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ALDOL ADDITION REACTIONS OF CHIRAL CROTONATE IMIDES

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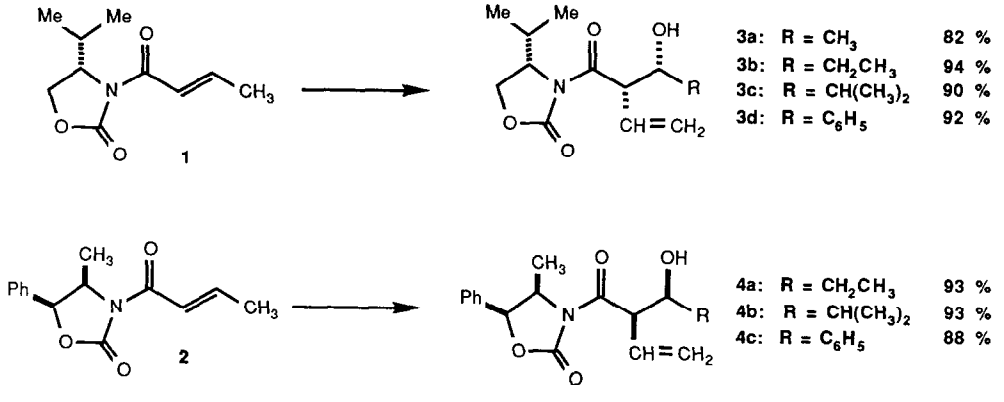
Abstract: Aldol addition reaction of the crotonate imides **1** and **2** affords the adducts **3** and **4** with high diastereoselection. Subsequent removal of the chiral auxiliary can be effected in good yield to provide a number of synthetically useful intermediates.

Several years ago we reported a highly diastereoselective aldol addition reaction based on carboximides of chiral oxazolidones.[1] The success of this reaction with simple imides encouraged us to investigate extensions to more functionalized systems. In this paper we wish to report our findings on the aldol addition reactions of the crotonate imides **1** and **2** (Scheme 1). The α-vinyl-β-hydroxy imides obtained from this reaction are versatile intermediates that have found applications in several total synthesis projects conducted in these laboratories.

Scheme 1



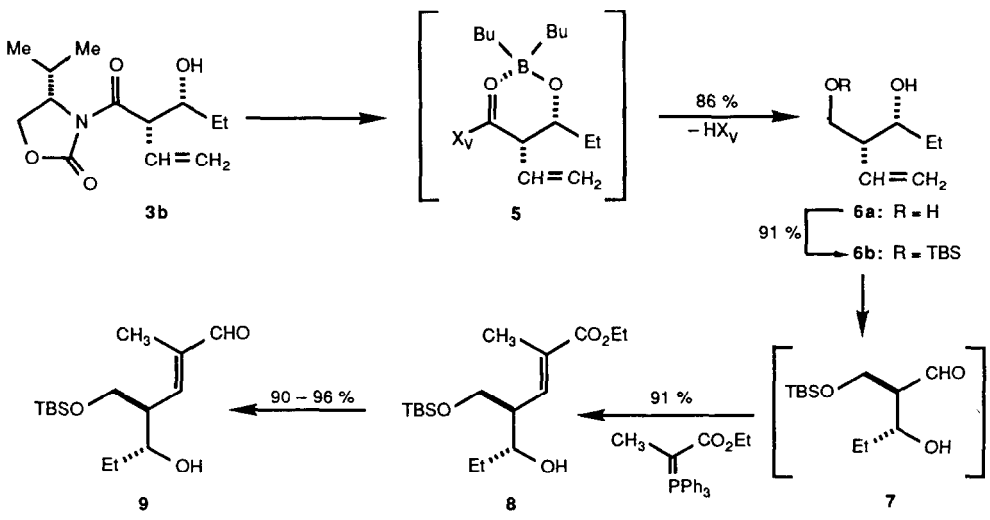
The crystalline imides **1** and **2** were readily prepared by acylation of the requisite chiral oxazolidones with (*E*)-2-butenoyl chloride as previously described.[2] Aldol addition of the derived dibutylboryl enolates proceeded with complete α–regioselectivity to give the imides **3** and **4** in high yield (Scheme 1). The diastereoselection observed in these additions was similar to that found with the corresponding propionate imides.[1] In all cases, capillary GC analysis of the silylated,[3] unpurified reaction mixture revealed that the major isomer was generated with >98% diastereoselection. Operationally, it was found that the use of triethylamine rather than diisopropylethylamine in the enolization of **1** and **2** was essential for good results. With the more hindered base, self-condensation reactions competed with enolization, leading to a complex product mixture. These reactions

were run according to the following typical procedure: To a stirred, -78°C solution of imide **2** (0.50 g, 2.04 mmol) in 8.5 mL of dichloromethane was added dibutylboron trifluoromethanesulfonate (0.56 mL, 2.23 mmol). The mixture was stirred for 5 min to dissolve the frozen triflate, and then treated with triethylamine (0.40 mL, 2.87 mmol). After 1 h at -78°C and 15 min at 0°C, the solution was recooled to -78°C and treated with freshly distilled isobutyraldehyde (0.27 mL, 3.0 mmol). The solution was kept for 1 h at -78°C and 1 h at 0°C, and then partitioned between 100 mL each 1 *M* $NaHSO_4$ and hexane-ethyl acetate (1:1). The organic phase was washed with brine and concentrated to an oil, which was dissolved in 15 mL of ether, cooled to 0°C, and treated with 2 mL each pH 7 buffer and 30% H_2O_2. After stirring rapidly for 1 h, the mixture was partitioned between 100 mL each water and hexane-ethyl acetate (1:1). The organic phase was washed with saturated $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated to an oil. Flash chromatographic purification (30% ethyl acetate-hexane) afforded 0.60 g (93%) of the aldol adduct **4b.**

The stereochemical assignment of the adducts **3** and **4** was initially based on the assumption that these reactions proceeded with the same sense of asymmetric induction as observed with the propionate imides. This assignment was subsequently confirmed through the successful use of these adducts in the enantioselective total synthesis of the macrolide tylonolide[4] and the polyether ionomycin.[5]

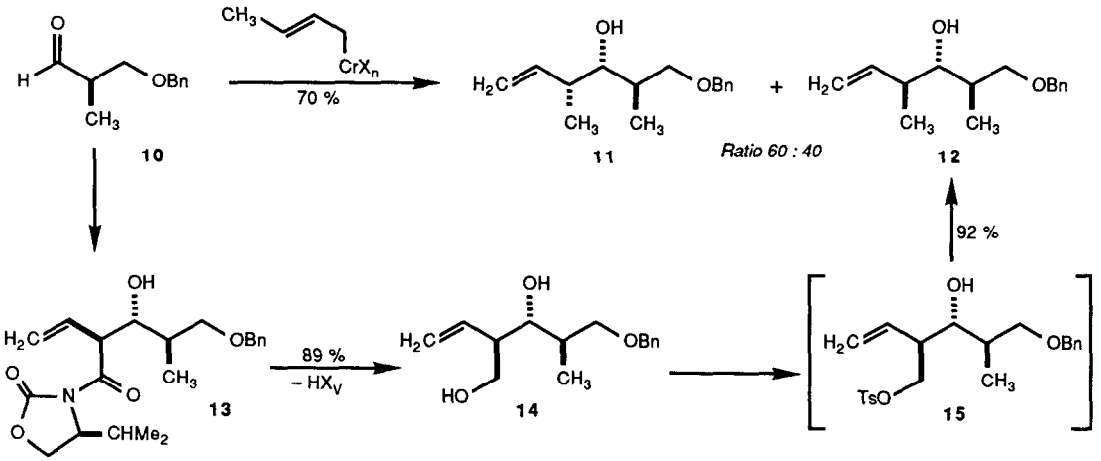
The sequence of reactions illustrated below (Scheme 2) demonstrates how the propionaldehyde adduct **3b** was employed in an efficient synthesis of the C_{11}-C_{15} tylonolide synthon **9**.[1b,4b] In order to prevent retroaldol reaction during the reductive cleavage of the imide, **3b** was first converted to the corresponding dibutylboryl aldolate **5**. The procedure employed was as follows: To a 0.25 *M* solution of **3b** in THF was added tributylboron (1.1 equiv) and glacial acetic acid (1.5 equiv). After 1.5 h, the solution of the aldolate was cooled to 0°C and treated with $LiBH_4$ (2.0 equiv of a 1.3 *M* solution in THF, 1 h). Oxidative workup (30% H_2O_2, pH 7, RT, 1.5 h) then afforded the diol **6a** in 86% yield.[6] Selective protection of the primary hydroxyl group (TBSCl, Et_3N, CH_2Cl_2, DMAP) proceeded in 91% yield to give silyl ether **6b**. Ozonolysis followed by reductive workup (Me_2S) afforded the aldehyde **7**, which upon treatment with (carbethoxyethylidene)-triphenylphosphorane provided ester **8** in 91% overall yield from **6b**. The key aldehyde **9** was then obtained in 90-96% overall yield by reduction (DIBAL in CH_2Cl_2) of **8** to the allylic alcohol followed by oxidation with MnO_2.

Scheme 2

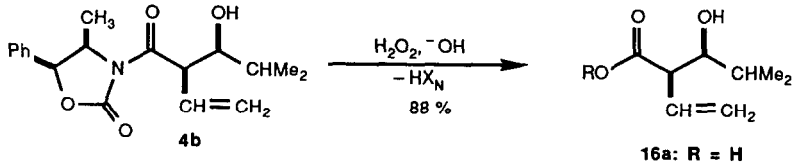


These aldol reactions have also proven to be valuable in a recently completed ionomycin total synthesis.[5b] In this project, the monoprotected diol **12** constituted the C_{17}-C_{21} ionomycin synthon. The initial synthesis of **12** proceeded *via* the addition of crotylmetal reagents to aldehyde **10**[7] (Scheme 3).[10] Based on ample precedent, we found that the Hiyama crotylchromium reagent added to **10** with excellent anti-syn diastereoselection;[11,12] however, the absence of significant carbonyl π-face discrimination (**11**:**12** = 60:40) by this and related transition metal derived crotyl nucleophiles led to the demise of this approach.[13] A much more selective route to **12** proceeded via initial aldol addition of the crotonate imide **1** to the aldehyde **10**. As anticipated from our previous experience with chiral aldehydes,[14] the facial bias of **10** was completely dominated by the resident chirality of the imide enolate, and **13** was obtained with high diastereoselection in 58% yield.[15] Reductive removal of the chiral auxiliary as described above proceeded in 89% yield to give the diol **14**. Selective tosylation of the primary hydroxyl group (TsCl, pyridine, 5°C) and subsequent reduction of **15** with lithium triethylborohydride then afforded **12** in 92% yield from **14**.

Scheme 3



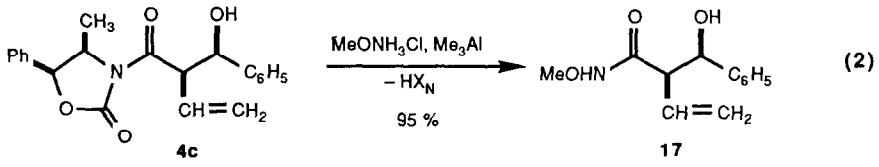
In the previously described transformations of the crotonate aldol adducts (Schemes 2,3), the pivotal reaction employed was carbonyl reduction. In earlier studies with these adducts, we were overly concerned that other reactions such as hydrolysis, transesterification or transamination might be severely compromised by α-epimerization or double bond conjugation. In more recent applications of these aldol adducts to a variety of projects, we have found the above concerns to be unwarranted for certain types of nonreductive refunctionalization reactions. For example, peroxide mediated hydrolysis of these adducts may be effected in good yield without detectable epimerization or double bond conjugation (eq 1). A representative procedure for the hydrolysis of **4b** follows: To a 0.1 *M* solution of **4b** in dioxane at 0°C was added H_2O_2 (12 equiv of a 30% aqueous solution) and LiOH (3 equiv). The mixture was stirred for 4 h and then quenched with aq. Na_2SO_3. Acidification followed by ether extraction and treatment with diazomethane afforded **16b**, $[\alpha]_D$ +116° (*c* 2.8, $CHCl_3$), in 88% yield after distillation.



(1)

16a: R = H
16b: R = Me

We have also found that these aldol adducts may be refunctionalized *via* transamination. Although the scope of this reaction has not been established, we have found that methoxyamine hydrochloride, as its derived aluminum amide,[16] effects transformation to the corresponding N-methoxyamide in excellent yield (eq 2). For example, treatment of **4c** with the reagent prepared from 3 equiv each methoxyamine hydrochloride and trimethylaluminum (dichloromethane, 0°C, 1 h) gave **17** in 95% yield. The effectiveness of this transamination in the case of **4c** is noteworthy, as retroaldol reaction of this substrate occurs under even mild base catalysis.



4c **17** (2)

In previous syntheses of 3-hydroxy-2-vinyl carbonyl compounds,[17,18] control of syn/anti product diastereoselection has been reported in only a limited number of cases.[17f,18] Of these, only this and the related system described by Masamune[18] provide both high syn diastereoselection and high enantioselection. The further transformation of these crotonate imide aldol adducts to enantiomerically pure β-lactams is described in the following communication.[19]

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References and Notes

1. (a) Evans, D.A.; Bartroli, J.; Shih, T.L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) For a preliminary account of this work, see Evans, D.A. *Aldrichimica Acta* **1982**, *15*, 23.
2. Evans, D.A.; Chapman, K.T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261.
3. The silylated aldol adducts were prepared by treating the crude adduct with chlorotrimethylsilane and 2,6 lutidine in DMF, followed by partitioning the reaction between hexane and water.
4. Morin, R.B.; Gorman, M.; Hamill, R.L.; Demarco, P.V. *Tetrahedron Lett.* **1970**, 4737. (b) Bartroli, J. Ph.D Thesis, California Institute of Technology, 1984.
5. Toeplitz, B.K.; Cohen, A.I.; Funke, P.T.; Parker, W.L.; Gougoutas, J.Z. *J. Am. Chem. Soc* **1979**, *101*, 3344. (b) Dow, R.L. Ph.D. Thesis, Harvard University, 1985.
6. We have found this to be the method of choice for the reductive cleavage of imide aldol adducts in general.
7. Prepared by Swern[8] oxidation of the corresponding alcohol.[9] This aldehyde is sensitive to racemization and it is important that the residual triethylamine from the Swern oxidation be removed (aq. sodium bisulfate) before concentration.
8. Mancuso, A.J.; Brownfain, D.S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148.
9. Evans, D.A.; Ennis, M.D.; Mathre, D.J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
10. Hoffmann, R.W. *Angew.Chem. Int. Ed. Engl.* **1982**, *21*, 555.
11. Hiyama, T.; Kimura, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1037.
12. Buse, C.T.; Heathcock, C.H. *Tetrahedron Lett.* **1978**, *19*, 1685.
13. A similar ratio has been observed by Kishi: Lewis, M.D.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2343.
14. Evans, D.A.; Bartroli, J. *Tetrahedron Lett.* **1982**, *23*, 807.
15. This yield is based on the alcohol precursor to **10**; see ref. 7.
16. Levin, J.I.; Turos, E.; Weinreb, S.M. *Synth. Commun.* **1982**, *12*, 989.
17. (a) Kozikowski, A.P.; Stein, P.D. *J. Org. Chem.* **1984**, *49*, 2301. (b) Kende, A.S.; Toder, B.H. *J. Org. Chem.* **1982**, *47*, 163. (c) Dugger, R.W.; Heathcock, C.H. *J. Org. Chem.* **1980**, *45*, 1181. (d) Tsuboniwa, N.; Matsubara, S.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 2569. (e) Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 7705. (f) Majewski, M.; Mpango, G.B.; Thomas, M.T.; Wu, A.; Snieckus, V. *J. Org. Chem.* **1981**, *46*, 2029.
18. Boschelli, D.; Ellingboe, J.W.; Masamune, S. *Tetrahedron Lett.* **1984**, *25*, 3395.
19. Evans, D.A.; Sjogren, E.B. *Tetrahedron Lett.* **1986**, accompanying communication.

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