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Diastereoselective Synthesis of the Top Half of Kijanolide

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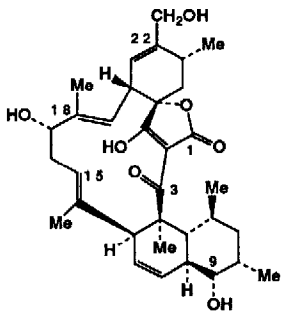
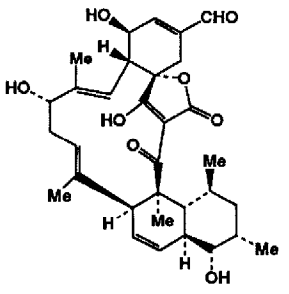
Abstract: *A highly diastereoselective synthesis of the top half (**4**) of kijanolide is described. The key step is the exo and diastereoface selective Diels-Alder reaction of triene **6** and chiral dienophile **6**.*

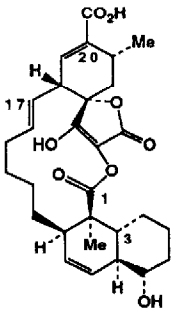
Kijanolide (**1**) and tetronolide (**2**), aglycones of the structurally novel antitumor antibiotics kijanimicin[1a] and tetrocarcin A,[1b] along with chlorothricolide (**3**), the aglycone of the antibiotic chlorothricin,[1c,d] have attracted considerable attention as synthetic targets in recent years.[3,4] We have reported enantioselective syntheses of the bottom halves of these molecules,[2b,3c] and wish to report here an efficient, diastereoselective synthesis of the top half fragment **4** of kijanolide. This synthesis features the highly regio- and exo selective Diels-Alder reaction of triene **5** and the novel dienophile **6** that establishes all of the stereocenters of **4** in a highly diastereoselective manner. It is also apparent that this synthesis, unlike other approaches to the spiro tetronate systems of **1**-**3**, is potentially enantioselective by virtue of the chirality of **6**.[4]



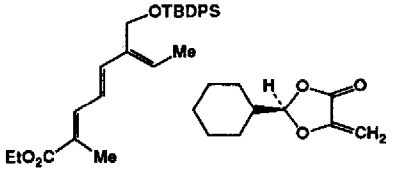
kijanolide (**1**)



tetronolide (**2**)

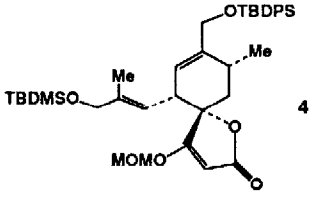


chlorothricolide (**3**)



5 **6**

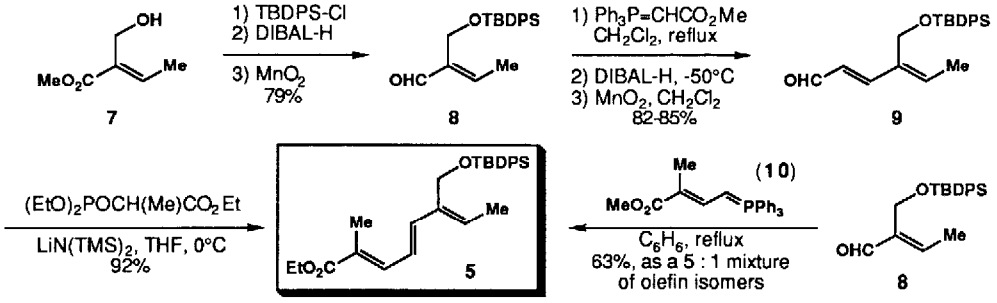
via an exo Diels-Alder reaction



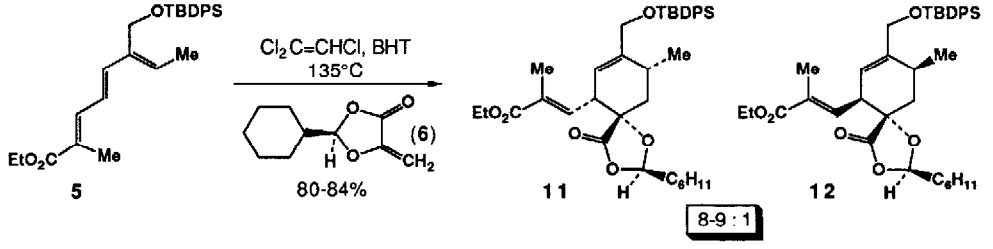
4

Triene **5** was synthesized starting from the known hydroxy ester **7**.[5] Thus, protection of the hydroxyl group as a *tert*-butyldiphenylsilyl (TBDPS) ether (TBDPS-Cl, imidazole, DMF, 23 °C, 98% yield), reduction of the ester function (DIBAL-H, Et_2O, -50 to -30 °C, 92-94% yield), and MnO_2

oxidation of the resulting allylic alcohol[6a,b] (20 equiv. of MnO_2, CH_2Cl_2, 23°C, 82-86% yield) provided enal **8**[6a] in 74-79% overall yield. This intermediate was smoothly elaborated to dienal **9**[6a,b] by sequential olefination with $Ph_3P{=}CHCO_2Me$ (CH_2Cl_2, reflux, 90% yield), carbomethoxyl reduction with DIBAL-H (2.5 equiv., Et_2O, -50 °C, 96% yield) and allylic alcohol oxidation by using MnO_2 (20 equiv., CH_2Cl_2, 23°C, 95-98% yield). Finally, subjection of **9** to a Horner-Wadsworth-Emmons reaction with the lithium anion of $(EtO)_2POCH(Me)CO_2Et$ [anion generated with $LiN(TMS)_2$] in THF at 0 °C provided trienoate **5**[6a,b] as a 28 : 1 mixture of olefin isomers in 87-89% yield. Alternatively, the methyl ester corresponding to **5** was prepared directly from **8** by treatment with the tiglate derived phosphorane **10** (benzene, reflux).[7] In this case, however, the triene was obtained as a 5 : 1 mixture of olefin isomers in only 63% yield.

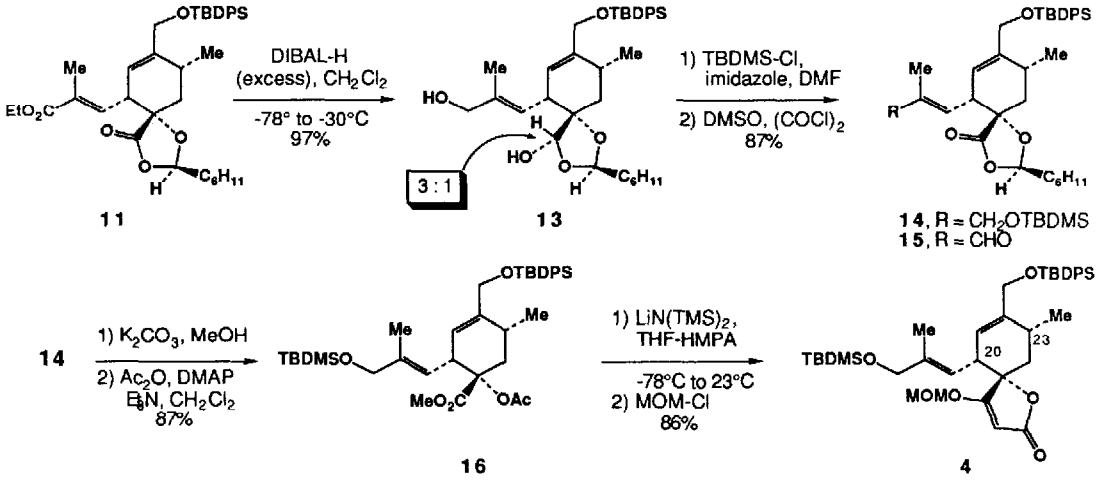


The key Diels-Alder reaction was performed by heating a mixture of **5** and **6** (1.2-1.5 equiv) in trichloroethylene (1 M) at 135°C for 16 h in the presence of BHT as a radical inhibitor. The desired exo-cycloadduct **11**[6a,b] was obtained as the major component of an 8-9 : 1 mixture of **11** and the endo isomer **12**[6a] (^1H NMR analysis and product isolation). A small amount (ca. 3%) of a regioisomer resulting from reversed orientation of the diene and dienophile was also obtained. The yield of **11** isolated chromatographically was 73%, and the combined yield of cycloadducts was 80-84%.[8]



Reduction of **11** with excess DIBAL-H in CH_2Cl_2 (4 equiv., -78 to -30 °C, 2 h) provided the unusual hemiacetal **13**[6a,b] in 97% yield as a 3 : 1 mixture of acetal anomers. The primary hydroxyl group was selectively protected as a *tert*-butyldimethylsilyl (TBDMS) ether (2 equiv. of TBDMS-Cl, imidazole, DMF, 23 °C, 89% yield) and the hemiacetal was then reoxidized using a

standard Swern protocol (DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C; then Et_3N; 98% yield)[9] to give **14**[6a] in 87% overall yield. Alternatively, Swern oxidation of **13** provided the corresponding lactone aldehyde **15** that may be useful in eventual studies on the coupling of the top and bottom halves. For the present purposes, however, the synthesis progressed via **14**. Thus, treatment of **14** with K_2CO_3 in MeOH at 0 °C and then acylation of the resulting hydroxy methyl ester with 2 equiv. of Ac_2O in the presence of 0.1 equiv. of DMAP and 4 equiv. of Et_3N in CH_2Cl_2 provided **16**[6a,b] in 87% overall yield. The Dieckmann cyclization technology introduced by Ireland in initial studies on the synthesis of the top half of chlorothricolide was then adopted for the conversion of **16** to the kijanolide top half fragment **4**.[10] Thus, **16** was treated with $LiN(TMS)_2$ in THF containing 20 equiv. of HMPA at -78 °C to generate the ester enolate. This solution was allowed to warm to 23 °C over a 1 h period, and then was treated 15 min later with 2.5 equiv. of chloromethyl methyl ether (MOM-Cl), giving the top half fragment **4**[6a,b] with an easily removable tetronate protecting group (86% yield). The stereochemistry of **4** was assigned to be as shown by comparison of relevant ^1H NMR data for **4** with data previously reported for 26,32-di-*O*-methylkijanolide (Table 1).[1a] The spectroscopic properties of **4** are also very similar to those reported by Yoshii for a similar intermediate.[4d]



In summary, we have developed an efficient and highly diastereoselective synthesis of **4** corresponding to the top half of kijanolide. The synthesis features the novel exo-selective Diels-Alder reaction of triene **5** and dienophile **6**, a transformation that is potentially enantioselective by virtue of the chirality of **6**. It is also apparent that this technology may prove useful for the synthesis of the top half fragments of tetronolide (**2**) and chlorothricolide (**3**). Additional progress towards the completion of total syntheses of these targets will be reported in due course.

Table 1. ^{1}H NMR Comparison of 4 and 26,32-Di-*O*-methylkijanolide (17)[a]

^{1}H Resonance	4	17
H-20	3.45 (partially obscured)	3.42 (d, J = 9.7 Hz)
H-21	5.33 (br s)	5.47 (s)
H-23	2.62 (br dq, J = 7.4, 7.4 Hz)	2.61 (dq, J = 7.0, 7.5 Hz)
Me-C(23)	1.16 (d, J = 7.4 Hz)	1.28 (d, J = 7.5 Hz)
H-24a	1.67 (d, J = 14.1 Hz)	1.76 (J = 14.1 Hz)
H-24b	2.28 (dd, J = 14.1, 7.4 Hz)	2.33 (J = 14.1, 7.0 Hz)

(a) ^{1}H NMR spectra were measured in $CDCl_3$ and are reported in δ units.

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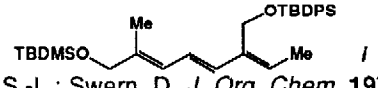
6. (a) The spectroscopic properties (300 or 500 MHz ^{1}H NMR, IR, mass spectrum) of all new compounds are in complete agreement with the assigned structures. (b) A correct CH analysis was obtained for this compound.
7. (a) Buchta, E.; Andree, F. *Chem. Ber.* **1960**, 93, 1349. (b) Numerous attempts to perform this olefination by using the corresponding γ-phosphonotiglate (Patenden, G.; Weedon, B. C. L. *J. Chem. Soc. C* **1968**, 1997) were thwarted by competitive dienolization of **8** and elimination of TBDPS-OH.
8. The selectivity and efficiency of the Diels-Alder reaction of **6** and triene ***i*** (leading directly to **14**) is comparable, but purification of the major cycloadduct from this mixture proved to be more difficult than the purification of **11**. The synthesis of ***i*** from **5** is also less efficient than the conversion of **11** to **14** described in text.



i

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