and **5**. Transformation of **8** (manno series) into **9** (gluco series) was also feasible in two steps, i.e., (1) Swern oxidation and (2) $BH_3$·$(Et)_3N$ reduction, in excellent overall yield; the stereoselectivity of the reduction was greater than 8:1 in favor of the gluco series.[16]

After deprotection [$H_2$/Pd(OH)$_2$ on C/MeOH/rt], **8** and **9** were subjected to methanolysis under acidic conditions (HCl/MeOH/90 °C) to yield **10**[17] (90% overall yield; $\alpha_D$ in MeOH +38.9°) and **11**[17] (90% overall yield; $\alpha_D$ in MeOH +63.2°), respectively. The assigned structures **10** and **11** were fully consistent with the spectroscopic data; in particular, the $^1$H NMR spectrum provided conclusive evidence for the stereochemistry assigned.[18]

The axially substituted *C*-glycosides **16** and **17** were also synthesized from **6**. Thus, **6** was transformed into the *p*-nitrobenzoates **12α**[19] (51% overall yield; $\alpha_D$ +31.0°) and **12β**[19] (46% overall yield; $\alpha_D$ −18.3°) in three steps, i.e., (1) AcOH–$H_2O$ (6:4)/40 °C, (2) $Pb(OAc)_4/C_6H_6$/O °C, and (3) $p$-$O_2NC_6H_4COCl$/py/$CH_2Cl_2$/rt. Based on the following considerations, we anticipated that the desired C-glycosidation would preferentially occur from the oxonium ion generated from **12α,β** under acidic conditions (Scheme I). First, a nucleophilic attack on the conformers A and B of the oxonium ion leading to the chair-like transition state should be more favorable than one leading to a boat-like transition state. Second, nucleophilic attack on conformer A should be slower than that on conformer B, since the C(1)-$CH_2R$ group of A would cause a more serious steric interaction for the incoming nucleophile than the C(3)-$OCH_2Ph$ group of B. Third, the product that resulted from an axial attack on the conformer B would flip over to the alternative chair conformation to yield the desired C(1)-axially substituted *C*-glycoside. Treatment of **12β** with $CH{\equiv}CCH_2Si(CH_3)_3$ in $CH_3CN$ containing $BF_3$·$Et_2O$[20] yielded the anticipated product **13** (70% yield; $\alpha_D$ −1.8°) along with a small amount of the equatorial isomer (the stereoselectivity = ca. 10:1). However, the stereoisomer **12α** was recovered unchanged under the same conditions. Under more forcing conditions, the 1,6-anhydroglucose moiety participated also in the C-alkylation reaction. Thus, it was more practical to transform **12α** to **12β**,[21] followed by C-alkylation.

Ozonolysis ($O_3$/MeOH/−78 °C), followed by reduction ($NaBH_4$/EtOH/O °C), furnished the diol **14** (92% overall yield; $\alpha_D$ −8.4°), which was transformed into the methyl glycoside **16**[17,18] ($\alpha_D$ in MeOH +83.4°) in 90% overall yield in two steps [(1) $H_2$/Pd(OH)$_2$ on C/MeOH/rt and (2) HCl/MeOH/90 °C]. The corresponding gluco product was also obtained from **14**; protection of the primary alcohol [PhCOCl/py/$CH_2Cl_2$/rt], Swern oxidation, and reduction of the resultant ketone ($BH_3$·THF/THF/O °C)[22] yielded **15** (80% overall yield; $\alpha_D$ +8.1°) along with a small amount of the corresponding manno product (the stereoselectivity = 18:1). Transformation of **15** into the gluco methyl glycoside **17**[17,18] ($\alpha_D$ in MeOH +53.3°) was performed in 90% overall yield utilizing the same sequence of reactions as **14** to **16**.

The methods outlined herein should be flexible enough to synthesize a variety of the carbon analogues of disaccharides with α- and β-glycoside bonds. Investigations along this line, as well as the conformational studies of these *C*-disaccharides, will be reported elsewhere.

**Acknowledgment.** Financial support from the National Institutes of Health (NS 12108) is gratefully acknowledged. NMR spectrometers used in this research were funded by NSF Grant (CHE-84-10774) and NIH Shared Instrumentation Program (1 S10 RR01748).

**Registry No.** **1**, 106929-08-2; **2**, 106929-09-3; **3**, 106929-10-6; **4**, 106929-11-7; **5**, 106974-26-9; **6**, 106929-12-8; **7**, 106929-13-9; **8**, 106929-14-0; **9**, 106974-27-0; **10**, 106929-15-1; **11**, 107032-98-4; **12α**, 106929-16-2; **12β**, 106974-28-1; **13**, 106929-17-3; **14**, 106929-18-4; **15**, 106974-30-5; **16**, 106974-29-2; **17**, 106974-31-6; $CH{\equiv}CCH_2Si(CH_3)_3$, 13361-64-3.

**Supplementary Material Available:** $^1$H NMR spectra of *C*-disaccharides **10**, **11**, **16**, and **17**, and key intermediates (8 pages). Ordering information is given on any current masthead page.

(16) $BH_3$·THF reduction of this substrate gave a 3:2 mixture of the gluco and manno products (see ref 22).

(17) Under the methanolysis conditions, an approximately 5:1 mixture of the axial and equatorial methyl glycosides were formed. Analytically pure axial methyl glycosides were obtained by acetylation ($Ac_2O$/py), chromatographic separation, and base hydrolysis (aqueous NaOH).

(18) The $^1$H NMR spectrum of **10**, **11**, **16**, and **17** was recorded on a Bruker AM 500 spectrometer (500 MHz) in $CD_3OD$. The following spin–spin coupling constants were observed. **10**: $J_{1',2'}$ = 3.7 Hz, $J_{2',3'}$ = 9.3, $J_{3',4'}$ = 10.2, $J_{4',5'}$ = 10.1, $J_{5',6'}$ = 1.8 and 5.3, $J_{6',6'}$ = 11.8, $J_{4',A}$ = 5.2, $J_{4',B}$ = 3.8, $J_{A,B}$ = 14.1, $J_{1,A}$ = 8.8, $J_{1,B}$ = 3.2, $J_{1,2}$ < 1.0, $J_{2,3}$ = 2.2, $J_{3,4}$ = 9.4, $J_{4,5}$ = 8.9, $J_{5,6}$ = 2.3 and 6.7, and $J_{6,6}$ = 11.6. **11**: $J_{1',2'}$ = 3.7 Hz, $J_{2',3'}$ = 9.3, $J_{3',4'}$ = 10.3, $J_{4',5'}$ = 10.9, $J_{5',6'}$ = 1.7 and 5.4, $J_{6',6'}$ = 11.8, $J_{4',A}$ = 3.5, $J_{4',B}$ = 4.7, $J_{A,B}$ = 15.3, $J_{1,A}$ = 9.2, $J_{1,B}$ = 1.7, $J_{1,2}$ = 9.2, $J_{2,3}$ = 9.1, $J_{3,4}$ = 9.7, $J_{4,5}$ = 8.7, $J_{5,6}$ = 2.4 and 5.2, and $J_{6,6}$ = 11.8. **16**: $J_{1',2'}$ = 3.7 Hz, $J_{2',3'}$ = 9.4, $J_{3',4'}$ = 10.8, $J_{4',5'}$ = 11.3, $J_{5',6'}$ = 2.4 and 6.4, $J_{6',6'}$ = 11.6, $J_{4',A}$ = 3.3, $J_{4',B}$ = 5.5, $J_{A,B}$ = 14.4, $J_{1,A}$ = 9.2, $J_{1,B}$ = 4.6, $J_{1,2}$ = 3.7, $J_{2,3}$ = 2.5, $J_{3,4}$ = 9.8, $J_{4,5}$ = 7.6, $J_{5,6}$ = 3.8 and 7.0, and $J_{6,6}$ = 11.3. **17**: $J_{1',2'}$ = 3.7 Hz, $J_{2',3'}$ = 9.5, $J_{3',4'}$ = 10.6, $J_{4',5'}$ = 8.8, $J_{5',6'}$ = 2.3 and 4.9, $J_{6',6'}$ = 12.0, $J_{4',A}$ = 2.7, $J_{4',B}$ = 5.5, $J_{A,B}$ = 14.8, $J_{1,A}$ = 10.1, $J_{1,B}$ = 3.1, $J_{1,2}$ = 9.2, $J_{2,3}$ = 9.2, $J_{3,4}$ = 8.4, $J_{4,5}$ = 8.8, $J_{5,6}$ = 2.7 and 4.6, and $J_{6,6}$ = 12.3.

(19) We were unable to establish the stereochemistry of **12α** and **12β** firmly based on the NMR spectra. However, the reactivity difference observed in the alkylation of **12α** and **12β** strongly suggests the stereochemistry assignment as indicated.

(20) Wu, T. C.; Kishi, Y., unpublished results.

(21) Base hydrolysis ($K_2CO_3$/MeOH/rt) and *p*-nitrobenzoylation ($p$-$NO_2C_6H_4COCl$/py/$CH_2Cl_2$/rt) yielded approximately a 1:2 mixture of **12α** and **12β** in 75–80% yield.

(22) Garegg, P. J.; Maron, L. *Acta Chem. Scand., Ser. B* **1979**, *33B*, 453.

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## A New Approach to the Total Synthesis of Pseudomonic Acid C

*Summary:* The glycolate ester enolate Claisen rearrangement was used to introduce the side chain stereochemistry in a synthesis of pseudomonic acid C.

*Sir:* Pseudomonic acid C (**1c**) is a member of a family of *C*-pyranoside antibacterials which have been isolated from fermentations of a strain of *Pseudomonas fluorescens*.[1] Notwithstanding a narrow range of activity constrained mainly to gram-positive bacteria,[2] their good activity against various skin pathogens[3] combined with a novel and challenging structure have made them inviting targets for

(1) (a) Pseudomonic acid A: Banks, G. T.; Barrow, K.; Chain, E. B.; Fuller, A. T.; Mellows, G.; Woolford, M. *Nature (London)* **1971**, *234*, 416. (b) Pseudomonic acid B: Chain, E. B.; Mellow, G. *J. Chem. Soc., Chem. Commun.* **1977**, 318. (c) Pseudomonic acid C: Clayton, J. P.; O'Hanlon, P. J.; Rogers, N. H. *Tetrahedron Lett.* **1980**, *21*, 881. (d) Pseudomonic acid D: O'Hanlon, P. J.; Rogers, N. H.; Tyler, J. W. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2655.

(2) (a) White, A. R.; Masters, P. J.; Sutherland, R. *Proc. Int. Congr. Chemother.*, **1983**, *3*, 4.6/7-24. (b) Tasker, T. C. G.; Boon, R. J.; Masters, P. J.; King, J. D. *Ibid.* **1983**, *3*, 4.6/7-25.

(3) (a) Reid, J.; Cooper, D. L. *Proc. Int. Congr. Chemother., 13th* **1983**, *3*, 4.6/7-26. (b) Davies, B. I.; Wuite, J.; Go, M.; Lambers, J. *Ibid.* **1983**, *3*, 4.6/7-27.

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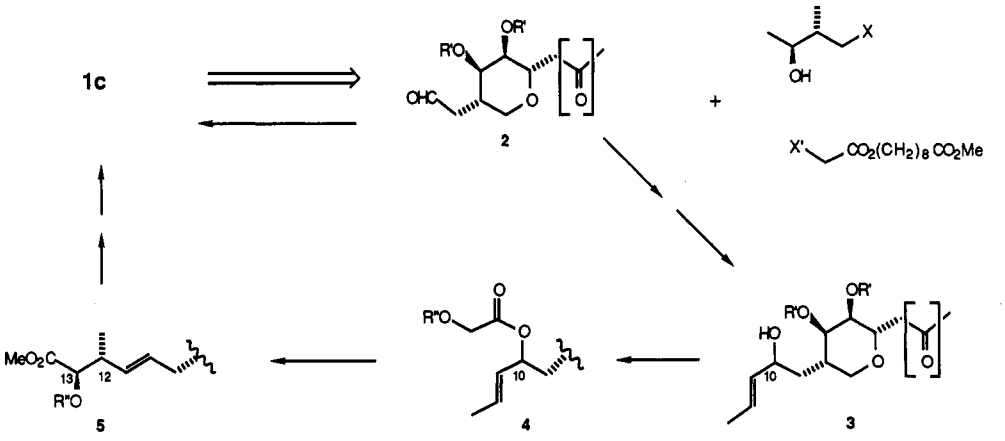
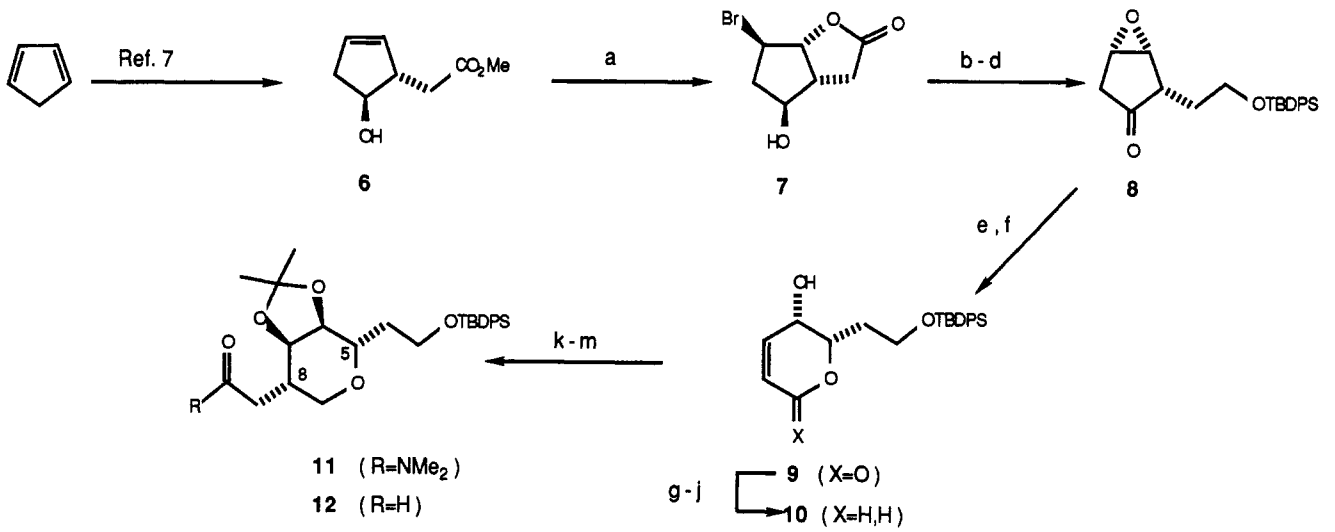
**Scheme I**

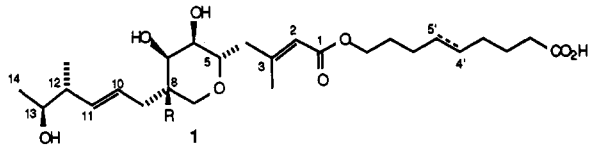



**Scheme II**[a]




[a] (a) KOH, $H_2O$, then NBS, THF (62%); (b) $LiBH_4$, $Et_2O$, then 15% NaOH (100%); (c) *t*-$BuPh_2SiCl$,[8] (88%); (d) PCC[9] (95%); (e) *m*-CPBA; (f) $Et_3N$ (74% from 8); (g) *t*-$BuMe_2SiOTf$[11] (90%); (h) Dibal; (i) $Et_3SiH$, $BF_3$-$Et_2O$, $CH_2Cl_2$, −78 °C (55% overall); (j) HOAc, THF, $H_2O$ (3:1:1)[13] (75%); (k) $MeC(OMe)_2NMe_2$, xylene (95%); (l) catalytic $OsO_4$, NMO (90%); (m) $CH_3COCH_3$, *p*-TsOH (90%).

total synthesis.[4] Herein we report a conceptually new approach to the synthesis of **1c** which should also be amenable to the preparation of analogues.




**Pseudomonic Acid**
**A : R=H; C10,11 epoxide**
**B : R=OH; C10,11 epoxide**
**C : R=H**
**D : R=H; C4',5' olefin**

Simplifying disconnection at the C-2,3 and C-10,11 olefins would give the keto aldehyde **2** (Scheme I), which could then be converted back into the natural product in a convergent manner by Wittig–Horner or Julia coupling reactions. Whereas this approach has been employed in most of the previous syntheses, we decided that a more direct route in which the side chain stereochemistry at C-12 and C-13 could be related back to the chirality around the pyran ring of **2** would be worthy of study. One such possibility would involve the intermediacy of the allylic alcohol **3**. The stereochemistry at the hydroxyl center (C-10) could then be translated via a glycolate ester enolate Claisen rearrangement[5] (**4** → **5**) to the desired C-12 and C-13 positions. Obviously this approach requires that both the addition to the aldehyde **2** to give **3**, and the enolization and subsequent rearrangement of ester **4** occur with high stereocontrol.

Our synthesis began with the optically active hydroxy ester **6** (Scheme II), which was made by asymmetric hydroboration of cyclopentadiene in >95% optical purity by the method of Partridge.[6] After conversion to the epoxy ketone **8**,[7] via the bromo lactone **7**,[10] the requisite pyran

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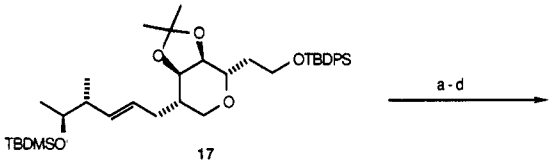
(6) Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 7171.

oxygen was introduced by Baeyer–Villiger oxidation and the epoxide opened by base promoted $\beta$-elimination to give the unsaturated lactone **9**. Protection of the free hydroxyl group was followed by two-step reductive removal of the carbonyl group according to the method of Kraus,[12] which gave, after deprotection, allylic alcohol **10**. Claisen rearrangement,[14] cis hydroxylation,[15] and protection produced amide **11** in which each of the three stereocenters derived from **6** was introduced with complete stereospecificity. Reduction (DIBAL, −78 °C; 80%) then gave aldehyde **12**.

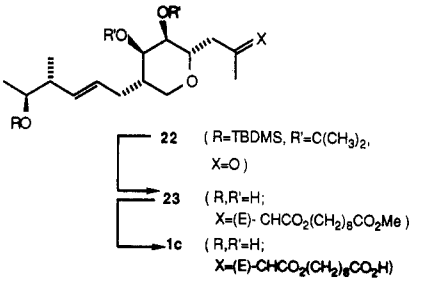
Elaboration to the full C-8 side chain first required the stereocontrolled addition of a vinyl carbanion to **12**, which we believed could be achieved after initial metal complexation of the aldehyde group to one of the adjacent oxygens (Scheme III). While similar additions to such seven-membered ring chelates are not without precedent,[16] much experimentation was needed until it was found that addition of an excess of propenylmagnesium bromide (M = MgBr) to **12** in the presence of zinc bromide (1 equiv, THF, −78 °C) gave the allylic alcohol **13a** and its epimer **13b** in a 4:1 ratio[17] in 75% yield.[18] After separation of the diastereomers by HPLC, we were confronted with the problem of carrying out the ester enolate Claisen rearrangement via the *Z* enolate **15** to give the required threo (anti) ester **16**. A reversal of the usual *E* selective deprotonation has now been achieved by using a protecting group on the glycolate ester which inhibits chelation between the ether and the carbonyl oxygens and by performing the deprotonation under strictly kinetic conditions.[19] Esterification of **13a** ($t$-$BuMe_2SiOCH_2CO_2H$, DCC, DMAP; 81%)[20] followed by deprotonation in the presence of $Me_3SiCl$[21] and rearrangement (LDA, in situ $Me_3SiCl$, THF, −78 → 25 °C; 55%) gave, after workup and esterification, **16** (R′ = $t$-$BuMe_2Si$) as the major component of a 4:1 mixture of threo (12*S*,13*R*) and erythro (12*R*,13*R*) products.[17a] Use of lithium *tert*-octyl-*tert*-butylamide (LOBA) gave a 7:1 ratio of the same two diastereomers but in only 30% yield. Conversion of the methyl ester to the C-14 methyl group [(1) DIBAL, 80%; (2) $I_2$, $PPh_3$, 75%; (3) $Bu_3SnH$, AIBN, EtOH, 25°[22]; 70%] gave **17** (R′ = $t$-$BuMe_2Si$).[23]

While the advantages of the above sequence are tempered somewhat by the modest stereoselectivity, a marked improvement has been realized by starting with the amide **11**. Addition of propynyl lithium to **11** ($BF_3$·$Et_2O$, THF, −78 °C, 96%)[24] gave ketone **18**, which was reduced with (*R*)-alpineborane[25] (THF, 25 °C, 88%) to give the *R* alcohol **19** with virtually complete stereocontrol (>20:1). Esterification ($PhCH_2OCH_2CO_2H$, DCC, DMAP; 93%) followed by careful reduction ($H_2$, 10% Pd/$BaSO_4$, pyridine, 25 °C, 86%) gave the cis unsaturated ester **20**, which was now rearranged according to the literature procedure[5,26] [(a) LDA, THF, −78 → 25 °C; (b) $Me_3SiCl$; 60%] via the *E* enolate **21** to give, after esterification, **16** (R′ = Bn) with complete (>20:1) stereocontrol.

Completion of the synthesis from **17** (R′ = $t$-$BuMe_2Si$) was straightforward. Conversion to the methyl ketone **22** was followed by Horner–Emmons condensation [$(MeO)_2P(O)CH_2CO_2(CH_2)_8CO_2Me$,[4j] NaH, THF, 25 °C; 80%; 4:1 *E*/*Z*] and deprotection of the major isomer (80% aqueous HOAc, 25 °C; 76%) to give methyl pseudomonate C (**23**), the $^1H$ NMR, $^{13}C$ NMR, IR and mass spectrum of




(a) 1.5 eq. n-$Bu_4NF$,THF (75%); (b) PCC ,NaOAc (97%); (c) MeLi, THF (71%); (d) PCC, $CH_2Cl_2$ (90%)




which were identical with those reported.[1c] Selective hydrolysis of the methyl ester (KOH, $NaHCO_3$, THF, EtOH,

(7) All new compounds had $^1H$ NMR, $^{13}C$ NMR, IR, MS, and elemental analyses compatible with the expected structures.

(8) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.

(9) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(10) Addition of 2 equiv of methyllithium to **7** gave the corresponding epoxy methyl ketone in 64% yield, which after protection of the ketone and oxidation could be carried forward in a manner analogous to **8**.

(11) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

(12) Kraus, G. A.; Frazier, K. A.; Roth, B. D.; Taschner, M. J.; Neuenschwander, K. *J. Org. Chem.* **1981**, *46*, 2417.

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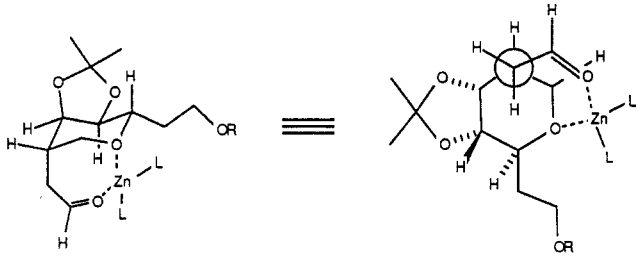
(15) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

(16) Reetz, M. T.; Kesseler, K.; Schmidtberger, S.; Wenderoth, B.; Steinbach, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 989.

(17) (a) The ratio was determined by HPLC and $^{13}C$ NMR analysis. (b) The structures of **15a,b** were determined by correlation to the products made by Midland reduction of the corresponding propargyl ketone with alpineborane[25] followed by reduction with $LiAlH_4$.

(18) Formation of the major isomer **15a** can be rationalized by least hindered addition to the chelate i.




(i)

(19) (a) The success of a silicon protecting group presumably derives from a combination of (1) the overlap of a vacant orbital on silicon with a lone pair of electrons on oxygen and (2) the steric bulk of the group. Deprotonation conditions in which the $Me_3SiCl$ was added after the base gave greatly reduced selectivity, indicating that some equilibration to the chelated enolate may be occurring. A complete study of this reaction will be reported elsewhere. (b) The absence of chelation also finds support in earlier, unrelated work by Keck: Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265. Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883.

(20) (a) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1979**, 4475. (b) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.

(21) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (b) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

(22) Wuts, P. G. M.; D'Costa, R.; Butler, W. *J. Org. Chem.* **1984**, *49*, 2582.

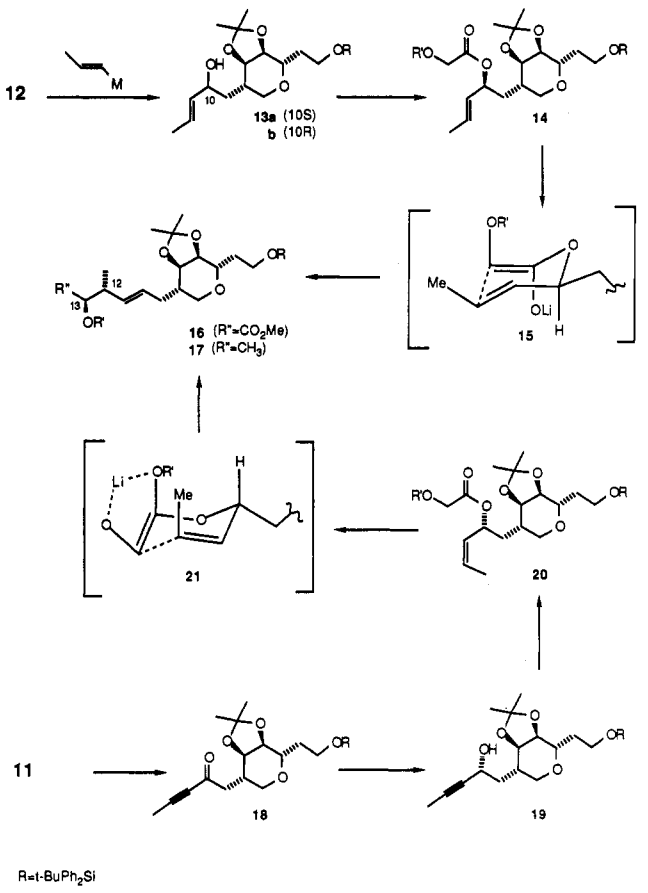
(23) **19** was identical with material made by Julia coupling of aldehyde **14** with the required optically active sulfone. Details will be reported in the full paper.

(24) Yamaguchi, M.; Waseda, T.; Hirao, I. *Chem. Lett.* **1983**, 35.

(25) (a) Midland, M. M.; McDowell, D. C.; Hawtch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867. (b) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1982**, *47*, 1606.

(26) We thank Professor James Kallmerten of Syracuse University for many helpful discussions concerning this rearrangement.

**Scheme III**




25 °C; 75%) then gave the natural product **1c**, $[\alpha]^{25}_D$ +7.64 (*c* 0.78, $CHCl_3$), which exhibited the expected biological activity.

In summary, we have developed a new stereospecific approach to the *C*-pyranoside nucleus found in the pseudomonic acids, along with a modification of the glycolate ester enolate Claisen rearrangement, both of which should find further application in natural product synthesis.

**Acknowledgment.** We thank the Physical Chemistry Department of Hoffmann-La Roche Inc. for the determination of physical and analytical data, as well as Milton Jones and Toomas Mitt for their experimental assistance and Claudette Czachowski for typing this manuscript.

**Supplementary Material Available:** $^1H$ and $^{13}C$ NMR data of key compounds (3 pages). Ordering information is given on any current masthead page.

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## Synthetic Studies of the Rubradirins: A Strategy for the Incorporation of the Ansa Bridge

*Summary:* An intramolecular Wadsworth-Emmons cyclization strategy is described for the construction of a rubradirin-related model system.

*Sir:* Rubradirin, an ansamycin isolated in 1964 from *Streptomyces achromogenes* var. *rubradiris* by workers at the Upjohn Company,[1] is a potent inhibitor of polypeptide biosynthesis[2] and its aglycone a potent inhibitor of RNA polymerase.[3] Two biologically less active congeners, rubradirins B and C, have also been isolated from this *Streptomyces* strain.[4] In continuation of our synthetic studies of these molecules,[5] we describe herein a model study which has led to the construction of a heptasubstituted naphthalene derivative containing an aliphatic ansa bridge bereft of most of the functionality but of the same size as that found in rubradirin (Chart I).

In this effort we planned to react 2,3-dichloro-*p*-benzoquinone (**2**) with the trisubstituted diene **1** (Scheme I). After appropriate manipulation of the oxidation state of the Diels-Alder cycloadduct, a regioselective Michael addition-elimination reaction was planned using methyl *N*-methyl-$\beta$-aminopropionate as the nucleophile. We assumed that the mesomeric effect of the methoxy group would guide the entry of the amine as depicted.[5e,6] Last, reduction of the quinone, O-methylation, and conversion of the ester to a $\beta$-keto phosphonate derivative was envisioned to provide the bridged naphthalene derivative through use of an intramolecular Wadsworth-Emmons condensation reaction.[7]

The required diene **1** was prepared from 7,7-dimethoxyheptanal (**7**)[8] by reaction with isopropenylmagnesium bromide followed by acetal exchange using ethylene glycol (Scheme II). The intermediate alcohol was oxidized by the Swern procedure, and the resulting enone was treated with LDA and $Me_3SiCl$ to provide **1**. Next, a Diels-Alder reaction of **1** with 2 equiv of 2,3-dichloro-*p*-benzoquinone[9] provided the new quinone **9**. This quinone was treated with NBS to yield an $\alpha$-bromo ketone,[10] which was stirred in turn with $K_2CO_3$ and MeI to yield the 6-methoxynaphthoquinone **3**. Reaction of **3** with methyl *N*-methyl-$\beta$-aminopropionate[11] proceeded smoothly in

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