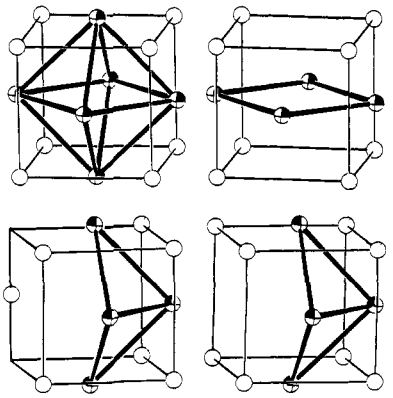

Figure 3. Cube–octahedral relationship found in $Mo_6(\mu_3\text{-}X)_8^{4+}$ compounds (top left); Mo_4O_8 moiety in $Mo_4Cl_4(O\text{-}i\text{-}Pr)_8$ (top right); Mo_4O_8 moiety in $Mo_4Br_4(O\text{-}i\text{-}Pr)_8$ (bottom right); $Mo_4I_7^{2+}$ moiety in $Mo_4I_{11}^{2-}$ (bottom left).

In the crystal,[9] the $Mo_4Br_4(O\text{-}i\text{-}Pr)_8$ molecule has C_{2v} symmetry. The four molybdenum atoms form a "butterfly" or opened tetrahedron with five short Mo–Mo distances, 2.50 Å (averaged), and one long Mo–Mo distance, 3.287 (1) Å. A view of the molecule is given in Figure 2. In contrast to the $Mo_4Cl_4(O\text{-}i\text{-}Pr)_8$ molecule, which has eight equivalent μ_2-O-*i*-Pr ligands, there are a pair of symmetry related terminal O-*i*-Pr ligands, a pair of symmetry related μ_3-O-*i*-Pr ligands, and four equivalent μ_2-O-*i*-Pr ligands. The four bromide ligands are terminal. The five short Mo–Mo distances, 2.50 Å (averaged), are longer than the four equivalent Mo–Mo distances, 2.387 (1) Å, in $Mo_4Cl_4(O\text{-}i\text{-}Pr)_8$.

The structures of $Mo_4Cl_4(O\text{-}i\text{-}Pr)_8$ and $Mo_4Br_4(O\text{-}i\text{-}Pr)_8$ are, however, closely related to one another. Both contain Mo_4 units within a cube of O-*i*-Pr ligands and as such may be viewed as fragments of the well-known $Mo_6(\mu_3\text{-}X)_8^{4+}$ unit.[10] The $Mo_4Br_4(O\text{-}i\text{-}Pr)_8$ structure may also be compared with the $Mo_4I_{11}^{2-}$ structure reported by McCarley et al.[11] The latter also contains a "butterfly" Mo_4 unit with five short Mo–Mo distances, 2.58 Å (averaged), and one long Mo–Mo distance, 3.035 (5) Å. This too may be viewed as a derivative of the $Mo_6(\mu_3\text{-}X)_8^{4+}$ unit: the central $Mo_4I_7^{2+}$ unit contains six I^- ligands at the corners of the cube, while the seventh bridges the two weakly bonded (nonbonded) molybdenum atoms (Mo–Mo = 3.035 (5) Å) at the midpoint of the edge of the idealized I_8 cube. These relationships to the $Mo_6(\mu_3\text{-}X)_8^{4+}$ unit are shown in Figure 3. In $Mo_4Cl_4(O\text{-}i\text{-}Pr)_8$, $Mo_4Br_4(O\text{-}i\text{-}Pr)_8$ and $Mo_4I_{11}^{2-}$, there are four Mo-halide bonds directed along lines radiating from the center of the idealized X_8 cube.

McCarley noted:[11] "In C_{2v} symmetry, the Mo–Mo bonding in $Mo_4I_{11}^{2-}$ can be described as $(3a_1 + a_2 + b_1 + b_2)_b^{12}(a_2 + b_1)^3$. The latter $a_2 + b_1$ orbitals involve mainly interactions at the distance 3.035 (5) Å between d orbitals lyings in planes perpendicular to the Mo(1)–Mo(2) axis. These orbitals should have neither strongly bonding or antibonding character." It seems that we have now verified this qualitative MO description, since the $Mo_4Br_4(O\text{-}i\text{-}Pr)_8$ molecule has only 12 electrons available for metal–metal bonding.

Finally, we noted that for the series of compounds of formula $Mo_4X_4(OR)_8$ we have found a bisphenoid of four molybdenum atoms with two localized Mo≡Mo bonds for X = F and R = *t*-Bu, and square Mo_4 unit with delocalized M–M bonds of order 1.5 for X = Cl and R = *i*-Pr, and a "butterfly" Mo_4 unit for X = Br and R = *i*-Pr, all of which readily accommodate 12 electrons in metal–metal bonds. Clearly for Mo≡Mo bonds, two plus two gives four, in more ways than one! Though to our knowledge there are no other square 12-electron M_4 cluster compounds, there are square $Cu(I)_4$ (d^{10}) compounds of formula $Cu_4(\mu\text{-}X)_4$.[12,13] Tetrahedral,[14] rectangular,[15] rhombohedral,[16] "butterfly",[11] and now square Mo_4 clusters are known.

Many questions are raised and further studies are in progress.[17]

Registry No. $Mo_4Cl_4(O\text{-}i\text{-}Pr)_8$, 80878-94-0; $Mo_4Br_4(O\text{-}i\text{-}Pr)_8$, 80878-95-1; $Mo_4Cl_3(O\text{-}i\text{-}Pr)_9$, 80890-28-4; $Mo_4Br_3(O\text{-}i\text{-}Pr)_9$, 80890-29-5; $Mo_2(O\text{-}i\text{-}Pr)_6$, 62521-20-4; CH_3COCl, 75-36-5; CH_3COBr, 506-96-7.

Supplementary Material Available: Listings of fractional coordinates and isotropic thermal parameters (2 pages). Ordering information is given on any current masthead page.

(9) Crystal data for $Mo_4Br_4(O\text{-}i\text{-}Pr)_8$ at −160 °C: space group $A2/a$, a = 20.042 (5) Å, b = 10.980 (2) Å, c = 18.602 (4) Å, β = 112.60 (1)°, Z = 4, d_c = 2.067 g cm^{-1}. Of the 3338 unique reflections collected with use of Mo Kα radiation, 6° ≤ 2θ ≤ 50°, the 2963 having $F > 2.33\sigma(F)$ were used in the full-matrix refinement. Final residuals are R_F = 0.0376 and R_{wF} = 0.0363.

(10) Schafer, H.; von Schnering, H. G. *Angew. Chem.* **1971**, *385*, 75. Guggenberger, L. J.; Sleight, A. W. *Inorg. Chem.* **1969**, *8*, 2041. Healy, P. C.; Kepert, D. L.; Taylor, D.; White, A. H. *J. Chem. Soc., Dalton Trans.* **1973**, 646.

(11) Stensrad, S.; Helland, B. J.; Babich, M. W.; Jacobson, R. A.; McCarley, R. E. *J. Am. Chem. Soc.* **1978**, *100*, 6257.

(12) X = CH_2SiMe_3: Jarvis, J. A. J.; Kilbourn, B. T.; Pearce, R.; Lappert, M. F. *J. Chem. Soc., Chem. Commun.* **1973**, 475.

(13) X = O-*t*-Bu: Greiser, T.; Weiss, E. *Chem. Ber.* **1976**, *109*, 3142.

(14) $Mo_4S_4X_4$ compounds (X = Cl, Br, I) contain a central Mo_4S_4 cube and a tetrahedral Mo_4 unit with Mo–Mo distances of 2.80 Å: Perrin, C.; Chevrel, R.; Sergent, M. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1975**, *280*, 949.

(15) $Mo_4Cl_8L_4$ (L = phosphine): ref 1a.

(16) $Ba_{1.13}Mo_8O_{16}$: ref 1b.

(17) We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Science Foundation, the Marshal H. Wrubel Computing Center, and the taxpayers of Indiana for financial support of this work. We are also grateful to Dr. Peter Thornton, Queen Mary College, London University, for carrying out magnetic susceptibility measurements.

Carbohydrates in Organic Synthesis. Synthesis of 16-Membered-Ring Macrolide Antibiotics. 5.[1] Total Synthesis of *O*-Mycinosyltylonolide: Synthesis of Key Intermediates

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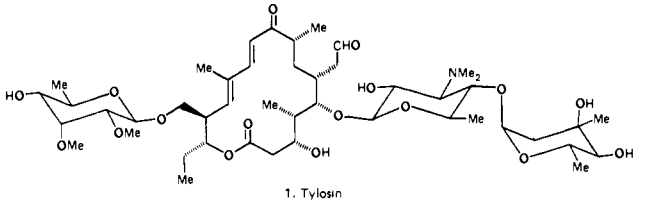
Received October 20, 1981

Tylosin (**1**)[2,3] is one of the most important and complex ma-



1, Tylosin

crolide antibiotics of the 16-membered-ring family and is extensively used today as both a nutrient and a therapeutic agent.[4] In continuing our studies in the utilization of carbohydrates in organic synthesis[5] and in particular the synthesis of macrolide antibiotics,

† Fellow of the A. P. Sloan Foundation, 1979–1983; recipient of a Camille and Henry Dreyfus Teacher-Scholar Award, 1980–1985.

(1) (a) Part 3: Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 1222. (b) Part 4: Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *Ibid.* 1224.

(2) Isolation: Hamill, R. L.; Haney, M. E., Jr.; Stamper, M.; Wiley, P. F. *Antibiot. Chemother.* (*Washington, D.C.*) **1961**, *11*, 328.

(3) Structure: Omura, S.; Matsubara, H.; Nakagawa, A.; Furusaki, A.; Matsumoto, T. J. *Antibiot. Chemother.* (*Washington, D.C.*) **1980**, *33*, 915.

(4) McGuire, J. M.; Bonieces, W. S.; Higgins, C. E.; Hoehn, M. M.; Stark, W. M.; Westhead, J.; Wolfe, R. N. *Antibiot. Chemother.* (*Washington, D.C.*) **1961**, *11*, 320.

(5) For some recent reviews on this concept see: (a) Hanessian, S.; Dixit, D. M.; Liak, T. J. *Pure Appl. Chem.* **1981**, *53*, 129. (b) Hanessian, S. *Acc. Chem. Res.* **1979**, *12*, 159. (c) Hanessian, S. *Pure Appl. Chem.* **1977**, *49*, 1201. (d) Frazer-Reid, B.; Anderson, R. C. *Fortschr. Chem. Org. Naturst.* **1980**, *39*, 1; (e) Frazer-Reid, B. *Acc. Chem. Res.* **1974**, *8*, 192.

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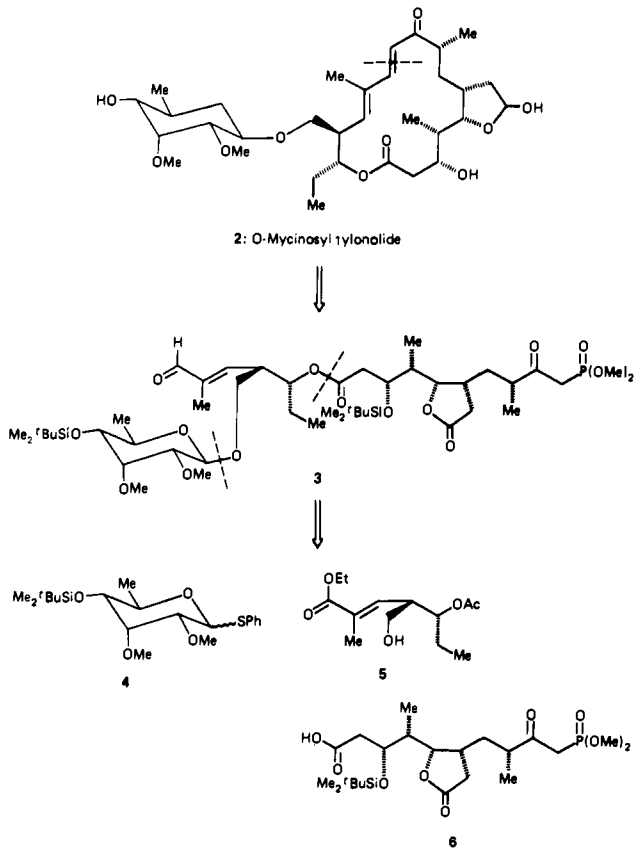
Scheme I

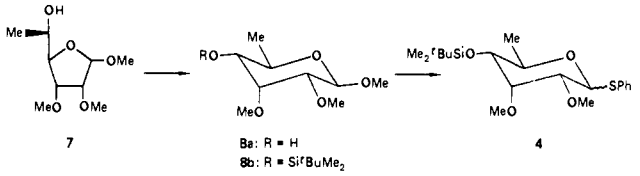


we now announce the total synthesis of *O*-mycinosyltylonolide (**2**) (Scheme I) from α-D-glucose[6] and L(+)-rhamnose. *O*-Mycinosyltylonolide is a major degradation product of tylosin,[7] and a potential biosynthetic and synthetic precursor of this antibiotic once useful technology for the glycosidation of basic N-containing sugars becomes available.

The general strategy for the synthesis of **2** as outlined retrosynthetically in Scheme I was developed by disconnections at the indicated sites, namely the enone, the ester, and the glycosidic bonds. This strategic bond disconnection and appropriate functional group interchanges leads rapidly and sequentially to the long-chain precursor **3** and the three key intermediates **4**, **5**, and **6**. The present communication describes the construction of all three fragments **4**–**6** from carbohydrate precursors in their optically active forms, and the following paper[8] details experiments for their efficient coupling, macrocyclization, and final elaboration of *O*-mycinosyltylonoide (**2**).

The first key intermediate, mycinose derivative **4**, was synthesized as outlined in Scheme II. The carbohydrate precursor **7**, efficiently prepared from L(+)-rhamnose by a modification of the procedures of Brimacombe[9a] and Levene,[9b] was rearranged to the pyranoside system **8a**[10] by exposure to methanolic anhydrous

Scheme II



HCl (10%) (60 °C, 24 h, 84% yield) and silylated (1.1 equiv of *t*-$BuMe_2SiCl$, 1.1 equiv of imidazole, DMF, 25 °C, 15 h) to afford **8b** (95%). Although Hanessian's elegant method for the conversion of methyl glycosides to phenyl thioglycosides ($PhSSiMe_3$, *n*-Bu_4NI, ZnI_2, $ClCH_2CH_2Cl$, heat)[11] performed well in the present case (**8b** → **4**[12] ca. 1:1 anomeric mixture by ^1H NMR spectrometry, 75% yield), a new, simpler procedure was devised for this transformation. Thus, when **8a** was exposed to $PhSSiMe_3$ (2.0 equiv) in CH_2Cl_2 in the presence of trimethylsilyl triflate ($Me_3SiOSO_2CF_3$, 1.0 equiv) at 0 °C followed by silylation as above, the thioglycoside **4** was formed in 85% overall yield (mixture of anomers, ca. 1:1)[13]

4 was formed in 85% overall yield (mixture of anomers, ca. 1:1)[13]

For the synthesis of key intermediates **5** and **6** from α-D-glucose, efficient schemes were devised via the epimeric nitriles **11** (Scheme III) and **10** (Scheme IV), respectively, both obtainable from the same precursor, crystalline triflate **9**.[14] Thus, nitrile **10** was found to be the kinetic product obtained by reaction of triflate **9** with anhydrous KCN (10 equiv) in DMF at 25 °C (6 h, 80% yield), whereas nitrile **11** resulted as the thermodynamic product isolated from the above reaction after 48 h as the major component (60%). The two nitriles can be easily separated chromatographically (flash column, silica, 40% ether in petroleum ether; R_f (**10**) 0.42, R_f (**11**) 0.23). The conversion of the epimeric nitriles **11** and **10** to the "left" and "right" tylonolide wings, fragments **5** and **6**, proceeded as follows.

Scheme III depicts the sequence for the construction of fragment **5** from nitrile **11**. Reduction of **11** [(a) 1.0 equiv of dibal, CH_2Cl_2, −78 °C, 0.5 h and then dilute H_2SO_4, 25 °C, 0.5 h; (b) 1.0 equiv of LAH, ether, 0 °C, 0.5 h; (c) 10% Pd–C, H_2, EtOH, 25 °C, 0.5 h)] followed by benzylation (1.5 equiv of $PhCH_2Br$, 1.4 equiv of KH, THF, 60 °C, 6 h) afforded compound **12** in 66% overall yield. Removal of the acetonitrile from **12** (Amberlite IR-120, H_2O, 90 °C, 8 h) led to the lactol **13** (98%), which was sequentially subjected to reduction (3 equiv of $NaBH_4$, EtOH, 25 °C, 48 h)[6c] and cleavage (2.2 equiv of $NaIO_4$, EtOH–H_2O, 2:1, 0 °C), furnishing the hydroxyaldehyde **14** (94% overall yield). Condensation of **14** with the stable phosphorane Ph_3P=CMeCOOEt (1.5 equiv, toluene, 60 °C, 3 h) afforded stereoselectively the unsaturated *E*–ester **15**[16] (87%), which was acetylated (1.5 equiv of Ac_2O, 1.5 equiv of pyr, 0.1 equiv of DMAP, CH_2Cl_2, 25 °C, 1 h) and selectively debenzylated using Hanessian's me-

(6) The strategy for the construction of the 16-membered-ring macrolide antibiotics from α-D-glucose was announced by us in 1979: (a) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *Tetrahedron Lett.* **1979**, 2327. Similar strategies were reported by Ziegler: (b) Ziegler, F. E.; Gilligan, P. J.; Chakraborty, U. R. *Ibid.* **1979**, 3371. (c) Ziegler, F. E.; Gilligan, P. J. *J. Org. Chem.* **1981**, *46*, 3874. (d) Tatsuta, K.; Amemiya, Y.; Maniwa, S.; Kinoshita, M. *Tetrahedron Lett.* **1980**, 2837. (e) Tatsuta, K.; Amemiya, Y.; Kanemura, Y.; Kinoshita, M. *Ibid.* **1981**, 3997.

(7) Tylonolide, the complete aglycon of tylosin, has been prepared by degradation of tylosin and partially synthesized from an acyclic precursor by Masamune (Masamune, S.; Hayase, Y.; Chan, W. K.; Sobczak, R. L. *J. Am. Chem. Soc.* **1976**, *98*, 7874) and totally from α-D-glucose by Tatsuta (ref 6e).

(8) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 0000.

(9) (a) Brimacombe, J. S.; Stacey, M.; Tucker, L. C. W. *Proc. Chem. Soc. (London)* **1964**, 83. (b) Levene, P. A.; Compton, J. *J. Biol. Chem.* **1936**, *116*, 169.

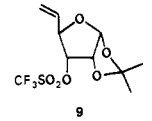
(10) All new intermediates were fully characterized by spectroscopic (^1H NMR, IR, MS, $[\alpha]_D$) and analytical (combustion analysis and/or exact mass) means. Yields refer to isolated spectroscopically and chromatographically homogeneous materials.

(11) Hanessian, S.; Guindon, Y. J. *Carbohydr. Res.* **1980**, *86*, C3.

(12) All physical properties are recorded in the Supplementary Material.

(13) When **8b** was utilized in this reaction, considerable desilylation occurred concomitant with thioglycosidation.

(14) Triflate **9** (mp 53–54.5 °C (petroleum ether)) was obtained from

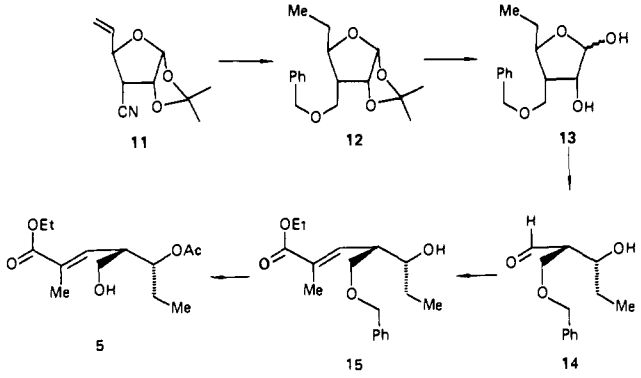


α-D-glucose in ca. 35% overall yield as follows: glucose diacetonide was oxidized (RuO_2–$NaIO_4$)[15a] reduced ($NaBH_4$),[15a] benzoylated (PhCOCl–pyr), selectively deprotected (dilute H_2SO_4),[15b] olefinated [$(EtO)_3CH$–H^+, heat],[15b] debenzoylated (K_2CO_3–MeOH), and triflated [$(CF_3SO_2)_2O$–pyr].

(15) (a) Horton, D.; Baker, D. C.; Tindall, C. O. Jr. *Carbohydr. Res.* **1972**, *24*, 192. (b) Josan, J. S.; Eastwood, F. W. *Ibid.* **1968**, *7*, 161.

(16) The *E* geometry of this α,β-unsaturated ester was deduced from ^1H NMR spectrometry by the absence of any NOE enhancement of the olefinic proton on irradiation of the vinyl methyl group (and vice versa).

Scheme III



thod[11] (10 equiv of $PhSSiMe_3$, 1.5 equiv of n-Bu_4NI, 5 equiv of ZnI_2, $ClCH_2CH_2Cl$, 60 °C, 2 h) to afford the requisite second key intermediate **5** (74% overall).

Finally, the synthesis of the third key intermediate **6** from nitrile **10** is presented in Scheme IV. Reduction of **10** [(a) 1.0 equiv of Dibal, CH_2Cl_2, −78 °C, 0.5 h and then dilute H_2SO_4, 25 °C, 0.5 h; (b) 1.0 equiv of LAH, ether, 0 °C, 0.5 h) followed by mesylation (1.2 equiv of MsCl, 1.2 equiv of Et_3N, CH_2Cl_2, −20 °C) and reductive removal of the mesylate (1.0 equiv of LAH, THF, 60 °C, 0.5 h) furnished intermediate **16** (55% overall yield). Regioselective hydroboration of the olefin in **16** (1.1 equiv of disiamylborane, THF, 25 °C, 1 h and then NaOH, 30% H_2O_2), benzylation of the resulting primary alcohol (1.5 equiv of $PhCH_2Br$, 1.4 equiv of KH, THF, 25 °C), and removal of the acetonide (Amberlite IR-120, H_2O, 90 °C, 8 h) led to the lactol **17** in 90% overall yield. Wittig reaction of **17** with the stabilized phosphorane $Ph_3P{=}CHCOOEt$ (1.4 equiv, toluene, 25 °C, 48 h) gave the expected unsaturated *E*-ester, which was protected as the acetonide (20 equiv of $Me_2C(OMe)_2$, 0.1 equiv of camphorsulfonic acid, benzene, 60 °C, 0.5 h) leading to the key Michael acceptor **18** in 82% overall yield. The next required operation was a stereocontrolled C–C bond formation in order to achieve the required backbone extension and to build a crucial chiral center at C-6. Based on previous experiences[1b,6c] in similar Michael additions of organometallic reagents to acceptors of the general type of **18**, we anticipated the emergence of the desired compound **19** as the major product of the reaction of dimethylallyllithium cuprate with **18**. Indeed, the adduct **19** was obtained as the major product (contaminated with its diastereoisomer, ca. 5:1 ratio by ^1H NMR spectrometry) when this highly efficient reaction (84%) was carried out under the previously prescribed conditions.[1b] This mixture was quantitatively converted to the corresponding γ-lactones by removal of the acetonide ($HOCH_2CH_2OH$, catalytic HCl(aq), 25 °C), at which stage the crystalline compound **20** was obtained in pure form by chromatography (68% yield) followed by crystallization, (ether–petroleum ether), mp 42–43 °C. The X-ray crystallographic structure of **20** (Figure 1)[17] confirmed the assigned stereochemistry of these intermediates. Intermediate **21** was synthesized from **20** by reduction of the γ-lactone (2.0 equiv of Dibal, CH_2Cl_2, −78 °C, 0.5 h) followed by sequential protection of the lactol (1% anhydrous HCl in MeOH, 25 °C, 15 min) and the secondary hydroxyl group (excess Me_2-*t*-BuSiCl, excess imidazole, DMF, 25 °C) in 75% overall yield. The aldehyde **22** was then produced by regio- and stereoselectivehydroboration (excess BH_3, THF, 0 °C then $NaOH$–H_2O_2) of the olefin **21** (giving rise to two terminal alcohols, separated chromatographically, silica, 60% ether in petroleum ether; $R_{f(major)}$ 0.40, $R_{f(minor)}$ 0.18) and oxidation of the major reulting alcohol (10 equiv of CrO_3·pyr·HCl, NaOAc, 0.02 M in CH_2Cl_2, 0 °C, 2 h) (70% overall yield). The correct stereochemistry of the major isomer in this series was proven by the final conversion to naturally derived intermediates (see the following paper).[8] Reaction of the lithio derivative of dimethyl methylphosphonate (1.5 equiv, THF, −78 °C, 5 min) followed by immediate oxidation of the resulting hydroxy phosphonate (2 equiv of CrO_3·pyr·HCl, NaOAc, CH_2Cl_2, 25 °C) furnished the keto phosphonate **23** (92% overall yield), which upon debenzylation (10% Pd–C, H_2, EtOAc, 25 °C) and Jones oxidation (acetone, 0 °C) led directly to the requisite key intermediate **6** in 65% overall yield from **23**.

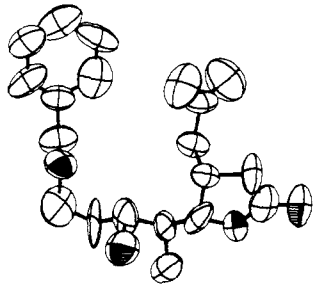
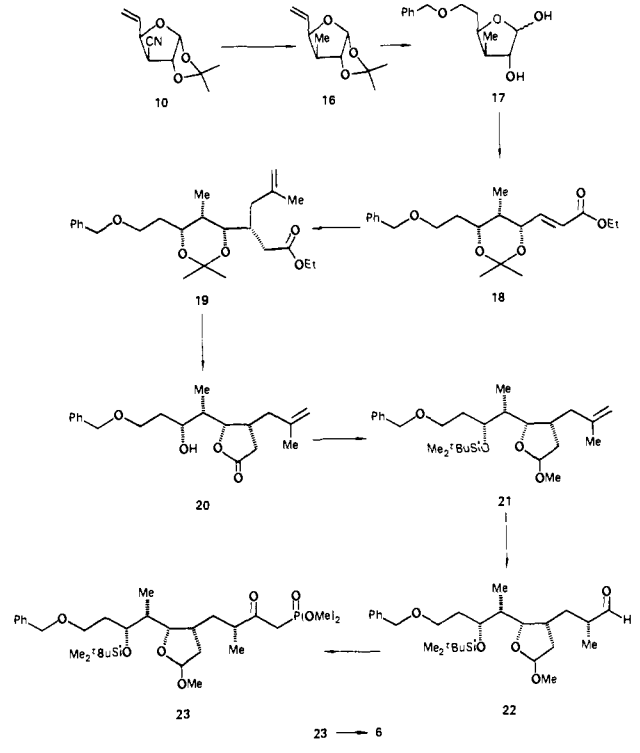


Figure 1. ORTEP plot of the X-ray structure of compound **20**.

Scheme IV



This successful and efficient construction of the building blocks **4**–**6** in their natural enantiomeric form brought the total synthesis of *O*-mycinosyltylonolide (**2**) within attainable range. The crucial experiments leading to this target are described in the following communication.[8,18]

Registry No. 4, α isomer, 80879-31-8; **4**, β isomer, 80879-32-9; **5**, 80879-33-0; **6**, 80879-34-1; **7**, 80879-35-2; **8a**, 24679-54-7; **8b**, 80879-36-3; **9**, 80879-37-4; **10**, 80879-38-5; **11**, 80879-39-6; **12**, 80879-40-9; **13**, 80879-41-0; **14**, 80879-42-1; **15**, 80890-17-1; **16**, 78822-30-7; **17**, 80890-30-8; **18**, 80879-43-2; **19**, 80879-44-3; **20**, 80879-45-4; **21**, 80879-46-5; **22**, 80879-47-6; **23**, 80879-48-7.

Supplementary Material Available: A list of physical properties of **4**–**6** and **20** (1 page). Ordering information is given on any current masthead page.

(17) We are indebted to Dr. Patrick Carroll and Robert Zipkin, both of the Department of Chemistry, University of Pennsylvania, for their assistance in solving this X-ray structure.

(18) This work was financially supported by the National Institutes of Health (Grant GM 26879), Merck Sharp & Dohme, the A. P. Sloan Foundation, and the Camille and Henry Dreyfus Foundation.