Synthesis of 6-Methylpretetramid, the Fully Aromatic Precursor of Tetracycline

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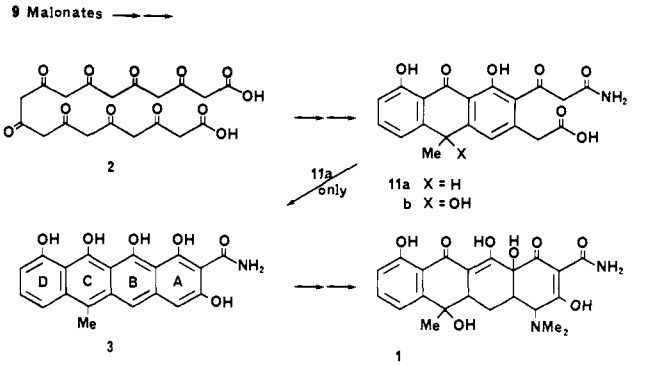
The antibiotic tetracycline (**1**) arises by a polyketide pathway, presumably via decacarbonyl intermediate **2** formed by self-condensation of nine malonate units (Scheme I).[1] Neither **2** nor any other acylic precursor of **1** has been identified and the earliest intermediate to be isolated is 6-methylpretetramid (**3**) in which the carbon skeleton is complete and all four of the rings have been assembled.[2] Compound **3** has been synthesized previously both by a de novo route[3a] and by degradation of tetracyclines.[4] Herein we describe a new route to **3** in which the last ring closure is inspired by the biosynthetic pathway.[3b]

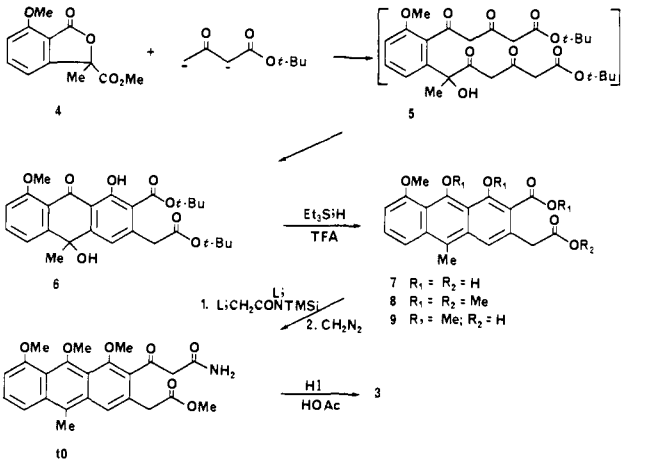
Earlier reports from this laboratory have described syntheses of polyketide-type aromatic natural products from polycarbonyl compounds; examples have included metabolites containing benzene, naphthalene, and anthracene ring systems.[5] The regiospecificity of cyclizations has been controlled by selective protection of individual carbonyl groups or in some cases solely by choice of reaction conditions. Attempts to extend this approach directly to pretetramid **3** and other naphthacene derivatives have been frustrated by difficulties associated with assembly and cyclization of decacarbonyl compounds. As an alternative we have taken an approach based upon a preformed D ring (i.e., phthalide **4**), with the remaining rings being assembled from two oligocarbonyl chains built up from it.

Phthalide **4**[6] was prepared from 7-methoxyphthalide[7] in 70% yield by treatment with 2 equiv of lithium diisopropylamide at −78 °C followed by methyl chloroformate (1 equiv, 1 h) and then iodomethane (10 equiv, 8 h). Treatment of **4** with 5 equiv of *tert*-butyl acetoacetate dilithium salt (formed with LDA) for 48 h in refluxing THF gave bis(diketo ester) **5** which cyclized during workup to give anthrone **6**[8] in 57% yield after flash chromatography. Reduction of **6** with Et_3SiH and CF_3CO_2H in CH_2Cl_2 gave anthranol **7**, which, due to its sensitivity to air oxidation, was immediately methylated (Me_2SO_4, K_2CO_3, acetone, 7 h, reflux) to form protected anthracene **8**[9] in an overall 66% yield. Addition of the dilithium salt of *N*-(trimethylsilyl)acetamide[10] (formed with LDA) to the monoanion of **8** gave a complex mixture of products of mono and bis condensation. Better results were obtained with ester acid **9**[11] (formed from **8** by treatment with 1 equiv of KOH in MeOH, 8 h, reflux, 85% yield). Condensation of the dianion of *N*-(trimethylsilyl)acetamide (10 equiv) with the potassium salt of **9** (20 °C, 36 h), followed by methylation (CH_2N_2/Et_2O, THF, 0.5 h), yielded protetrone **10**[12] (25%). Ring closure and demethylation of **10** by hydriodic acid (1:1 mixture with acetic acid, 3 h, reflux) gave pretetramid (**3**)[13] in 50% yield (Scheme II).

Scheme I



Scheme II



The final ring closure is of particular interest in this synthesis because of its close resemblance to the biological process for formation of **3** in which protetrone **11a** is believed to be involved. Protetrone **11b**, having a higher oxidation state than **11a**, has been isolated from a point-blocked mutant of the tetracycline-producing organism.[14] However, the compound is a shunt metabolite rather than an intermediate in the tetracycline pathway; incubation with an unblocked organism failed to give **1**, probably because **11b** fails to be reduced to **11a**.

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(4) (a) Hochstein, F. A.; Stephens, C. R.; Conover, L. H.; Regna, P. P.; Pasternack, R.; Gordon, P. N.; Pilgrim, F. L.; Brunings, K. J.; Woodward, R. B. *J. Am. Chem. Soc.* **1953**, *75*, 5455–5475. (b) Green, A.; Boothe, J. H. *J. Am. Chem.* **1960**, *82*, 3950–3953. (c) Green, A.; Wilkinson, R. G.; Boothe, J. H. *J. Am. Chem. Soc.* **1960**, *82*, 3946–3950.

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(6) Compound **4**: mp 64–65 °C; anal. C,H; ^1H NMR ($CDCl_3$) δ 1.87 (3 H, s, CH_3), 3.73 (3 H, s, ester OCH_3), 4.01 (3 H, s, ether OCH_3), 7.01 (1 H, d, J = 9 Hz), 7.14 (1 H, d, J = 9 Hz), 7.67 (1 H, t, J = 9 Hz).

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(8) Compound **6**: mp 197–198 °C; anal. C,H; ^1H NMR ($CDCl_3$) δ 1.50 (9 H, S, *t*-Bu), 1.52 (3 H, s, CH_3), 1.68 (9 H, s, *t*-Bu), 3.68 (2 H, s, CH_2), 3.98 (3 H, s, OCH_3), 6.94 (1 H, d, J = 8 Hz), 7.30 (1 H, s), 7.36 (1 H, d, J = 8 Hz), 7.52 (1 H, t, J = 8 Hz), 13.26 (1 H, br s, OH).

(9) Compound **8**: mp 124–125 °C; anal. C,H; ^1H NMR ($CDCl_3$) δ 3.02 (3 H, s, CH_3), 3.78 (3 H, s, OCH_3), 3.90 (2 H, s, CH_2), 3.98 (3 H, s, OCH_3), 4.05 (6 H, s, 2 OCH_3), 4.12 (3 H, s, OCH_3), 6.90 (1 H, d, J = 8 Hz), 7.50 (1 H, t, J = 8 Hz), 7.90 (1 H, d, J = 8 Hz).

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(11) Compound **9**: mp 169–171 °C; MS, *m/e* 398.1353 (calcd for **9**, 398.1366); ^1H NMR ($CDCl_3$) δ 2.95 (3 H, s, CH_3), 3.86 (2 H, s, CH_2), 3.91 (3 H, s, OCH_3), 3.97 (6 H, s, 2 OCH_3), 4.06 (3 H, s, OCH_3), 6.82 (1 H, d, J = 7 Hz), 7.42 (1 H, dd, J = 7, 9 Hz), 7.81, (1 H, d, J = 9 Hz), 7.95 (1 H, s), 8.84 (1 H, br s, OH).

(12) Compound **10**: a glassy solid; MS, *m/e* 439 (M^+, 18), 422 (M − NH_2, 12), 396 (M − HNCO, 100), 354 (45), 321 (16), 97 (30), 71 (35), 57 (34); ^1H NMR ($CDCl_3$) δ 2.96 (3 H, s, CH_3), 3.71 (3 H, s, OCH_3), 3.88 (5 H, br s, CH_2 + OCH_3), 3.92 (3 H, s, OCH_3), 4.10 (2 H, s, CH_2), 5.52 (1 H, br s, NH), 6.84 (1 H, d, J = 8 Hz), 7.02 (1 H, br s, NH), 7.44 (1 H, t, J = 8 Hz), 7.82 (1 H, d, J = 8 Hz), 7.88 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 15.33 (6-Me), 38.84 (CH_2CO_2Me), 51.21 ($COCH_2CONH_2$), 52.15 (ester OMe), 56.49, 63.95, 64.10 (ether OMe's), 104.54, 117.34, 123.58, 126.68 (protonated Ar C's), 118.40, 119.10, 125.86, 127.98, 130.20, 132.77, 134.69 (quaternary Ar C's), 153.28, 156.86, 157.65 (Ar CO's), 168.78 ($CONH_2$), 172.11 (CO_2Me), 203.42 (ketonic CO).

(13) Compound **3**: mp 220–240 °C dec in vacuo (lit.[4a] mp 200–300 °C dec); MS, *m/e* 365.0893 (calcd for **3**, 365.0896); UV in H_2SO_4/H_3BO_3 agreed well with reported values.[4a]

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A Fully Synthetic Route to Tunicaminyluracil

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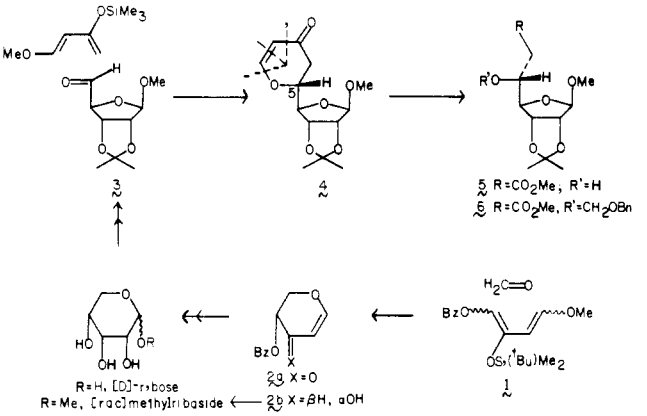
The tunicamycins form a family of closely related nucleosides of novel structure with demonstrated antibiotic and antiviral capabilities.[1] The inhibitory properties of the tunicamycins on the biosynthesis of certain polysaccharides, glycolipids, and glycoproteins render them of considerable current interest as resources for studying the finer details of the bioprocessing and utilization of complex carbohydrates.[2] The facinating though mysterious behavioral nuances manifested by seemingly closely related tunicamycin congeners (see structures **18**)[3] sharpen their value for such probing. Moreover, the reports that certain tunicamycins significantly decrease the uptake of mannose and glucosamine into the glycoproteins of L-1210 ascites leukemia cells suggest a potential anticancer role for this family, provided that host liver toxicity could be diminished.[4]

Previous synthetic work in the tunicamycin area had centered around means to couple suitably protected and matched "ribosyl" and "galactosyl" derivatives in order to arrive at the novel C_{11} (undeculose) moiety.[5a,b] Indeed, Suami[5a] has recently reported the preparation of various acylated derivatives of tunicaminyluracil (see structure **17**) through such a coupling approach. Furthermore, a closely related compound (i.e., structure **17** with NCbz instead of NAc) has been transformed by Suami[6] to several natural tunicamycins.

We have been investigating the possibility of a total synthesis wherein the relative dissymmetries in the ribosyl and galactosyl regions of tunicaminyluracil would be established *through stereochemical communication (i.e., asymmetric induction)*. Such an effort would be in contrast to that of Suami,[5a] whereby the relative relation of the two dissymmetric regions was secured through merger of naturally derived chiral subunits. Our goal has been reduced to practice in a manner that is described.

Cyclocondensation of the ribose-derived aldehyde **3**[7-9] with (*E*)-1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene under catalysis by $Eu(fod)_3$[10] affords an 85% yield of the carbon-linked disaccharide **4**, mp 70-71 °C.[11] Subsequent events proved what was expected on the basis of previous precedents,[12] i.e., that the process had occurred in the sense corresponding to α-side attack of the diene on the aldehyde conformer implied in structure **3**.

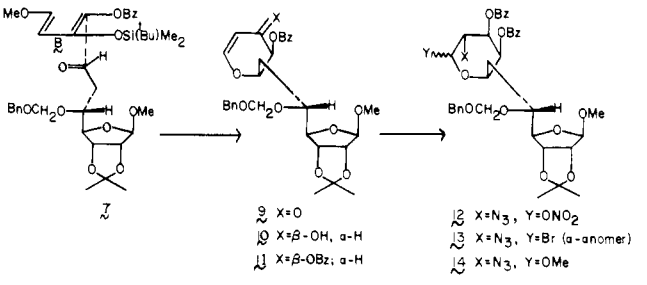
Ozonolysis of compound **4** (O_3, CH_2Cl_2, -78 °C), followed by oxidative treatment (KOH, H_2O_2) and esterification (CH_2N_2), furnished first the β-hydroxy ester **5**, mp 37-38 °C (86%) and then ($(i\text{-Pr})_2NEt$, $BnOCH_2Cl$) its BOM ether **6** in 96% yield.



The setting for the decisive stereochemical challenge was completed by conversion ((i) LAH, Et_2O, 0 °C; (ii) PCC,[13] NaOAc) of **6** to aldehyde **7**. *For success to be achieved, it would be necessary for the asymmetry of C_5 of the* D*-ribosyl unit to dictate the emergence of the new hexose in the* D*-galactosyl sense.* An attractive scenario for fashioning the hexose in a de novo manner would be by a cyclocondensation reaction via the aldehyde conformer implied in structure **7**. Such a conformer might be favored by chelation of a Lewis acid between the aldehyde and BOM ligands.[14] Attack of the diene on the face of the aldehyde opposite to that of the proximate pentose ring would provide a pyranose in the D configuration. If the attack occurred in an overall endo sense,[15] there would be fashioned a D-galactosyl precursor.

In the event, reaction of **7** with homogeneous diene **8**[16] under catalysis by $Ce(OAc)_3$-BF_3·OEt_2 ($PhCH_3$, -78 °C)[17] afforded a 45% conversion to a single isomer which subsequent events amply demonstrate to be the desired **9**. In addition, ca. 20% starting aldehyde could be recovered in homogeneous form. Reduction with sodium borohydride in the presence of $CeCl_3$[18] afforded alcohol **10** which, on benzoylation, provided dibenzoate **11** in 90% yield.

Azidonitration according to Lemieux[19] afforded the anomeric nitrates **12**, which were converted (LiBr, MeCN) to a single



bromide and then by methanolysis ($AgOTf(Me_2N)_2CO$, THF)[20]

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