sodium bicarbonate, and saturated sodium chloride. The organic phase was dried over magnesium sulfate, filtered, and concentrated to give a brown oil, which was chromatographed on silica gel to give 0.041 g (33%) of **23e** as a white solid: ^{1}H NMR ($CDCl_3$) δ 8.25 (2 H, d, J = 9), 7.56 (2 H, d, J = 9), 6.64 (2 H, AB quartet, J = 11), 5.29 (2 H, 2), 4.47 (1 H, qd, J = 3, 8), 4.31 (1 H, m), 3.68 (2 H, AB quartet, J = 18), 3.49 (1 H, dd, J = 10, 18), 3.43 (1 H, dd, J = 3, 5), 3.37 (1 H, dd, J = 8, 18), 1.35 (3 H, 3, J = 6); UV λ_{max} (dioxane) 313, 264 nm.

Preparation of Potassium (5*R*,6*S*)-2-((Cyanomethyl)thio)-6-[(*R*)-1-hydroxyethyl]-3-(5-tetrazolyl)carbapenem (28). A mixture of **23e** (0.055 g, 0.11 mmol), 0.06 g of 10% palladium on carbon, 2 mL of 0.1 M dipotassium hydrogen phosphate/potassium dihydrogen phosphate, pH 7 buffer, 4 mL of water, 8 mL of terahydrofuran, and 2 mL of ethanol was hydrogenated at 45 psi hydrogen for 1 h. The mixture was filtered through Celite, eluting with water. The filtrate was washed with 50 mL of diethyl ether and concentrated under vacuum to a volume of 3 mL. Reverse-phase preparative TLC chromatography (5% ethanol in H_2O) allowed isolation of a band R_f = 0.8. The silica was eluted with 40 mL of acetonitrile:water/4:1. Concentration and lyophilization gave 0.030 g (82%) of **28** as a white powder: IR (KBr) 3400, 2950, 2250, 1770, 1620 cm^{-1}; ^{1}H NMR (D_2O) δ 4.48 (1 H, m, J = 2.5, 8, 9.5), 4.35 (1 H, quintet, J = 6.5), 3.92 (2 H, AB quartet, J = 17), 3.61 (1 H, dd, J = 2.5, 6.5), 3.48 (1 H, AB quartet, J = 9.5, 17), 3.37 (1 H, AB quartet, J = 8, 17), 1.37 (3 H, d, J = 6.5); UV λ_{max} 294 nm.

Acknowledgment. We thank J. Kahan for antibacterial assays and H. Kropp for DHP susceptibility measurements.

Registry No. 3, 88669-70-9; **4a**, 88669-71-0; **5** (R = Et), 13616-37-0; **5** (R = CH_2Ph), 76812-76-5; **6a** (R = Et), 88669-72-1; **6b** (R = Et), 88669-73-2; **6c** (R = Et), 88669-74-3; **6d** (R) *t*-Bu), 88669-75-4; **6e** (R = *t*-Bu), 88669-76-5; **7a** (R = Et), 88669-77-6; **7b** (R = Et), 88669-78-7; **7c** (R = CH_2Ph), 88669-79-8; **7e** (R = *t*-Bu), 88669-80-1; **8a**, 64953-18-0; **8e**, 88669-81-2; **9a**, 88669-82-3; **9c**, 88669-83-4; **10a**, 88669-84-5; **10e**, 88669-85-6; **11a**, 88669-86-7; **11e**, 88669-87-8; **12a**, 88669-88-9; **12b**, 88669-89-0; **12e**, 88669-90-3; **13a**, 88669-91-4; **14a**, 88669-92-5; **14b**, 88669-93-6; **14c**, 88669-94-7; **14e**, 88669-95-8; **15a**, 88669-96-9; **15b**, 88669-97-0; **15d**, 88669-98-1; **16a**, 88669-99-2; **16b**, 88670-00-2; **16e**, 88685-62-5; **17b**, 88670-01-3; **17e**, 88670-02-4; **18**, 88670-03-5; **19**, 88728-84-1; **19** (acid), 88670-04-6; **20**, 88670-05-7; **21**, 88685-63-6; **22e**, 88670-06-8; **23e**, 88670-07-9; **24e**, 88670-08-0; **25**, 88670-09-1; **26**, 88670-10-4; **27**, 88670-11-5; **28**, 88670-12-6; **29**, 88670-13-7; $ClCH_2C{=}NH(NMe_2)$, 88670-14-8; *p*-nitrobenzyl chloromethyl carbonate, 50780-46-6; *tert*-butyl 5-tetrazolylacetate, 88670-15-9; *p*-nitrobenzyl alcohol, 619-73-8; chloromethyl chloroformate, 22128-62-7; methyl acrylate, 96-33-3.

Supplementary Material Available: Spectral data (4 pages). Ordering information is given on any current masthead page.

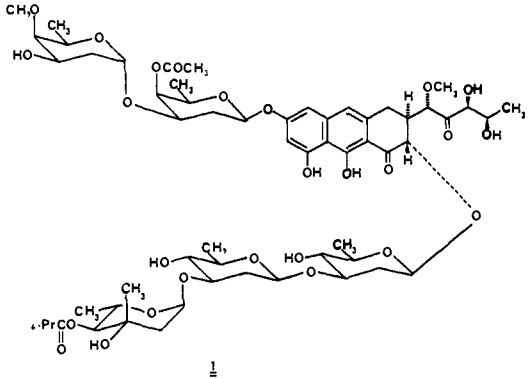
Total Synthesis of Tri-*O*-methylolivin

John H. Dodd, John E. Starrett, Jr., and Steven M. Weinreb*

Contribution from the Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802. *Received September 19, 1983*

Abstract: Olivin (**2**) is the aglycon of the antitumor antibiotic olivomycin A (**1**). A total synthesis of **3**, the trimethyl ether of olivin, has been successfully achieved by a convergent route. The key β-methoxyenone synthon **15** was prepared from 3,5-dimethoxyphenylacetic acid (**4**) and ketal ester **5**. Condensation of **15** and methyl orsellinate dimethyl ether gave tricyclic ketone **17** which was subsequently elaborated into **3**.

Olivomycin A (**1**) is a clinically effective cancer chemotherapy agent produced by *Streptomyces olivoreticuli*. This compound is a member of the aureolic acid group of antitumor antibiotics which are characterized by a complex tricyclic aglycon attached to various di- and trisaccharides.[1a] Acidic hydrolysis of **1** affords



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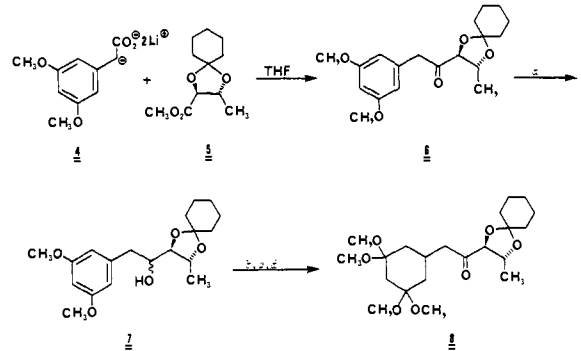
the aglycon olivin having the structure and absolute stereochemistry shown in formula **2**.[1b] Relatively little synthetic work has been reported in this area to date. Franck,[2] Thiem,[3] and Roush[4] have described preliminary approaches to olivin using carbohydrate synthons. Recently we delineated a general annulation strategy for convergent synthesis of the aureolic acid aglycons and we have

Scheme I[a]



[a] Key: (a) $NaBH_3$, EtOH, room temperature, 2 h. (b) Li/NH_3, EtOH, 1 h. (c) Puridinium *p*-toluenesulfonate, MeOH room temperature, 14 h. (d) Pyridine/CrO_3, CH_2Cl_2, 0 °C–room temperature, 40 min.

(1) (a) For reviews see: Remers, W. A. "The Chemistry of Antitumor Antibiotics"; John Wiley: New York, 1979; pp 133–175. Skarbek, J. O.; Brady, L. R. *Lloydia* **1975**, *38*, 369. (b) Bakhaeva, G. P.; Berlin, Y. A.; Chuprunova, O. A.; Kolosov, M. N.; Peck, G. Y.; Piotrovich, L. A.; Shemyakin, M. M.; Vasina, I. V. *J. Chem. Soc., Chem. Commun.* **1967**, 10 and references cited therein.

(2) Franck, R. W.; John, T. V. *J. Org. Chem.* **1980**, *45*, 1172.
(3) Thiem, J.; Wessel, H. P. *Liebigs Ann. Chem.* **1981**, 2216.
(4) Roush, W. R.; Harris, D. J.; Lesur, B. M. *Tetrahdron Lett.* **1983**, *24*, 2227.

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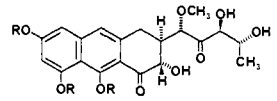
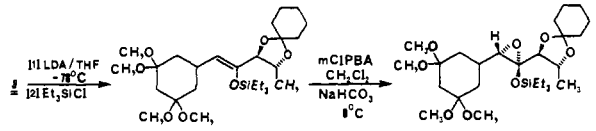
now developed a total synthesis of tri-*O*-methylolivin (**3**) which utilizes this approach.[5]



2 R=H
3 R=CH_3

Condensation (Scheme I) of the dianion prepared from 3,5-dimethoxyphenylacetic acid (**4**) (2 equiv of *n*-BuLi/THF, 0 °C) with ester **5**[5] (0.67 equiv) gave ketone **6** (89% yield).[6] Reduction of **6** with sodium borohydride afforded alcohol **7** as a 5:3 mixture of epimers which was not separated (100%). Birch reduction of **7** gave an unstable bis-enol ether, which was converted to the corresponding bis-ketal and subsequently oxidized to give bis-ketal ketone **8** (35% from **7**).

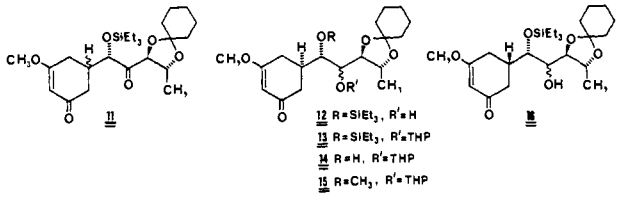
Conversion of ketone **8** to its kinetic enolate[7] with LDA and silylation with triethylsilyl chloride afforded a *single* enol ether **9**. We have tentatively assigned the *Z* geometry to this compound on the basis of the known propensity of bulky α-substituted ketones to form enolates having this configuration.[8] Peracid oxidation



8 **9** **10**

of **9**, to our surprise, gave the relatively stable epoxide **10** (68% from **8**). Siloxy epoxides have been postulated as intermediates in the peracid-mediated conversion of silylenol ethers to α-siloxy ketones, but to our knowledge this is the first time such a species has actually been isolated.[9,10] This expoxide is a *single* stereoisomer as evidenced by ^1H and ^{13}C NMR,[7] and we have assigned it the α stereochemistry depicted in **10** on the basis of its ultimate conversion to tri-*O*-methylolivin (**3**).[11]

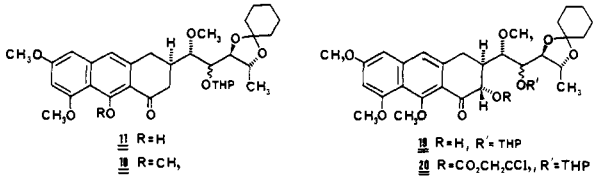
Treatment of **10** with pyridinium *p*-toluenesulfonate (CH_2Cl_2, room temperature, 1.5 h) gave **11** having both the desired β-methoxyenone and α-siloxy ketone functionality (63%). This material was an inseparable 1:1 mixture of ring epimers. The sidechain carbonyl group of **11** could be selectively reduced with sodium borohydride (EtOH, −78 °C, 1 h) to give a chromatographically separable 1:1 mixture of alcohols **12** and **16** (65%).[12,13] The desired ring isomer **12** was protected as the tetrahydropyranyl ether **13** (dihydropyran, PPTS, CH_2Cl_2, reflux, 4 h; 81%), and



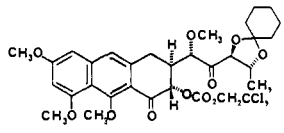
11 **12** R=$SiEt_3$, R'=H; **13** R=$SiEt_3$, R'=THP; **14** R=H, R'=THP; **15** R=CH_3, R'=THP; **16**

the silyl ether group was subsequently removed with tetrabutylammonium fluoride (THF, room temperature, 5 min; 100%) to yield **14**. Methylation of alcohol **14** ($(MeO)_2SO_2$, NaH, THF, room temperature, 3 h; 70%) afforded a properly elaborated β-methoxyenone synthon **15**.

Condensation of **15** with methyl orsellinate dimethyl ether (LDA, THF, −78 °C) gave tricyclic phenolic ketone **17** (55%),[5] which was O-methylated to afford **18** ($MeOSO_2F$, NaH, THF, 30 min; 68%). Ketone **18** was transformed to its trimethylsilyl enol ether (LDA, TMSI, THF, −78 °C) which without purification was oxidized with *N*-methylmorpholine *N*-oxide/OsO_4 (acetone/H_2O (2:1), −5 °C, 19 h)[14] to give, after aqueous workup, *exclusively* the *trans* acyloin **19**. This compound was protected



17 R=H; **18** R=CH_3; **19** R=H, R'=THP; **20** R=$CO_2CH_2CCl_3$, R'=THP; **21** R=$CO_2CH_2CCl_3$, R'=H



22

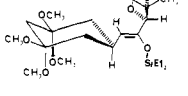
(trichloroethyl chloroformate/pyridine, room temperature, 11 h) to produce carbonate **20** (52% from **18**), and removal of the THP protecting group (PPTS, MeOH, 26 h) gave alcohol **21** (89%). Swern oxidation[15] of **21** yielded ketone **22** (85%) identical with material prepared from olivomycin A.[16] Finally, the cyclohexylidene ketal protecting group of **22** was removed (*p*-TsOH, MeOH, reflux, 2 h) and the carbonate was then cleaved (Zn dust, KH_2PO_4, THF, H_2O, 0.5 h) to afford tri-*O*-methylolivin (**3**) (68% from **22**) identical with an authentic sample synthesized from natural olivomycin A (**1**).[16]

We are currently attempting to prepare a derivative of olivin suitable for attachment of the carbohydrate residues. Also, work is in progress on preparation of the related aureolic acid aglycon chromomycinone.[5]

Acknowledgment. We are grateful to Dr. T. Doyle (Bristol Laboratories) for a very generous sample of olivomycin A and to the National Cancer Institute (CA25145) for support of this research. We thank R. Garigipati for conducting some preliminary model experiments and Professor R. W. Franck for frequent valuable discussions during the course of this project. S.M.W. Thanks the John Simon Guggenheim Memorial Foundation for a Fellowship.

Supplementary Material Available: Spectral and physical characterization data on new compounds (10 pages). Ordering information is given on any current masthead page.

(5) Dodd, J. H.; Garigipati, R. S.; Weinreb, S. M. *J. Org. Chem.* **1982**, *47*, 4045. Dodd, J. H.; Weinreb, S. M. *Tetrahedron Lett.* **1979**, 3593.
(6) We thank Professor A. Kende for suggesting this coupling procedure.
(7) Hatch, R. P.; Shringarpure, J.; Weinreb, S. M. *J. Org. Chem.* **1978**, *43*, 4172.
(8) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.
(9) Rubottom, G. M.; Gruber, J. M.; Boeckman, R. K.; Ramaiah, M.; Medwid, J. B. *Tetrahedron Lett.* **1978**, 4603.
(10) The unusual stability of **10** may be due to an "internal buffering" effect by the many oxygens in the molecule, thus slowing epoxide rearrangement to the α-siloxy ketone. The identical silylenol ether lacking the four bis-ketal methoxyl groups gives *only* the siloxy ketone on treatment with mCPBA.
(11) From molecular mechanics calculations it appears that the most stable conformation of **9** is i. Epoxidation of the double bond of i from the least



hindered α face affords **10**. In addition, hydrogen bonding of the allylic ketal oxygen of i to the peracid would also produce the observed product stereochemistry. We thank Professor P. Jurs, Mr. E. Whalen-Pedersen, and Mr. Gary Small for performing these calculations.
(12) Alcohol **12** is a 3:1 mixture of epimers which may be separated for subsequent steps by silica gel chromatography.
(13) Work is currently in progress on isomerization of the undesired ring epimer **16** to **12** via the corresponding cyclohexane 1,3-dione.
(14) McCormick, J. P.; Tomasik, W.; Johnson, M. W. *Tetrahedron Lett.* **1981**, *22*, 607.
(15) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957.
(16) Natural olivomycin A (**1**) was treated sequentially with (1) Me_2SO_4/K_2CO_3 acetone, Δ; (2) 2.0 M HCl/MeOH, room temperature, 8 h; and (3) CH_2N_2, Et_2O/THF, 3 h, to afford trimethylolivin (**3**). Further treatment of **3** with (1) cyclohexanone, pTsOH, 12 h, room temperature and (2) $ClCO_2CH_2CCl_3$/pyridine, 11 h, room temperature, gave compound **22**.