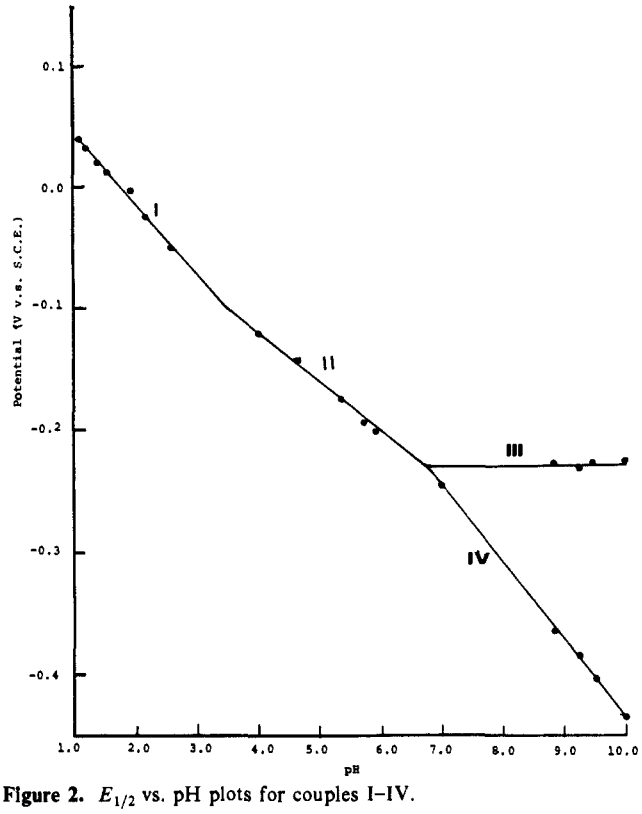

Figure 2. $E_{1/2}$ vs. pH plots for couples I–IV.

Band II may be better considered to arise from the $^1A_{1g} \rightarrow E_g(^3E_g)$ transition, and the $E_g(^3E_g)$ level acquires singlet character by mixing with the $E_g(^1E_g)$ state. Very weak absorptions are also observed in the low-energy tail of band II that are possibly attributed to the transitions from ground state to the $B_{1g}(^3E_g)$ and $B_{2g}(^3E_g)$ levels. The ν(Os=O) stretcing frequency in the ^1E_g and ^3E_g excited state levels (~700–730 cm^{-1}), estimated from the vibrational spacing in band I and II, is substantially smaller than that in the $^1A_{1g}$ ground state (870 cm^{-1}), *indicating the weakening of the Os—O bond upon light excitation.*

In aqueous medium (pH 1–6), complex B gave a cyclic voltammogram that showed a reversible three-electron redox wave (*n = 3.00 ± 0.10 by coulometry*). At pH 1.1, the $E_{1/2}$ and ΔE_p (peak-to-peak separation) values for this couple are 0.035 V vs. SCE and 20–30 mV, respectively (scan rate = 50–200 mV/s). The $E_{1/2}$ vs. pH plot is linear (Figure 2) with slopes of −60 and −42 mV at pH ranges of 1–3.2 and 3.2–6.5, respectively. The results indicate that the electrode reaction is, at pH 1–3.2,

$$trans\text{-}[Os^{VI}(TMC)O_2]^{2+} + 3e^- + 3H^+ \rightarrow [Os^{III}(TMC)(OH_2)(OH)]^{2+} \quad (I)$$

at pH 3.2–6

$$trans\text{-}[Os^{VI}(TMC)O_2]^{2+} + 3e^- + 2H^+ \rightarrow trans\text{-}[Os^{III}(TMC)(OH)_2]^{+} \quad (II)$$

$trans$-$[Os^{III}(TMC)(OH_2)(OH)]^{2+}$ (C) has been characterized spectroscopically (λ_{max} ~280 nm) and this can be quantitatively reoxidized (electrochemically or aerially) back to B. The reversibility of couple I is in contrast to the observed electrochemical behavior of $trans$-$[Os^{VI}(en)_2O_2]^{2+}$ (en = 1,2-diaminoethane) and $trans$-$[Os^{VI}(NH_3)_4O_2]^{2+}$. Both of their cyclic voltammograms display irreversible reduction waves.[6] At pH >7, couple I or II splits into two waves corresponding to the following electrode reactions:

$$trans\text{-}[Os^{VI}(TMC)O_2]^{2+} + e^- \rightarrow trans\text{-}[Os^{V}(TMC)O_2]^{+} \quad (III)$$

$$trans\text{-}[Os^{V}(TMC)O_2]^{2+} + 2e^- + 2H^+ \rightarrow trans\text{-}[Os^{III}(TMC)(OH)_2]^{+} \quad (IV)$$

(6) Che, C. M.; Cheng, W. K., unpublished results.

As expected, *the $E_{1/2}$ value for couple III (−0.225 V vs. SCE) is pH-independent.* For couple IV, the linear $E_{1/2}$ vs. pH plot with slop of −60 mV/pH unit is obtained in agreement with a *two-proton two-electron transfer process* (Figure 2). The direct two-electron reduction from Os(V) to Os(III) indicates that the intermediate Os(IV) oxo species is unstable and undergoes rapid disproportionation in water. This is in contrast to the chemistry of $[Ru^{IV}(TMC)O(OH_2)]^{2+}$ that has been found to be stable in aqueous medium.[1c,7]

The electrochemistry found for B is similar to that of Meyer's work on $[Os^{VI}(trpy)(O)_2(OH)]^+$ except that the latter system is more oxidizing than the former. We note that at pH 1.1, and irreversible reduction wave attributed to the reduction of Os(III) to Os(II) is observed at ~−0.64 V vs. SCE.

Acknowledgment. We acknowledge financial support from the Committee of Conference and Research Grants of University of Hong Kong; Wing-King Cheng is a Croucher Foundation Studentship holder (1984–1987).

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Stereoselective Synthesis of Pikronolide, the Aglycon of the 14-Membered Ring Macrolide Pikromycin, from D-Glucose.[1] Role of MPM and DMPM Protection

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Pikromycin is well-known as the first macrolide antibiotic isolated from an *Actinomyces* by Brockmann and Henkel more than 35 years ago.[2] The total synthesis of its aglycon pikronolide (**1**)[3] as well as pikromycin itself, however, still remains unfinished, mainly because the construction of the β-hydroxy ketone system at the C-3–C-5 of **1** is extremely difficult.[4] Even under mild hydrolytic conditions, pikromycin readily gave the 4,5-anhydro compound kromycin.[4b,5] For the total synthesis of **1** it is very important to overcome such a side reaction, and hence selection of appropriate hydroxyl protecting groups undoubtedly holds the key to success.[4] Recently, we reported highly stereoselective syntheses of methynolide[6] and tylonolide[1] from D-glucose using some stereocontrolled reactions and selective deprotections[7] of benzyl-type [Bn (benzyl),[8] MPM (4-methoxybenzyl),[9] and DMPM (3,4-dimethoxybenzyl)[10]] protecting groups for hydroxy functions at crucial synthetic steps.

(1) Chiral Synthesis of Polyketide-Derived Natural Products. 10. For part 9, see: Tanaka, T.; Oikawa, Y.; Hamada, T.; Yonemitsu, O. *Tetrahedron Lett.*, in press.
(2) Brockmann, H.; Henkel, W. *Naturwissenschaften* **1950**, *37*, 138; *Chem. Ber.* **1951**, *84*, 284.
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(8) (a) Oikawa, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1985**, *26*, 1541. (b) Oikawa, Y.; Tanaka, T.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1984**, *25*, 5397.
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(10) Oikawa, Y.; Tanaka, T.; Horita, K.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1984**, *25*, 5393.

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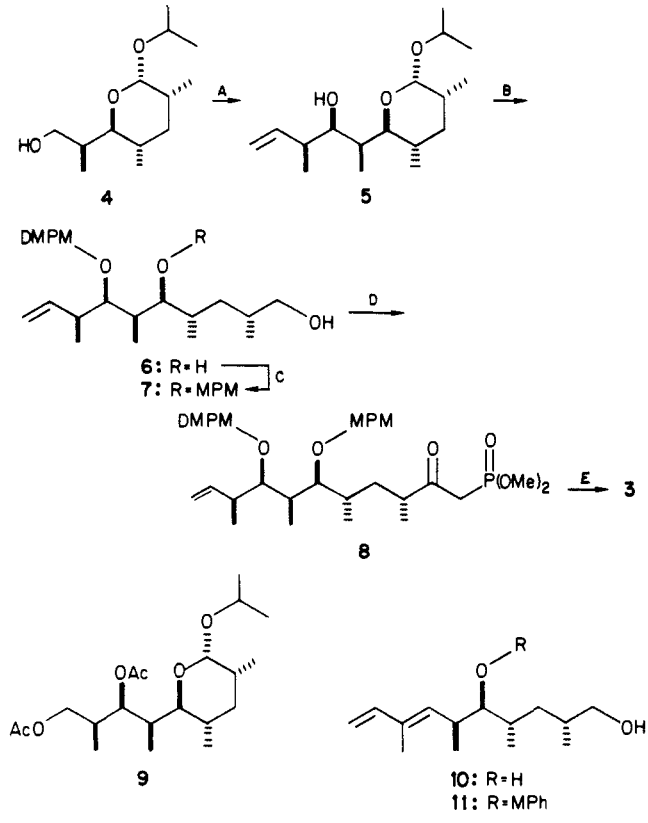
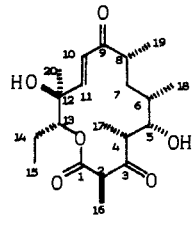
Scheme I[a]

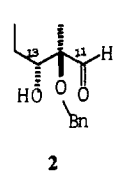


[a](A) (1) Me_2SO, $(COCl)_2$, Et_3N, CH_2Cl_2 (95%); (2) MeCH=$CHCH_2SnBu_3$ (2.4 equiv), BF_3–Et_2O (2.2 equiv), CH_2Cl_2, −90 °C (94%). (B) (1) DMPMCl (8 equiv), $KCH_2S(O)Me$ (10 equiv), room temperature (95%); (2) 1 N HCl, THF, 50 °C, 12 h; (3) $Ca(BH_4)_2$, EtOH, room temperature, 3 h (91%, overall). (C) (1) $Me_2C(OMe)_2$, CSA, room temperature, 0.5 h; (2) MPMCl (12 equiv), $KCH_2S(O)Me$ (10 equiv), Me_2SO, room temperature; (3) 0.1 N HCl (60%, overall). (D) (1) Me_2SO, $(COCl)_2$, Et_3N, CH_2Cl_2 (95%); (2) $MeP(O)(OMe)_2$, *n*-BuLi, THF, −80 °C (91%); (3) PDC, DMF (87%). (E) (1) OsO_4, NMO, MeCOMe–H_2O (74%); (2) $NaIO_4$ (100%); (3) CrO_3, H_2SO_4, MeCOMe, −20 °C, 5 min (72%).

We report here the first total synthesis of **1**, in which the selective removal of DMPM, MPM, and Bn protecting groups acted again a decisive role. Compounds **2** and **3** seemed to be the most promising intermediates in our synthetic methodology.[1,6] Compound **2** was synthesized quite easily from D-glucose.[6] In the synthesis of **3**, the selection of protecting groups was extremely important, and we chose DMPM[10] and MPM[9] protections for the C-3 and C-5 hydroxy groups, respectively.



1



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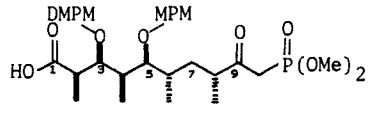
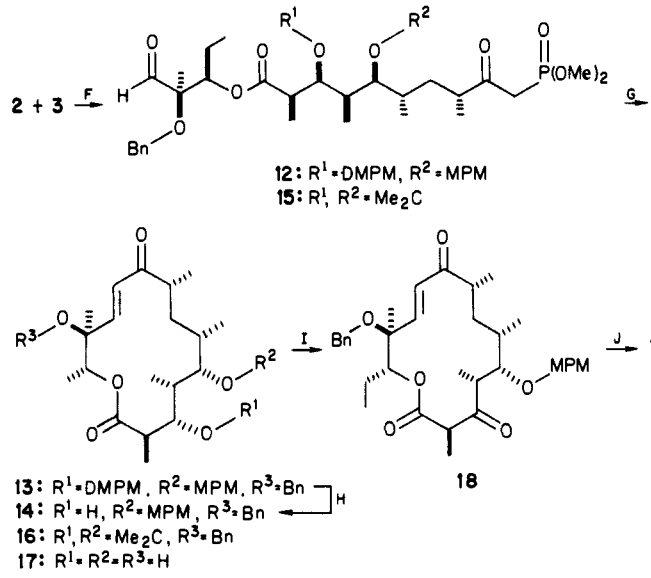


3

Scheme II[a]



[a](F) 2,4,6-$Cl_3C_6H_2COCl$, NEt_3, THF, DMAP, C_6H_5Me, room temperature, 1 h (60%). (G) K_2CO_3 (6 equiv), 18-crown-6 (12 equiv), C_6H_5Me, 80 °C, 1 h (89%). (H) DDQ (1 equiv), C_6H_5Me–H_2O (20:1), 0 °C, 4.5 h (42%). (I) Me_2SO, $(COCl)_2$, Et_3N, CH_2Cl_2, −50 °C (91%). (J) DDQ (10 equiv), CH_2Cl_2–H_2O (20:1), room temperature, 16 h (81%).

Swern oxidation[11] of the alcohol **4**[6] readily gave the aldehyde, which was treated with excess crotyltributylstannane.[12] The erythro-selective Cram addition (stereoselectivity >30:1) took place quite smoothly to give **5**, $[\alpha]_D^{21}$ +112°,[13] which has all the chiral centers required for **3**. The configuration of **5** was confirmed after conversion into **9**, which was also derived from **4** via the Sharpless asymmetric epoxidation.[14]

The DMPM protection[10] of the hydroxy group of **5** was rather difficult, but the reverse addition (see below) of DMPM chloride and a base gave the DMPM ether, which was converted to the open-chain diol **6**. After methoxyisopropyl protection of the primary alcohol of **6**, the sterically crowded secondary alcohol was treated with MPM chloride in the usual way,[9] but no reaction occurred. Treatment with a large excess of NaH and MPM chloride caused the formation of dienes **10** and **11**. However, when the chloride was added first and then dimsylpotassium (reverse addition), the MPM protection took place quite rapidly to give the oily product, which was hydrolyzed to give the expected product **7**, $[\alpha]_D^{23.5}$ −11.8°. Swern oxidation of **7** gave the aldehyde, which was treated with a phosphonate[15] followed by PDC oxidation[16] to give the keto phosphonate **8**, $[\alpha]_D^{25}$ +15°. Oxidation of **8** with OsO_4 followed by cleavage with $NaIO_4$ gave the aldehyde, which was oxidized with the Jones reagent to give **3** (Scheme I).

Yamaguchi's esterification[17] between **2** and **3** gave readily the ester **12**, $[\alpha]_D^{12}$ +20.6°, which was subjected to Nicolaou's macrocyclization.[18] The reaction was completed within only 1 h, and the 14-membered enone **13**, $[\alpha]_D^{16.5}$ −4.2°, was isolated in

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excellent yield.[19] Deprotection of DMPM groups with DDQ in the presence of MPM protections usually proceeded with excellent selectivity,[1,7,10] but unfortunately **13** gave only unsatisfactory results (3.0–4.3:1 selectivity).[20] The C-3 hydroxy compound **14**, $[\alpha]_D^{13.5}$ −2.6°, was readily converted to the C-3 keto compound **18** by Swern oxidation. The final conversion of **18** into **1** proceeded efficiently without any detectable formation of kromycin; namely, when **18** was retreated with a large excess of DDQ at room temperature, rapid deprotection of the MPM group occurred within 5 min and then the Bn group was gradually removed to give pikronolide (**1**)[21] in high yield[22] (Scheme II).

Acknowledgment. We are grateful to Professor M. Yamaguchi for providing his reagent and helpful discussions. We are indebted to N. Kakusawa for technical assistance.

Supplementary Material Available: $[\alpha]_D$, ^1H NMR, mass, and IR data for **1**, **3**, **5–9**, **12–14**, **18** (6 pages). Ordering information is given on any current masthead page.

(19) The ester **15**, synthesized similarly via **5**, was also subjected to the macrocyclization.[18] The reaction required a rather long time (20 h) and the 14-membered ring enone (**16**) was isolated in moderate yield (66%).

(20) When the *O*-acetate of **7** was treated with DDQ (1.2 equiv) in toluene–H_2O (20:1) at −10 to −5 °C for 5.5 h, deprotection of the DMPM group proceeded with excellent selectivity (22:1).

(21) Mp 140–141.5 °C (*n*-hexane–EtOAc), $[\alpha]_D^{18.5}$ +66° (*c* 0.187, MeOH) [lit.[3b] mp 139 °C, $[\alpha]_D$ +70°(MeOH)].

(22) So far, attempts to obtain **1** by oxidation of **17** derived from **16** have been unsuccessful; i.e., Swern oxidation gave only the C-5 keto compound, which was also obtained very slowly by $RuCl_2(PPh_3)_3$ oxidation.[23]

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Enantioselective Total Synthesis of (+)-Negamycin and (−)-Epinegamycin by an Asymmetric 1,3-Dipolar Cycloaddition

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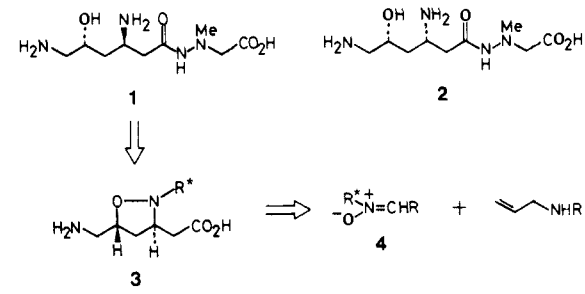
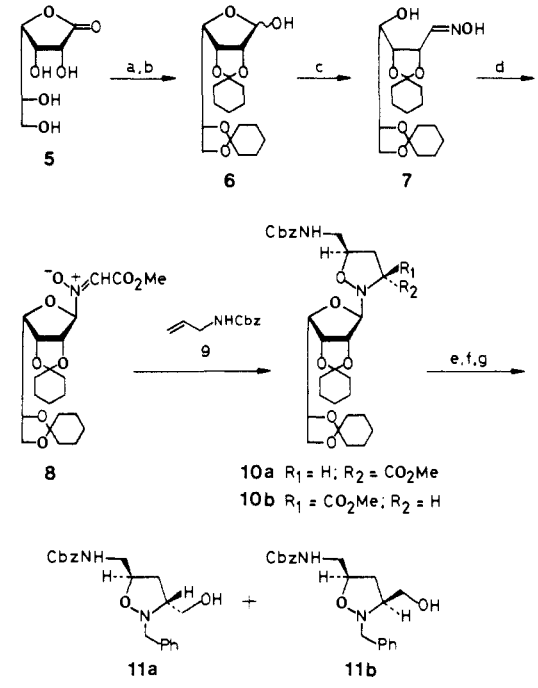
Negamycin (**1**),[1] a structurally unique peptide-like natural product which exhibits striking activity against Gram-negative bacteria, including *Pseudomonas aerginosa*,[2] has attracted considerable synthetic interest[3,4] since its structure elucidation in 1971.[5] Herein we report an efficient chiral entry into (+)-negamycin in natural form (**1**) and the unnatural isomer (−)-3-epinegamycin (**2**). Our strategy for the synthesis of (+)-**1** is outlined retrosynthetically in Scheme I. The key step envisioned would involve a highly enantioselective 1,3-dipolar cycloaddition of an appropriate chiral nitrone[6] (**4**) to the allylamine. This cycloaddition would simultaneously create two new asymmetric centers adaptable to the 3*R*,5*R* stereochemistry of (+)-**1**. Our first objective was to develop a suitable, chiral nitrone and to demonstrate acceptable diastereoselection during the cycloaddition. Toward this end, we chose the carbohydrate as the chiral template (Schemes II).

Scheme I



Scheme II[a]



[a] (a) 1,1-Dimethoxycyclohexane, TsOH, benzene, reflux, 10 h; (b) DIBAL, toluene/THF (1:1), −78 °C, 1 h; (c) NH_2OH·HCl, py, room temperature, 2 h; (d) (**7** → **10**) methyl glyoxylate, **9**, toluene, reflux, 14 h; (e) 10% HCl/MeOH (3:8), 90 °C, 4 h; (f) $PhCH_2Br$, K_2CO_3, DMF, 50 °C, 1 h; (g) $LiAlH_4$, Et_2O, room temperature, 30 min.

D-Gulono-γ-lactone (**5**) was first converted to 2,3:5,6-di-*O*-cyclohexylidene-D-*gulo*-furanose (**6**), $[\alpha]^{20}_D$ −12.3° ($CHCl_3$), by treatment with 1,1-dimethoxycyclohexane (benzene, TsOH) followed by DIBAL reduction in 88% yield from **5**. Compound **6** was converted quantitatively to the oxime **7**, $[\alpha]^{20}_D$ +45.5° ($CHCl_3$). The nitrone **8**, generated in situ by the reaction of **7** with methyl glyoxylate probably as a mixture of *E* and *Z* isomers, was allowed to react with the allylamine derivative **9** (toluene, reflux, 14 h) to produce an inseparable mixture of the 3*R*,5*R*-trans (**10a**) and 3*S*,5*R*-cis (**10b**) adducts in 84% yield. After removal of the D-gulosyl auxiliary group by acid hydrolysis, the product was subjected to N-benzylation ($PhCH_2Br$, K_2CO_3, DMF) followed by $LiAlH_4$ reduction to provide the chromatographically separable (silica gel, 50:1 $CHCl_3$/MeOH) trans alcohol **11a**, mp 99–100 °C, $[\alpha]^{25}_D$ −16.7° ($CHCl_3$), and cis alcohol **11b**, $[\alpha]^{25}_D$ −29.0° ($CHCl_3$), in a ratio of 2:3 (55% overall yield from **10a** + **10b**). Thus utilization of the D-gulosyl chiral template in this process resulted in a highly stereobiased synthesis of **11a** and **11b**

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