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# SYNTHESIS OF 28,29-BISNOR-(±)-KIJANOLIDE

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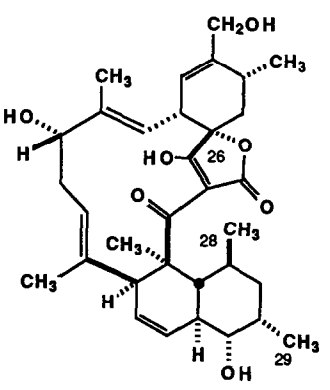
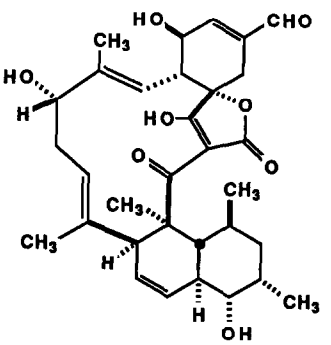
Abstract: O(26)-Methyl-28,29-bisnor-(±)-kijanolide (**23**) has been synthesized via aldol reaction of spirotetronate **3** with octahydronaphthalene aldehyde **4** and subsequent macrocyclization of the resulting product.

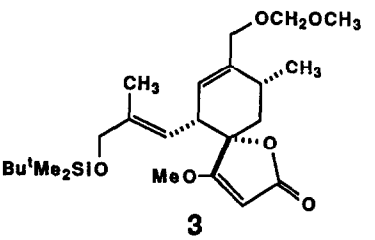
Kijanolide (**1**) and tetronolide (**2**), the aglycons of novel macrocyclic antitumor antibiotics kijanimicin[1a] and tetrocarcins,[1b] have attracted considerable synthetic attention since their discovery in 1980. To date considerable efforts have been devoted to synthesis of the two bridging units, spirotetronic acid and octahydronaphthalene systems.[2,3] We now report the synthesis of 28,29-bisnorkijanolide (kijanolide numbering) via assemblage of appropriately functionalized top-half **3** and bottom-half **4**.[4]



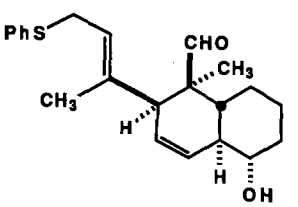

**1**




**2**




**3**

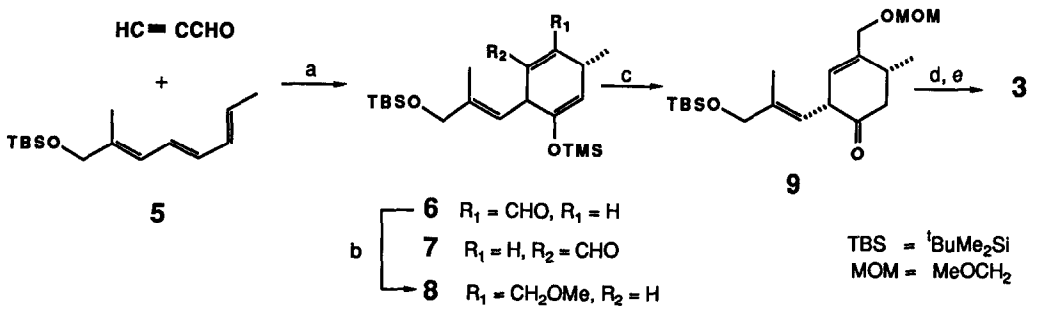



**4**

The required tetronate **3** was synthesized (Scheme 1) according to the methodology previously reported by us[2a] and with significant improvements in some key steps. Thus, it has been found that Diels-Alder reaction between propynal and siloxytriene **5**[5] proceeds in highly regioselective manner in the presence of $Yb(fod)_3$ providing a 20:1 ratio of **6** and **7** with 5 mol% of the lanthanide reagent (68% chromatographed yield).[6] This remarkable reverssal in regiochemistry from uncatalyzed reaction (**6**/**7** = 1:1.7)[2a] would be attributed to a steric hindrance in the transition state leading to undesired isomer **7** due to coordination of the dienophile with the bulky lanthanide complex. Next, selective hydrolysis of the enol silyl ether of intermediate **8** could be most nicely achieved by treatment with $Et_3N$-HF[7] for a short time giving over 90% yield of ketone **9**. This ketone is quite sensitive to epimerization as expected, and therefore it was

subjected immediately after isolation to two-step annulation involving addition of dichlorocerium methoxycarbonylacetylide and MeONa-catalyzed lactonization to afforded spirotetronate **3** in 43% overall yield from **6**.

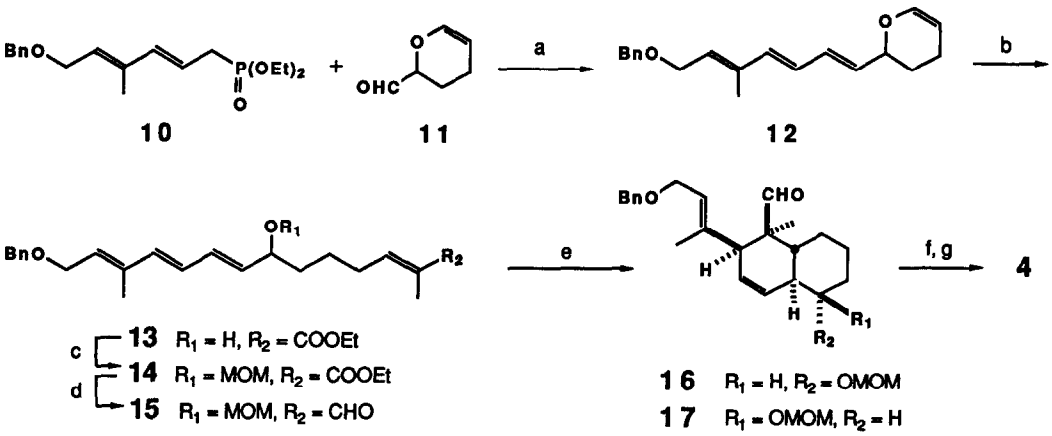
Scheme 1[a]




[a](a) $Yb(fod)_3$ (5 mol%), $Cl_2C{=}CHCl$, 60 °C (68%, **6**/**7** = 20:1); (b) i-$Bu_2AlH$, $Et_2O$, 0 °C, 15 min (82%), then $MeOCH_2Cl$, i-$Pr_2NEt$, $CH_2Cl_2$, RT, 2.5 h (95%); (c) $Et_3N$-HF (3 equiv), THF, 0 °C, 5 min; (d) $Cl_2CeC{=}CCOOMe$ (5 equiv), THF, -100 to -45 °C, 75 min (73% from **8**); (e) 1M MeONa in MeOH (10 equiv), reflux, 1.5 h, then t-$BuMe_2SiCl$, imidazole, DMF, RT, 15 min (76%).

Hydronaphthalene **4** was synthesized by utilizing Lewis acid catalyzed intramolecular Diels-Alder reaction[8] of tetraenal **15**, which was prepared from acrolein dimer (**11**) via a five-step sequence (Scheme 2) involving Horner-Emmons reaction with phosphonate **10**[3b] and chain elongation of the resulting triene **12** by Wittig reaction with $Ph_3P{=}CHCOOEt$. Cycloaddition of **15** in the presence of $Me_2AlCl$ produced trans-octalin **16** (30%) and **17** (28%) as major products. The desired isomer **16** was subjected to debenzylation by a catalytic transfer hydrogenation,[9] and the liberated hydroxyl was replaced with phenylthio group by the method of Hata[10] to afford **4**.

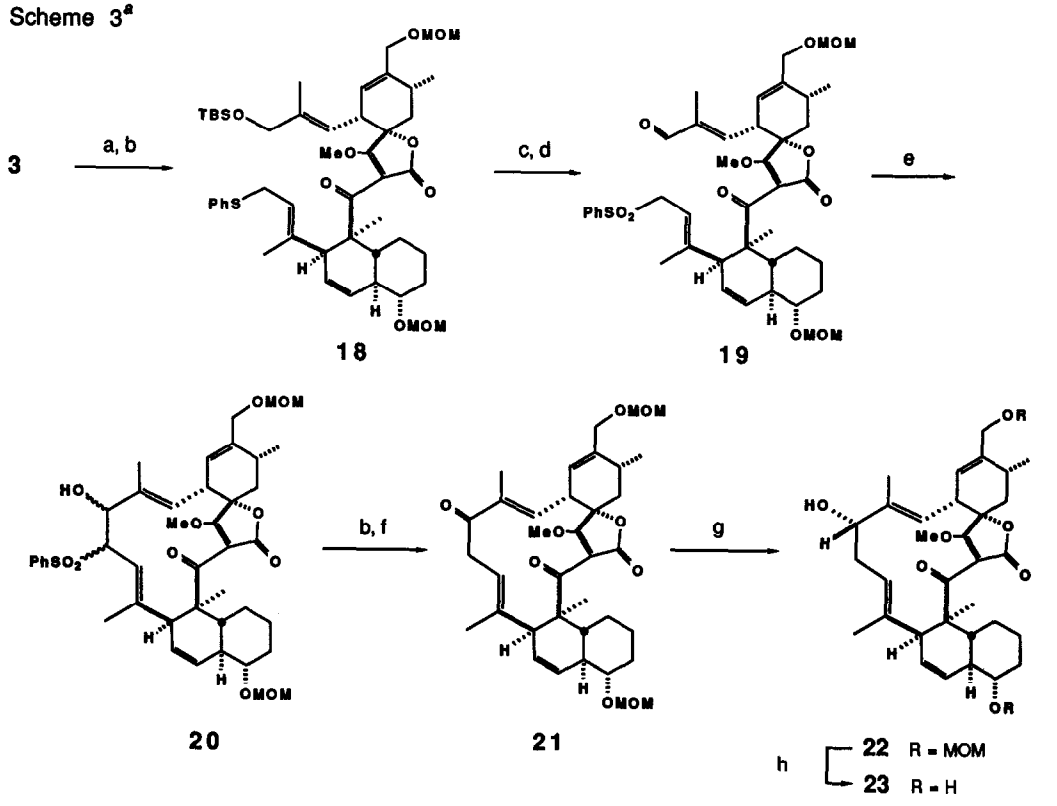
Scheme 2[a]




[a](a) t-BuOK, THF, -70 °C (62%); (b) 10% HCl-THF (1:4.5), RT, 40 min, then $Ph_3P{=}COOEt$, MeCN, reflux, 1 h; (c) $MeOCH_2Cl$, i-$Pr_2NEt$, $CH_2Cl_2$, RT, 2.5 h (91%); (d) Dibal-H, $Et_2O$, -80 to 0 °C, then PCC, molelcular sieves 4Å, Celite, $CH_2Cl_2$, RT, 40 min (59%); (e) $Me_2AlCl$ (1 equiv), $CH_2Cl_2$, -80 to -20 °C, 3 h, then chromatographic separation (**16**, 30%; **17**, 28%); (f) cyclohexene, $Pd(OH)_2/C$, EtOH, reflux, 1 h (61%); (g) $Ph_2S_2$, n-$Bu_3P$, pyridine, RT, 30 min (72%).

Formation of the macrocyclic structure was commenced with an aldol reaction between **3** and **4** (Scheme 3). Tetronate **3** was first subjected to α-lithiation with 2,4,6-trimethylphenyllithium in the presence of LiBr (bromomesitylene + t-BuLi),[11] then allowed to react with **4**. The resulting carbinol product (90% yield, 66% conversion) was subjected to Swern oxidation using trifluoroacetic anhydride[12] and DMSO to give a ca. 1:1 mixture of diastereomeric acyltetronates. The more polar isomer isolated in 39% yield was later assigned to **18** on the basis of the result in cyclization experiments (vide infra). Compound **18** was transformed into aldehyde-sulfone **19**, mp 178-80 °C, by three-step sequence in high yield. Treatment of **19** with t-$C_5H_{11}ONa$ in benzene at room temperature produced 13-membered β-hydroxysulfone **20** in 82% yield. On the other hand, the diastereomer of **19**, which has opposite configurations of all stereocenters in the octalin system, was largely recovered unchanged under the same conditions. This failure in macrocyclization is verified by a severe steric hindrance in the transition state of the internal aldol reaction as examined with molecular models. Compound **20** was transformed into 13-membered ketone **21**, mp 199-201 °C, by Swern oxidation[12] (95%) followed by Al-Hg reduction[13] of the resulting α-ketosulfone (71%). The ketone carbonyl in **21** was stereoselectively

Scheme 3[a]




[a](a) mesityllithium, LiBr, THF, -78 °C, 2.5 h, then **4** -78 °C (50 min) to -60 °C over 30 min (90%); (b) TFAA, DMSO, $CH_2Cl_2$, -78 °C, 1 h, then $Et_3N$, to -30 °C (39%); (c) 0.2% HF-MeCN, RT, 1 h, then active $MnO_2$, $CH_2Cl_2$, RT, 4 h; (d) MCPBA, $CH_2Cl_2$, 0 °C, 30 min (82% from **18**); (e) Na t-amylate (1 equiv), benzene, RT, 10 min (82%); (f) Al-Hg, THF-$H_2O$, 3.5 h (71%); (g) LiB(sec-Bu)$_3$H (1 equiv), THF, -80 °C, 5 min (93%); (h) $LiBF_4$ (10 equiv), MeCN-$H_2O$, reflux, 1 h (56%).

reduced with $LiB(sec\text{-}Bu)_3H$ to afford axial alcohol **22**, mp 200-201 °C, in 93% yield. The stereochemistry was determined by comparison of $^1H$-NMR spectra of **22**[14] and 26,32-di-O-methyl kijanolide.[1a] Both are very similar in terms of the chemical shifts and coupling constants. Finally, the MOM protecting groups in **22** was removed by treatment with $LiBF_4$ in refluxing acetonitrile[15] to provide **23**, mp 273-5 °C, in 56% yield.

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14. $^1H$-NMR data of **22** (400 MHz, $CDCl_3$, J in Hz): δ 0.82-0.96 (m, Hax-6), 1.20-1.25 (m, Heq-6 and Hax-8), 1.29 (d, J 7.3, 23-Me), 1.31 (s, 18-Me), 1.47 (s, 4-Me), 1.48 (s, 14-Me), 1.65-1.77 (m, Hax-7 and Heq-7), 1.77 (d, J 14.0, Heq-24), 1.86 (ddm, J 10.7, 10.7, H-10), 2.03 (dd, J 10.7, 10,7, H-5), 2.13-2.23 (m, Heq-8), 2.23 (dm, J ca. 16, H-16), 2.35 (dd, J 14.0, 7.0, Hax-24), 2.43 (ddd, J 16.8, 9.3, 3.1, H-16), 2.62 (qdm, J 7.3, 7.0, H-23), 3.31 (ddd, J 10.1, 10.1, 4.3, H-9), 3.36 (br d, J ca. 10, H-20), 3.38 (s, OMe), 3.42 (s, OMe), 3.97 (s, 26-OMe), 4.00 (br m, H-13), 4.15, 3.98 (each d, J ca. 12, H-32), 4.17 (br s, H-17), 4.66, 4.62 (each d, J 6.7. $OCH_2$), 4,81, 4.69 (each d, J 7.0, $OCH_2$). 5.14 (dm, J 9.8, H-19), 5.20 (dm, J 8.6 Hz, H-15), 5.48 (ddd, J 10.1, 5.0, 2.4, H-12), 5.50 ((br s, H-21), 6.04 (d, J 10.1, H-11).
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