 °C and freshly condensed isobutylene (9.0 mL, 95 mmol) was added via cannula followed by nBuLi (34 mL, 2.4 M in hexanes, 82 mmol, added at a rate such that the reaction temperature did not rise above –60 °C). When addition was complete, the mixture was allowed to warm to –40 °C for 30 min and then was cooled to –78 °C. A solution of freshly distilled $B(OMe)_3$ (8.5 g, 82 mmol) in THF (20 mL) was added such that the reaction temperature remained below –60 °C and the reaction was then stirred at –78 °C for 4 h prior to warming to 0 °C. An aqueous solution of 3 N HCl saturated with NaCl (50 mL) was added and the mixture was stirred vigorously until the upper organic layer remained clear. The layers were separated and the organic layer was used directly in the methallylation studies without purification. The solution could be titrated by reaction with benzaldehyde, and was typically found to to be approximately 0.15 M.
12. See: Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511 and references cited within.
13. As Kabalka has pointed out, ^{13}C NMR analysis of acetonides where one of the alcohols is 3° does not allow for the straightforward disclosure of the relative stereochemistry as it does for two 2° alcohols. However, nOe studies can also be used to determine the relative position of the alkyl substituents.[14]
14. Brzezinski, L. J.; Levy, D. D.; Leahy, J. W. *Tetrahedron Lett.* **1994**, *35*, 7601.