This procedure enabled the introduction of bromomethyl functionality[12] in polystyrene resins if bromotrimethylsilane was used in place of chlorotrimethylsilane. A reaction time longer than that for chloromethylation was required, however, to obtain a satisfactory DF value.

(12) IR (KBr): ν_{C-Br} 1226 cm^{-1}.

Convergent Synthesis of Vineomycinone B2 Methyl Ester

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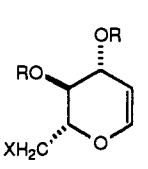
The vineomycines are antitumor antibiotics that were first isolated from a culture of *Streptomyces matensis* subsp. *vineus* which was active against Gram-positive bacteria and sarcoma 180 solid tumors in mice.[2,3] The characteristic features of vineomycinone B2 (**1**) are the *C*-glycosyl bond to the olivose derivative, and the alkyl chain bearing a stereogenic center on the opposite side of the molecule. The combination of the challenging structure and the interesting biological properties has motivated synthetic efforts.[4] To date two groups have disclosed total syntheses of **1**.[5,6] We report a triply convergent total synthesis of **1** which exploits methodology developed earlier in this group.[7]

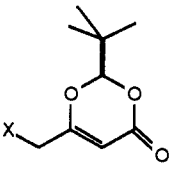
Vineomycinone B2 methyl ester is easily perceived as arising from the conjunction of three subunits: an olivose linked to anthrarufin through a *C*-glycosyl bond, and a chiral chain terminating in a methyl ester. Recognizing that each of the subunits can be prepared efficiently from commercially available materials simplifies the problem. This strategy has the advantage of a high degree of convergency. The distance between the asymmetric centers of the sugar and the chiral center on the side chain precludes any stereochemical communication between the two appendages.[5] The two homochiral fragments were prepared in high optical purity, and no separation of diastereoisomers was required.

The olivose derivative **5** was prepared from iodide **2**[8] in 95% overall yield (Chart I) by treatment with lithium aluminum hydride,[9,10] followed by protection of the hydroxyl groups.[11] Seebach's excellent method[12] was brought to bear on the synthesis of the side chain. Allylic bromination of **3** with *N*-bromosuccinimide and catalytic benzoyl peroxide in carbon tetrachloride, under irradiation by a floodlamp, gave a 40% yield of monobromide **6** accompanied by ca. 20% of the starting material and 15% of dibrominated product. The chromatographic separation of these materials, though tedious, was easily accomplished. Anthrarufin was converted in four steps to protected iodoanthracene **7** in 44% overall yield.[7]

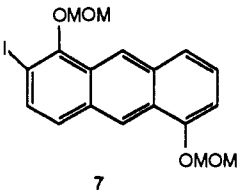
Chart I



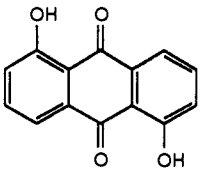
2: X = I; R = Ac
5: X = H; R = TBDMS



3: X = H
6: X = Br

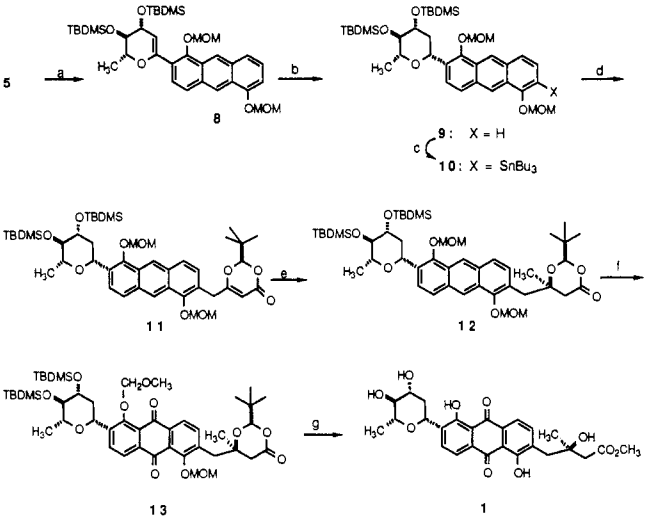


7



4

Scheme I[a]



[a] (a) (i) *t*-BuLi, pentane–THF, 0 °C; (ii) $ZnCl_2$, THF, 23 °C; (iii) **7**, $Pd(PPh_3)_2Cl_2$ + DIBAL-H, THF, 23 °C, 75%; (b) $NaBH_3CN$, HCl, EtOH, 88%; (c) *n*-BuLi, TMEDA, THF, 0 °C, then Bu_3SnCl, 90%; (d) **6**, $Pd_2(dba)_3{\cdot}CHCl_3$, PPh_3, THF, 70 °C, 45–50%; (e) $(CH_3)_2CuLi$, ether, 60%; (f) bis(pyridine) silver permanganate, silica gel, CH_2Cl_2; (g) HCl, MeOH, 23 °C, 35% overall from **12**.

The assembly of **1** was accomplished according to Scheme I. The aryl *C*-glycosyl bond was formed first: the lithio anion which was derived from **5**[13] was treated with a solution of 2.0 equiv of anhydrous zinc chloride in tetrahydrofuran (THF) at 0 °C and was stirred at 23 °C for 1 h. The organozinc reagent was transferred to a solution of 0.66 equiv of iodoanthracene **7** and palladium (0) catalyst. The catalyst was generated from 0.10 equiv of $(PPh_3)_2PdCl_2$ and 0.30 equiv of diisobutylaluminum hydride in THF at 23 °C. These reaction conditions were described originally by Negishi.[14,15] *C*-Glycosyl anthracene **8**[16] was obtained as a clear oil in 75% yield after 12 h at 23 °C. The next task was to reduce the styryl double bond stereospecifically. This step provided an unexpected challenge. Catalytic hydrogenation either failed to reduce **8** or led to reaction mixtures in which both the central ring of the anthracene and the styrene double bond

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had been saturated, accompanied by partial reductive cleavage of the benzylic C–O bond of the sugar. Metallic ytterbium[17] led to a very clean and completely selective saturation of the central anthracene ring. One of the factors that complicated the reduction was the hydrolytic lability of the styryl enol ether double bond. This reactivity suggested the reduction conditions that were ultimately successful. Clean formation of **9**[16] took place in 88% yield by careful alternate addition of methanolic HCl and $NaBH_3CN$ to a solution of **8** in ethanol at 25 °C.[18] The pH of the mixture was kept at approximately 4.5 by monitoring the color of bromocresol green which had been added to the reaction mixture. Under these carefully controlled conditions the reaction was clean and did not result in loss of any of the protecting groups. The stereochemistry of the newly generated stereogenic center was confirmed by observing the NOE between the axial benzylic methine hydrogen and the methine proton adjacent to the methyl on the sugar.

Attention was focused on the introduction of the five-carbon chain. Several general approaches to this problem were evaluated; the higher degree of convergency that was attained with **6** made it the reagent of choice. Treatment of an equimolar mixture of **6** and stannylanthracene **10** with 0.06 equiv of $Pd_2(dba)_3{\cdot}CHCl_3$ and 0.12 equiv of triphenylphosphine[19] in THF at 70 °C for 48 h, with scrupulous exclusion of air, afforded 45–50% of **11**[16] along with ca. 15% of **9**. The stereogenic center on the side chain was introduced in good yield by addition of lithium dimethylcuprate to **11**.[12] The product (**12**;[16] 60% yield) was obtained as a single diastereoisomer, as determined by ^1H NMR at 300 MHz. This result was confirmed by ^1H NMR at 500 MHz on the quinone. The conversion of **12** to vineomycinone B2 methyl ester was accomplished in two steps. Oxidation of **12** with bis(pyridine) silver permanganate[20] in dichloromethane afforded anthraquinone **13**. All protecting groups were removed in a single operation by exposure of **13** to HCl in anhydrous methanol at 23 °C for 4 h to afford methyl ester **1** in 35% overall yield as a single isomer.[21] The synthetic material was identical with an authentic sample by spectroscopic comparison.[22]

To summarize, a general methodology for appending *C*-glycosyl units onto anthraquinones has been developed and has been used for a highly convergent synthesis of **1**. The ready availability of hydroxyanthraquinones suggests that this methodology is suitable for the synthesis of other, more complex members of this class of natural products.

Acknowledgment is made to the NIH (GM-38598) for their support. We thank Dr. Javid H. Zaidi for early contributions to this project and Dr. J. R. Falck for generously supplying us with spectra of the final product.

Supplementary Material Available: Reproductions of NMR and IR spectra for **1** (13 pages). Ordering information is given on any current masthead page.

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(22) **1**: IR (neat) 3400 (br), 2930, 2860, 1735, 1630, 1440, 1375, 1260, 990, 970 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 13.22 (s, 1 H), 13.10 (s, 1 H), 7.92 (d, J = 8.0 Hz, 1 H), 7.86 (d, J = 7.7 Hz, 1 H), 7.81 (d, J = 8.0 Hz, 1 H), 7.70 (d, J = 7.7 Hz, 1 H), 4.95 (dd, J = 11.0, 2.0 Hz, 1 H), 3.86 (ddd, J = 11.1, 8.8, 5.0 Hz, 1 H), 3.71 (s, 3 H), 3.54 (dq, J = 8.8, 6.1 Hz, 1 H), 3.22 (dd, J = 9.2, 8.8 Hz, 1 H), 3.11 (d, J = 13.6 Hz, 1 H), 3.03 (d, J = 13.6 Hz, 1 H), 2.58 (d, J = 16.1 Hz, 1 H), 2.55 (d, J = 16.1 Hz, 1 H), 2.53 (ddd, J = 12.6, 5.0, 2.0 Hz, 1 H), 1.49 (ddd, J = 12.6, 11.1, 11.0 Hz, 1 H), 1.42 (d, J = 6.1 Hz, 3 H), 1.30 (s, 3 H); mass spectrum (20 eV) *m/e* (no M^+), 384 (57), 281 (20), 280 (18), 207 (100), 117 (14), 111 (12), 109 (13), 99 (31), 97 (28); exact mass calcd for $C_{21}H_{20}O_7$ 384.1095, found 384.1152.

Highly Diastereoselective Reactions of Ytterbium-Mediated Alkynyllithium and Alkynylmagnesium Reagents with Chiral 2-Acyl-1,3-oxathianes: Reversal of Diastereoselectivity

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Eliel has devised a chiral 2-acyl-1,3-oxathiane **1** employing (+)-pulegone as a chiral auxiliary and has utilized it for the synthesis of optically active tertiary alcohols **2** bearing a carbonyl function at the α-position.[1] The enantiomeric purity of **2** rests upon the diastereoselectivity of nucleophilic addition of a Grignard reagent to acyloxathiane **1** to give **3** according to Cram's chelate model **4**[1] (Scheme I).

Although this process is versatile for the synthesis of various optically active tertiary alcohols, only one enantiomer can be derived from one substrate **1**. The other enantiomer **5** could be obtained by means of an opposite face selective attack of an organometallic species giving diastereomeric **6** according to a chelate model **7**. We have observed that use of lanthanide trichlorides to mediate addition of organolithium or -magnesium species can realize the above expectation. Precedence for a lanthanide-mediated reaction of alkyllithium and -magnesium reagents with carbonyl compounds comes from the work of Imamoto, who has disclosed extremely high nucleophilicity of alkylcerium and other organolanthanide reagents.[2,3] Since highly reactive organocerium reagents have been utilized in the synthesis of chiral amines from SAMP-hydrazones, both an alkyllithium and an alkylcerium reagent show the same diastereoselectivity.[4] Opposite diastereoselectivity caused by lanthanide reagents has been little studied.[5,6] This paper describes a reaction with extremely high diastereocontrol induced by ytterbium.

The reaction of 2-acyl-1,3-oxathiane **1** (R = Me, Et, Ph) with 1-pentynylcerium dichloride ($R'Li + CeCl_3 \rightarrow R'CeCl_2$; R′ = $CH_3CH_2CH_2C{\equiv}C$) gives diastereomer **6** predominantly, in contrast to the selective formation of **3** by R′Li.[7] The reaction with $R'YbCl_2$ ($R'Li + YbCl_3$) shows better diastereoselectivity to give **6** exclusively;[8] $R'YCl_2$ ($R'Li + YCl_3$) behaves similarly. Results are summarized in Table I.

The reaction of **1** with 1-pentynylmagnesium bromide (R′MgBr) gives mainly **3**. Ytterbium-mediated reaction gives

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(7) The diastereomer ratio (**3**/**6**) was determined by ^1H NMR analysis. The proton signal at C(2) of **3** (R = Me) appears at δ 4.96, and the corresponding proton of **6** (R = Me) is observed at δ 4.82. The intensity ratio of the two signals corresponds to the molar ratio of **3** and **6**. Moreover, optical rotations of the hydrolyzed products confirm the stereochemistry: Hydrolysis and successive reduction of **3** (R = Me; 34% de) gave (*R*)-2-methyl-3-pentyne-1,2-diol ($[\alpha]^{21}_D$ +0.33 ± 0.04°) whereas the same treatment of **6** (R = Me; 93% de) afforded the *S* isomer ($[\alpha]^{21}_D$ −0.75 ± 0.05°).

(8) $R'YbCl_2$ is prepared by the reaction of R′Li with $YbCl_3$. As the bond length of Yb–C is shorter than that of Ce–C, organoytterbium species make the chelate structure at the transition state compact, which may contribute to the high diastereoselectivity.

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