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# A HIGHLY STEREOSELECTIVE SYNTHESIS OF THE OCTAHYDRONAPHTHALENE SUBUNIT OF KIJANOLIDE AND TETRONOLIDE

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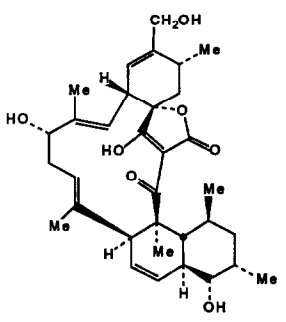
***Abstract:*** *A highly stereoselective synthesis of the octahydronaphthalene subunit **4** of kijanolide and tetronolide featuring the intramolecular Diels-Alder reaction of tetraenoate **5** is described.*

Kijanolide (**1**) and tetronolide (**2**), aglycones of the structurally novel antitumor antibiotics kijanimicin[2a] and tetrocarcin A,[2b] are highly attractive targets for total synthesis.[3,4] Of immediate interest to us was the possibility that the octahydronaphthalene fragment **4** could be assembled by the intramolecular Diels-Alder reaction of tetraene **3**. In particular, we were interested in questions of intramolecular Diels-Alder diastereoselectivity, especially the role that the C(4)-C(6) substituents would have on the stereochemical outcome of this reaction.[5] While our work was in progress, Marshall,[3] and more recently Yoshii,[4a] reported highly diastereoselective syntheses of octahydronaphthalene subunits corresponding to **4** via the Lewis acid catalyzed intramolecular Diels-Alder reactions of appropriately functionalized 2,8,10,12-undecatrienals. Our work evolved along different lines, particularly with respect to the selection of the Diels-Alder substrate and the tactics employed in its synthesis. While we have not yet prepared our initial target **3**,[6] the more highly functionalized surrogate **5** has been synthesized and shown to be an excellent precursor to **4**. It is noteworthy that each of the asymmetric centers of **5** are introduced by highly diastereoselective transformations of acyclic intermediates, and that this synthesis of **4** is the most stereoselective and efficient of those reported to date.

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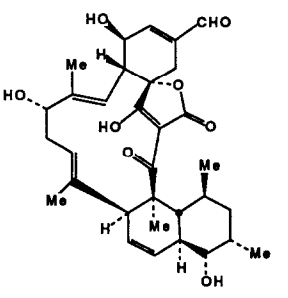


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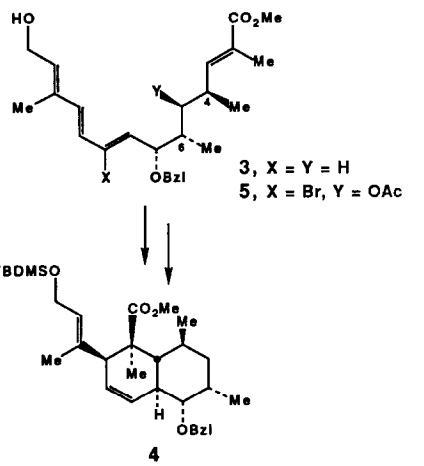
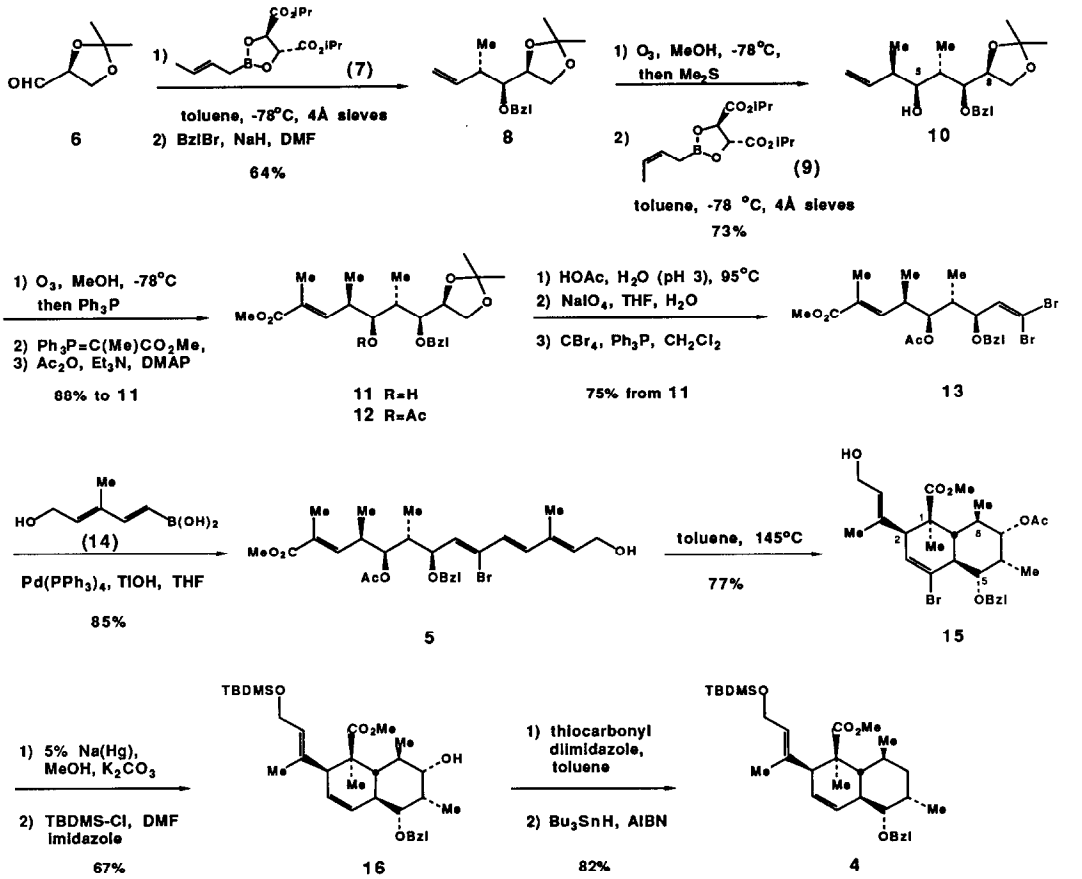



4

The synthesis commenced with the reaction of L-glyceraldehyde acetonide **6**, now readily available by a three step sequence from L-ascorbic acid,[7] with (R,R)-tartrate crotylboronate **7** that proceeds with 96% stereoselectivity for the alcohol corresponding to **8**.[8] Benzylation of the major diastereomer provided **8**[9a,b] ($[\alpha]_D^{23}$ -13.8°(C 2.2, $CHCl_3$)) in 64% overall yield.[10] Ozonolysis of this intermediate in MeOH (-78°C; $Me_2S$ workup) provided a crude aldehyde that was treated with the chiral (Z)-crotylboronate **9**[11] under standard conditions. A 94 : 5 : 1 mixture of three diastereomers was produced (HPLC analysis) from which **10**[9a,b] ($[\alpha]_D^{23}$ -3.6° (C 1.4, $CHCl_3$)) was isolated in 73% yield. We originally intended to remove the unwanted C(5) hydroxyl group at this stage, but were thwarted in all attempts to do so on this and related intermediates.[6] Attempts to reduce mesylate or tosylate derivatives with hydride reagents were compromised by preferential neighboring group participation by the C(8)-oxygen atom leading to tetrahydrofuran derivatives, while all efforts to effect a radical deoxygenation[12] on homoallyl alcohol intermediates like **10** provided cyclopropyl products resulting from cyclization of the homoallyl radical and hydrogen atom transfer to the cyclopropylcarbinyl radical intermediate. We decided, therefore, to postpone the deoxygenation step until after the Diels-Alder reaction. This, of course, introduces additional stereochemical complexity into the synthesis, particularly with respect to the potential influence of the C(5) substituent on the Diels-Alder step. We elected to pursue intermediates deriving from **10** since the C(5) oxygen function occupies an equatorial position in the transition state leading to **15**. As it turns out, however, this substituent plays no significant role in determining the stereochemical outcome of this reaction since the cyclization of C(5)-*epi*-**5**, synthesized by an analogous stereoselective sequence in which (S,S)-**7** is substituted for (R,R)-**9**, is as selective as **5** even though in the *epi*-series C(5)-OAc occupies an axial position in the transition state.

Ozonolysis ($O_3$, MeOH, -78°; then $Ph_3P$) of **10** provided a crude aldol that was treated with $Ph_3P{=}C(Me)CO_2Me$ in toluene at 45°C. Ester **11**[9a,b] ($[\alpha]_D^{23}$ -20.2° (C 1.05, $CHCl_3$)) so obtained (88%) was then acylated to give **12**[9a,b] ($[\alpha]_D^{23}$ -7.5° (C 2.0, $CHCl_3$)). Treatment of **12** with aqueous HOAc (pH 3, 95°C), cleavage of the resulting diol with $NaIO_4$ in aqueous THF and then dibromo olefination[13] provided **13**[9a,b] ($[\alpha]_D^{23}$ +12.4° (C 1.3, $CHCl_3$)) in 75% yield. Introduction of the conjugate triene unit was accomplished by using methodology developed in our earlier work on the synthesis of chlorothricolide.[5a] Thus, the sensitive dienyl boronic acid **14** was prepared in 75% yield by hydroboration (catecolborane, 23°C; then $H_2O$) of (Z)-3-methylpent-2-en-4-ynol, which in turn was synthesized from (E)-3-bromo-2-butenol[14] by a Sonogashira coupling[15] with trimethylsilylacetylene [cat. $(Ph_3P)_4Pd$, CuI, $Et_2NH$, $C_6H_6$, 23°C)] and desilylation ($K_2CO_3$, MeOH, 84% overall). Finally, treatment of **13** with 0.2 equiv of $(Ph_3P)_4Pd$ and 1.4 equiv. each of **14** and TlOH in THF for 5 min provided tetraene **5**[9a] ($[\alpha]_D^{23}$ +30.1° (C 1.6, $CHCl_3$)) in 85% yield.[16]

A toluene solution of **5** was heated in a resealable tube at 145°C under argon for 17h, providing cycloadduct **15**[9a,b] ($[\alpha]_D^{23}$ -15.6° (C 1.2, $CHCl_3$)) in 77% yield following chromatographic purification. Careful 300 MHz $^1H$ NMR analysis of the crude reaction mixture




indicated that the selectivity for **15** is at least 97 : 3, a remarkable result given the problems previously documented in the chlorothricolide series.[5,17] The stereochemistry of **15** was easily assigned based on coupling constant analysis: $J_{4a,8a} = J_{8,8a} = J_{4a,5} = 10.5$ Hz; $J_{7,8} = 11.0$ Hz; $J_{5,6} = 4.8$ Hz; $J_{6,7} = 4.5$ Hz; NOE studies subsequently performed on **4** verified the stereochemistry assigned to C(1) and C(2). The final elaboration of **15** to **4** proceeded without complication. First, **15** was treated with 5% Na(Hg) in MeOH containing $K_2CO_3$ to affect reductive debromination and deacylation, and then the primary alcohol was protected as a TBDMS ether. Finally, the unwanted hydroxyl group of **16**[9a] ($[\alpha]_D^{23}$ -45.6° (C 1.1, $CHCl_3$)) was removed by using the Rasmussen variant[18] of the Barton deoxygenation. The overall yield of **4**[9a,b] ($[\alpha]_D^{23}$ -21.1° (C 1.0, $CHCl_3$)) from **15** was 55%.

In summary, an exceptionally stereoselective synthesis of **4** has been accomplished by a sequence in which all seven stereocenters are introduced by reactions of acyclic substrates. Further progress towards completion of a total synthesis of either **1** or **2** will be reported in due course.

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