Concerning the Synthesis of the Elusive *anti,anti*-Dipropionate Stereotriad via the Crotylation of β-Hydroxy α-Methyl Aldehydes with (*Z*)-Crotyltrifluorosilane. Application to the Synthesis of the C(7)−C(16) Segment of Zincophorin

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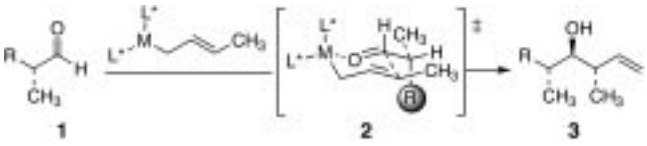
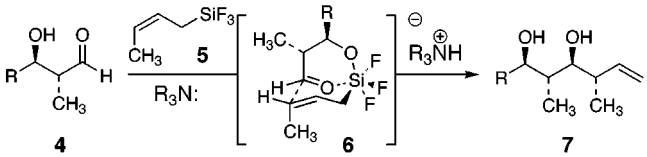
The *anti,anti*-dipropionate stereotriad **3**, a common subunit found in polyketide-derived natural products, has generally been acknowledged as difficult to synthesize.[2,3] The selective synthesis of this stereotriad by way of aldol or crotylmetalation protocols is inherently problematic as it must arise from a disfavored transition state,[4,5] where the reagent adds to the chiral aldehyde in an anti-Felkin manner (illustrated below for the reaction of **1** with a type 1 crotylmetal reagent).[6]



1 **2** **3**

In principle, dipropionate **3** can be prepared directly from **1** by using chiral reagents in mismatched double-asymmetric reactions. Masamune[7] and Hoffmann[8] have developed highly enantioselective enol boronate and crotylboronate reagents, respectively, and have achieved high selectivity for the *anti,anti*-dipropionate in challenging mismatched double-asymmetric reactions. However, the Masamune and Hoffmann reagents require several steps to prepare. Additionally, Marshall[9] and Panek[10] have demonstrated that chelate-controlled addition of chiral allenylstannane and crotylsilane reagents to α-methyl-β-benzyloxy-substituted aldehydes provide *anti,anti*-dipropionate **3** selectively. Here also, the Marshall and Panek reagents require multistep preparations. Other strategies for the synthesis of the *anti,anti*-dipropionate stereotriad have been reviewed.[3]

We report herein a new approach to this problem involving the crotylation reaction of α-methyl β-hydroxy aldehydes with (*Z*)-crotyltrifluorosilane (**5**),[11] which provides the *anti,anti*-dipropionate **7** with excellent selectivity using 2,3-*anti* β-hydroxy α-methyl aldehydes **4** as the starting material. We report as well an application of this methodology in a synthesis of the C(7)−C(16) segment of the ionophore antibiotic zincophorin.[12,13]



4 **6** **7**

Our strategy is based on the substrate-controlled asymmetric induction model illustrated by the bicyclic transition state **6**. The β-hydroxyl group of aldehyde **4** is coordinated to the silicon center of the (*Z*)-crotyltrifluorosilane **5** in **6**, thus forcing the aldehyde alkyl substituent to adopt an axial position in the Zimmerman−Traxler transition state. Bond formation would then occur opposite to the aldehyde α-methyl group, generating the desired *anti,anti*-dipropionate stereotetrad **7**. Examples of reactions that proceed by way of similar bicyclic transition states have been previously described.[11,14−17]

We chose to use (*Z*)-crotyltrifluorosilane (**5**) in these reactions on the basis of reports that **5** and other allyltrifluorosilane reagents require activation by an external nucleophile (e.g., CsF, ROH, R_2NH) in order to react with carbonyl compounds.[11,15,18−20] The initiating nucleophile is thought to add to the silicon center, generating a pentacoordinate silicate species, which then reacts with the carbonyl substrate through a six-membered cyclic transition state wherein the hexacoordinate silicon center adopts an octahedral geometry (as in **6**).

Results of reactions of **5** and α-methyl β-hydroxy aldehydes **8**−**12** are summarized in Table 1. Typically, reactions were performed by treating 1 equiv of the freshly prepared β-hydroxy aldehyde with 1 equiv (by weight) of 4 Å molecular sieves in CH_2Cl_2 (0.08 M) at 23 °C for 20 min. This solution was then treated with 3 equiv each of **5** and *i*-Pr_2NEt at 0 °C for 36 h.[21] A sequential acidic (1 N HCl, 15 min) and basic (3:1 THF−1 N NaOH, 1 h) workup was required to hydrolyze the resulting silylene ketals to the desired diol products. These crotylation reactions require strictly anhydrous conditions, as addition of water to the crotylation reactions of **8** and **9** results in substantially lower selectivity for the anti,anti adducts **13** and **15**. Additionally, it is necessary to run these reactions at concentrations less than 0.1 M to minimize production of aldehyde dimer,[22] which is formed competitively under more concentrated conditions. Finally, it should be noted that hydroxyl-protected derivatives of **8** react extremely sluggishly with **5** and generate primarily the 4,5-anti 5,6-syn adducts.

The crotylation reactions of the 2,3-anti aldehydes **8**−**10** were generally quite selective for the 3,4-anti-4,5-anti dipropionate products **13**, **15** and **17** (Table 1, entries 1−5). The diastereoselectivity ranged from 96:4 to 94:6 for **8a** and **9a**,**b** to 85:15 for **8b** and 82:18:6 for **10**. The reaction diastereoselectivity and yield were affected only slightly with changes

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(2) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489.
(3) Hoffmann, R. W.; Dahmann, G.; Andersen, M. W. *Synthesis* **1994**, 629.
(4) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151.
(5) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.
(6) Roush, W. R. In *Comprehensive Organic Synthesis*; Heathcock, C., Ed.; Pergamon Press: Oxford, 1991; Vol. 2; p 1.
(7) Tanimoto, N.; Gerritz, S. W.; Sawabe, A.; Noda, T.; Filla, S. A.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 673.
(8) Hoffmann, R. W.; Dresely, S. *Chem. Ber.* **1989**, *122*, 903.
(9) Marshall, J. A.; Perkins, J. F.; Wolf, M. A. *J. Org. Chem.* **1995**, *60*, 5556.
(10) Jain, N. F.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 12475.
(11) Sato, K.; Kira, M.; Sakurai, H. *J. Am. Chem. Soc.* **1989**, *111*, 6429.
(12) Brooks, H. A.; Garoner, D.; Poyser, J. P.; King, T. J. *J. Antibiot.* **1984**, *37*, 1501.
(13) Radics, L.; Incze, M.; Ujszaszy, K.; Schade, W.; Roth, M. *J. Antibiot.* **1984**, *37*, 836.
(14) Reetz, M.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833.
(15) Kira, M.; Sato, K.; Sekimoto, K.; Gewald, R.; Sakurai, H. *Chem. Lett.* **1995**, 282.
(16) Gewald, R.; Kira, M.; Sakkurai, H. *Synthesis* **1996**, 111.
(17) Wang, Z.; Meng, X.-J.; Kabalka, G. W. *Tetrahedron Lett.* **1991**, *32*, 1945.
(18) Kira, M.; Hino, T.; Sakurai, H. *Tetrahedron Lett.* **1989**, *30*, 1099.
(19) Kira, M.; Kobayashi, M.; Sakurai, H. *Tetrahedron Lett.* **1987**, *28*, 4081.
(20) Kira, M.; Sato, K.; Sakurai, H. *J. Am. Chem. Soc.* **1990**, *112*, 257.
(21) Lower yields of the homoallylic alcohol products were obtained when 1 or 2 equiv of **5** was used. Use of 1−8 equiv of (*Z*)-crotyltrifluorosilane had no effect on the reaction diastereoselectivity.
(22) Rychnovsky, S. D.; Skalitzky, D. J. *J. Org. Chem.* **1992**, *57*, 4336.

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Table 1. Reactions of (*Z*)-Crotyltrifluorosilane (5) and β-Hydroxy α-Methyl Chiral Aldehydes[a]

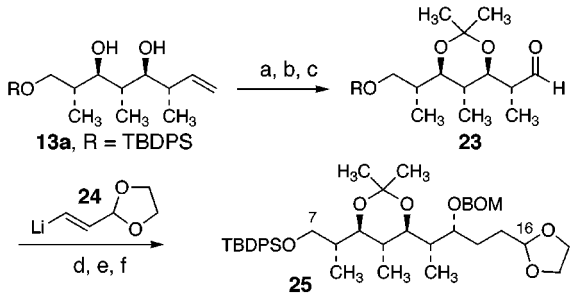
entry	aldehyde[b]	major products		ratio[c,d] (% yield)[e]
1	**8a**, P = TBDPS	**13a**	**14a**	93 : 6 : 1 (75)
2[f]	**8b**, P = PMB	**13b**	**14b**	85 : 15 (75)
3	**9a**, P = TBDPS	**15a**	**16a**	95 : 5 (75)
4[f]	**9b**, P = TBS	**15b**	**16b**	96 : 4 (63)
5	**10**, P = TBDPS	**17**	**18**	82 : 12 : 6 (76)
6[f,g]	**11**, P = TBDPS	**19**	**20**	50 : 24 : 36 (44)
7[f,g]	**12**, P = TBDPS	**21**	**22**	50 : 33 : 17 (48)

[a] All reactions were carried out with 3 equiv of **5** and 3 equiv *i*-Pr_2NEt in CH_2Cl_2at 0 °C in the presence of 4 Å molecular sieves for 36 h unless noted otherwise. [b] Aldehydes **8**−**12** were prepared by sequential dihydroxylation (cat. OsO_4, NMO) and oxidative cleavage ($NaIO_4$) of the corresponding terminal olefins.[4] [c] Product ratios were determined by ^1H NMR (400 or 500 MHz) analysis of the crude, unseparated mixture of products. In all cases, products were separable only by HPLC. [d] The product ratio refers to the two major products and the sum of all other diastereomers that were detected. [e] Yields are reported for the mixture of products. [f] 7 equiv of **5** and 5 equiv of *i*-Pr_2NEt were used. [g] 72 h reaction time.

in the aldehyde δ-alkoxy protecting group (Table 1, entries 1 and 2, 3 and 4) and γ-carbon stereochemistry (Table 1, entries 1 and 3). When the γ-carbon is unsubstituted, as in the case of **10**, somewhat diminished diastereoselectivity was realized (Table 1, entries 1 and 5).

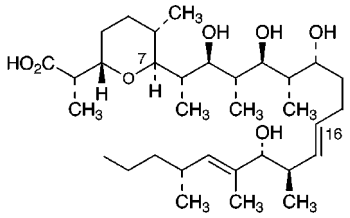
Surprisingly, a different pattern of stereoselectivity emerged in the reactions of the 2,3-syn α-methyl β-hydroxy aldehydes **11** and **12**. In these cases, the reactions were much less selective and the major products **19** and **21** possessed 3,4-syn-4,5-anti stereochemistry (Table 1, entries 6 and 7). All attempts to obtain the desired *anti,anti*-dipropionate products from **11** and **12** by changing reaction conditions were unsuccessful. Diastereomers **19** and **21** are expected to be the major products of (*Z*)-crotylation reactions that proceed by way of normal, nonchelated Zimmerman−Traxler transition states.[4,6] We have observed a similar dichotomy in the allylation and (*E*)-crotylations of 2,3-anti and 2,3-syn β-hydroxy aldehydes with allyl- and (*E*)-crotyltrifluorosilanes, in that reactions with 2,3-anti β-hydroxy aldehydes proceed preferentially via internally chelated transition states related to **6**, while the reactions of the 2,3-syn β-hydroxy aldehydes give major products consistent with pathways involving conventional Zimmerman−Traxler transition states, devoid of chelation involving the β-hydroxyl groups. A detailed analysis of these results will be deferred to a full paper on the topic.

Scheme 1[a]



[a] Reagents and conditions: (a) 2-methoxypropene, cat. PPTs, CH_2Cl_2; (b) OsO_4, NMO, *t*-BuOH−THF−H_2O (10:3:1), 94%; (c) $NaIO_4$, 10:1 THF−H_2O, 90%; (d) **24**, THF, −90 °C, 73% (86:14 selectivity); (e) H_2, Pd/C, PhH, 84%; (f) BOM-Cl, *i*-Pr_2NEt, CH_2Cl_2, reflux, 86%.

The all-anti stereopentad present in the C(8)−C(12) segment of zincophorin offered a unique opportunity to demonstrate the synthetic potential of this methodology. This segment is especially appropriate since its synthesis requires two very difficult mismatched double asymmetric reactions if enantioselective aldol or crotylmetalation technology is used. For example, attempts to prepare **13a** via the mismatched double asymmetric crotylboration of the TES ether of **8a** with (*R,R*)-tartrate (*E*)-crotylboronate[5] was completely unsuccessful (9:1 selectivity favoring the unwanted 3,4-anti-4,5-syn diastereomer).



We designed our synthesis so as to converge with the C(7)−C(16) segment **25** previously synthesized by Danishefsky.[23] The all anti stereopentad **13a**, obtained in 75% yield and 93:6:1 selectivity as previously described (Table 1, entry 1), was protected as an acetonide, and then the terminal olefin was dihydroxylated (94% yield, two steps). Oxidative cleavage of the resulting diol led to the sensitive aldehyde **23** (90%), which underwent a Felkin-selective (86:14, 73% yield) reaction with vinyllithium species **24** (Scheme 1). The major diastereomer was hydrogenated (84%), and then the alcohol was protected as a BOM ether (86%), thereby providing the C(7)−C(16) segment **25** of zincophorin, the spectroscopic properties (^1H NMR, IR, HMRS) of which were in excellent agreement with data for authentic **25** kindly provided by Professor Danishefsky.[24]

In summary, the crotylation of β-hydroxy α-methyl aldehydes with (*Z*)-crotyltrifluorosilane (**5**) offers an excellent way to install the *anti,anti*-dipropionate unit late in a synthetic scheme, as illustrated by the conversion of **8a** to **13a**. However, at least at present, this methodology is limited to 2,3-anti β-hydroxy aldehyde substrates.

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Supporting Information Available: Experimental procedures for all new compounds, including compounds generated for assignment of stereochemistry; ^1H and ^{13}C NMR spectra of selected intermediates (76 pages).

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(23) Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.* **1988**, *110*, 4368.

(24) The optical rotation of synthetic **25** ($[\alpha]^{28}_D = +26.2°$) was higher than the reported value ($[\alpha]^{25}_D = +21.9°$).[23] We are unable to account for this discrepancy.