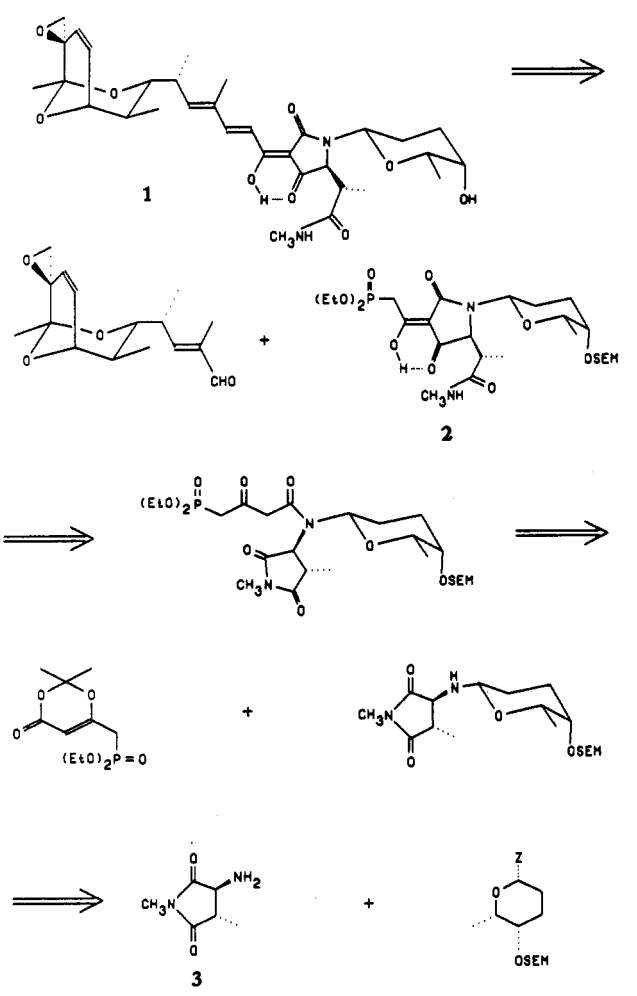
Synthetic Studies Directed toward Naturally Occurring Tetramic Acids. 3. Synthesis of (-)-Methyl Ydiginate and the Tetramic Acid Subunit for Streptolydigin

Summary: A concise stereocontrolled and enantioselective synthesis of the N-glycosylated tetramic acid subunit **2** required for streptolydigin (**1**) is described. Key features of the convergent synthesis include the condensation of aminosuccinimide **3** with pyrrolidinorhodinose **16** to β-glycosylamine **17** and eventual elaboration of tetramic acid **2** by a Dieckmann condensation. The structure and absolute stereochemistry of **17** was confirmed by correlation with (-)-methyl ydiginate (**4**) and its 4′-*O*-acetyl derivative **19**, previously obtained from a major degradation product of natural streptolydigin (**1**).

Sir: As part of our efforts directed toward the total synthesis of streptolydigin (**1**),[1] which exhibits antibiotic activity against gram-positive bacteria,[2] and antitumor activity against leukemic cells,[3] we required the tetramic acid synthon **2**. Furthermore, studies by Rinehart and Lee suggested that the biological activity of **1** may be primarily associated with the 3-dienoyl tetramic acid moiety.[4] Thus, access to **2** would also facilitate preparation of a variety of related structures for biological evaluation.

We had, several years ago, described a general methodology for elaboration of such tetramic acid synthons,[5,6] and the successful synthesis of the related dienoyl tetramic acid tirandamycin,[7-9] appeared to confirm the likely utility of a strategy for **1** in which introduction of the tetramic acid by means of a Horner-Emmons coupling is effected late in the synthetic sequence. Application of this protocol (as outlined in Scheme I) to streptolydigin (**1**), whose structure and absolute stereochemistry had been established previously,[10] was suggested by the presence of remote chiral centers in **1** and **2** and required the development of methods for creation of the relatively rare β-*N*-glycosyl linkage between a derivative of the trideoxy carbohydrate (-)-L-rhodinose[11] and amino imide **3**. The foregoing retrosynthetic analysis also required that both the amino imide **3** and the rhodinose derivative be obtained as optically pure diastereomers, and this requirement was a primary consideration in the selection of the sequences for preparation of these intermediates. The creation of the tetramic acid unit by sequential acylation and Dieckmann condensation mirrors the work of Rinehart and our later studies.[4,5,7] In this communication, we report the successful application of this general strategy to the synthesis of (-)-methyl ydiginate (**4**) and the tetramic acid **2**, required for **1**.

Scheme I



Turning to the preparation of the primary intermediates, (-)-L-rhodinose and its derivatives have been prepared previously by a number of synthetic routes,[12] however, none of the existing methods readily provided an appropriately protected intermediate of suitable optical purity. Use of (-)-L-rhodinose itself as an intermediate was precluded by our inability to differentially protect the pyranose isomer leading to the intractable mixtures of pyranose and furanose derivatives. Thus, a new route was devised which satisfied the above criteria utilizing an (*S*)-lactic acid derivative as the origin of the chirality (Scheme II).

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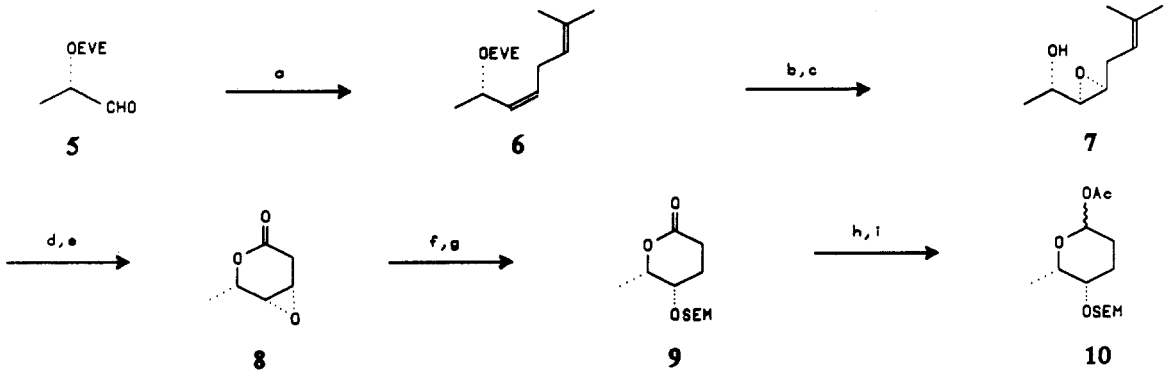
Scheme II[a]



[a] Reagents: (a) $(CH_3)_2C{=}CHCH_2CH_2PPh_3^+Br^-$ (1.3 equiv), KH (1.3 equiv), THF, 0 °C, 20 min; (b) CH_3OH, Dowex-50W-X2 (H^+), −20 °C, 36 h; (c) *t*-BuOOH (1.1 equiv), $Ti(O\text{-}i\text{-}Pr)_4$ (1.1 equiv), CH_2Cl_2, −20 °C, 18 h; (d) O_3, CH_3OH–CH_2Cl_2, −78 °C, then DMS; (e) PDC (3 equiv), CH_2Cl_2, 23 °C, 24 h; (f) SEMCl (2 equiv), $(i\text{-}Pr)_2NEt$ (2 equiv), CH_2Cl_2, 23 °C, 36 h; (g) H_2 (1 atm), Pd–C, EtOAc, 1.5 h; (h) $(i\text{-}Bu)_2AlH$ (1.2 equiv), CH_2Cl_2, 0 °C, 2 h; (i) Ac_2O (excess), DMAP (catalytic), Py–CH_2Cl_2 (1:1), 1 h.

The sequence was initiated from the known aldehyde **5**,[13] which was subjected to Wittig olefination to produce the protected dienol **6** in 74% yield.[14,15] After deblocking under standard conditions, directed epoxidation of the resulting dienol by the method of Sharpless[16] produced epoxide **7** as a single diastereomer.[17] Ozonolysis of **7** and pyridinium dichromate[18] (PDC) oxidation of the intermediate lactols provided the corresponding β,γ-epoxy δ-lactone **8** in 54% yield (overall from **6**). Treatment of **8** with $i\text{-}Pr_2NEt$ in the presence of SEMCl,[19] which effected concomitant opening of the epoxide and in situ derivatization of the resulting secondary alcohol, followed by catalytic reduction of the intermediate α,β-unsaturated lactone over Pd–C cleanly produced lactone **9** in 81% yield (from **8**). Reduction of **9** to the corresponding lactol(s) with $i\text{-}Bu_2AlH$, followed by acetylation gave the SEM-protected *O*-acetylrhodinopyranosides **10** (variable mixture of anomers) in 97% yield (31% over eight steps).

Preparation of the amino imide **3**[4,20] began with esterification of the known optically active allylic alcohol **11** ($[\alpha]^{23}_D$ +3.17° (*c* 0.85, CH_2Cl_2), ~90–95% optical purity)[16] with *N*-*t*-BOC glycine under standard conditions (Scheme III).[21] Enolate Claisen rearrangement of the resulting ester **12** then proceeded smoothly, as described by Bartlett, to provide the protected threo amino acid **13** (8:1 threo/erythro) in 79% overall yield.[22] Conversion to the related *N*-methyl amide (mp 143–144 °C) via the mixed anhydride and ozonolysis produced the solid hemiaminal(s) **14** (mp 159–161 °C) in 71% yield. Oxidation of **14** under mild conditions with PDC gave the *t*-BOC imide **15** (8:1 trans/cis) which was directly deblocked to afford the desired crystalline amino imide **3** (mp 102–103 °C, $[\alpha]^{23}_D$ −136° (*c* 0.39, $CHCl_3$), ~90% optical purity) in 60% yield (34% over six steps).[23]

We considered the suitability of a number of derivatives of the SEM-protected L-rhodinopyranoside for the critical coupling sequence during which the β-*N*-glycosyl linkage is established.[24] However, attempts to induce glycosidation through conventional activation of the anomeric position with halides, trichloroimidate,[25] or acetates **10** (in the presence of Lewis acids) resulted in decomposition, elimination to the glycal, or no reaction. These methods had in common the fact that coupling proceeds via cyclic oxonium ion intermediates. Thus, we sought a derivative which was stereochemically homogeneous at the anomeric center to minimize difficulties in the stereochemical analysis and whose mode of coupling might involve non-

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(14) This Wittig reaction was complicated by the tendency of the phosphonium salt toward elimination during formation of the ylide and the ready racemization of **5**. The ylide was best prepared by slow addition of the solid salt to a suspension of KH in THF with rapid stirring. The resulting ylide was then transferred by cannula to another vessel and the aldehyde introduced dropwise.

(15) The optical purity of **6** was checked after removal of the protecting group by conversion to a Mosher ester.[32] The ^1H NMR spectrum revealed the presence of a single diastereomer when compared to a racemic sample indicating an optical purity of >98% (the limit of detection).

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(18) All new substances exhibited spectroscopic data (IR, ^1H NMR (300 MHz), MS) consistent with the assigned structures and acceptable combustion or high-resolution mass spectral analytical data. Selected ^1H NMR data (δ at 300 MHz in $CDCl_3$, unless otherwise indicated). **2**: 4.80–4.50 (m, 3 H), 4.30–4.00 (m, 3 H), 4.10 (q, J = 7.1 Hz, 4 H), 3.70–3.30 (m, 6 H), 3.00 (m, 3 H), 2.40–1.30 (m, 5 H), 1.30 (t, J = 7.1 Hz, 6 H), 1.30–1.00 (m, 6 H), 0.90 (m, 2 H), 0.00 (s, 9 H). **4**: 5.02 (m, 1 H), 4.02 (d, J = 7 Hz, 1 H), 3.89 (s, 3 H), 3.72 (m, 1 H), 3.58 (br s, 1 H), 3.10–2.90 (m, 1 H), 3.02 (s, 3 H), 2.10–1.50 (m, 5 H), 1.38 (d, J = 8 Hz, 3 H), 1.23, (d, J = 7 Hz, 3 H). **16**: 4.75 (m, 1 H), 4.65 (m, 1 H), 4.08 (d, J = 10.4 Hz, 1 H), 3.60 (m, 3 H), 3.40 (s, 1 H), 2.87 (m, 2 H), 2.79 (m, 2 H), 2.10–1.40 (m, 8 H), 1.20 (d, J = 6.4 Hz, 3 H), 0.90 (t, J = 8.6 Hz, 2 H), 0.0 (s, 9 H). **17**: 4.75 (d, J = 7.1 Hz, 1 H), 4.65 (d, J = 7.1 Hz, 1 H), 4.03 (m, 1 H), 3.94 (d, J = 5.1 Hz, 1 H), 3.60 (m, 5 H), 2.94 (s, 3 H), 2.70 (m, 1 H), 2.20–2.00 (m, 2 H), 1.70–1.50 (m, 2 H), 1.34 (d, J = 6.4 Hz, 3 H), 1.21 (d, J = 7.4 Hz, 3 H), 0.88 (t, J = 8.8 Hz, 2 H), 0.0 (s, 9 H). **18**: 5.00 (dd, J_1 = 10 Hz, J_2 = 7 Hz, 1 H), 4.69 (d, J = 7 Hz, 1 H), 4.60 (d, J = 7 Hz, 1 H), 4.04 (d, J = 6 Hz, 1 H), 3.85 (s, 3 H), 3.75–3.40 (m, 4 H), 3.10–2.98 (m, 1 H), 3.00 (s, 3 H), 2.18–1.55 (m, 4 H), 1.38 (d, J = 8 Hz, 3 H), 1.20 (d, J = 7 Hz, 3 H) 0.89 (m, 2 H), −0.03 (s, 9 H). **19**: 5.09 (dd, J_1 = 8 Hz, J_2 = 6 Hz, 1 H), 4.78 (br s, 1 H), 3.97 (d, J = 7 Hz, 1 H), 3.89 (s, 3 H), 3.79 (m, 1 H), 3.08–2.98 (m, 1 H), 3.03 (s, 3 H), 2.10–2.00 (m, 1 H), 2.09 (s, 3 H), 1.95–1.80 (m, 3 H), 1.38 (d, J = 7 Hz, 3 H), 1.15 (d, J = 6 Hz, 3 H). **20**: 4.95 (br d, J = 10 Hz, 1 H), 4.70 (m, 2 H), 4.10 (m, 5 H), 3.80–3.30 (m, 8 H), 3.00 (s, 3 H), 2.45 (m, 1 H), 1.90–1.40 (m, 4 H), 1.40–1.10 (m, 12 H), 0.90 (m, 2 H), 0.00 (s, 9 H).

(19) For protection of alcohols with 2-[(trimethylsilyl)ethoxy]methyl chloride (SEMCl), see: Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett* **1980**, *21*, 3343.

(20) We observed that certain precursors (such as **15**) of amino imide **3** were apparently susceptible to racemization upon attempted isomerization from cis to trans; thus we could not rely upon equilibration to control the relative stereochemistry. In our hands, resolution of β-methyl aspartic acid[33] did not provide a practical source of sufficient quantities of **3** of high optical purity.

(21) Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; Wiley: New York, 1961; Vol. 2.

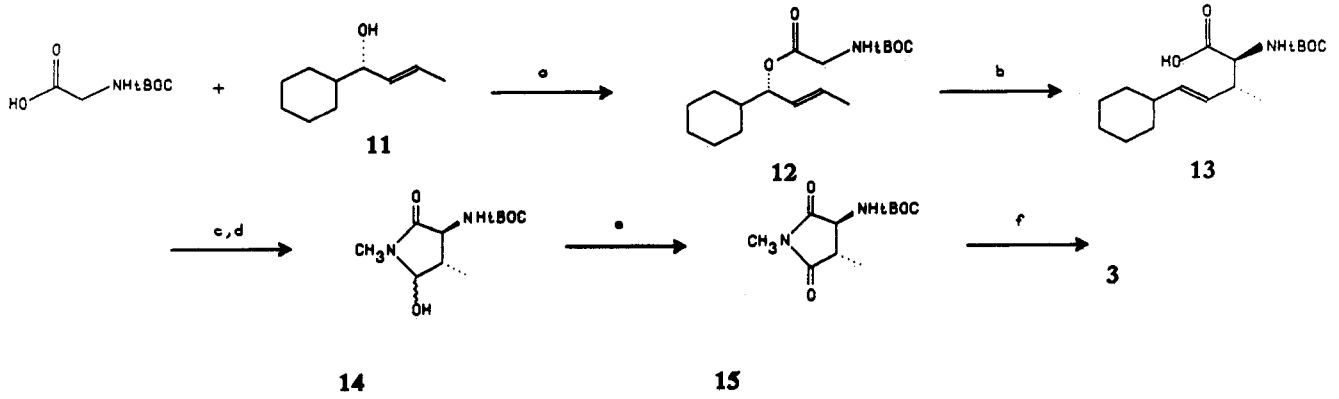
(22) Bartlett, P. A.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3933.

(23) The optical purity of synthetic **3** was confirmed by a combination of conversion to the Mosher amide[32] and NMR shift reagent studies.

(24) The glycosidic linkage in **1** was assigned as β-L by Rinehart,[8d] and we have applied this nomenclature to all the N-glycosylated derivatives of rhodinose which on the basis of ^1H NMR evidence adopt the same conformation in solution.

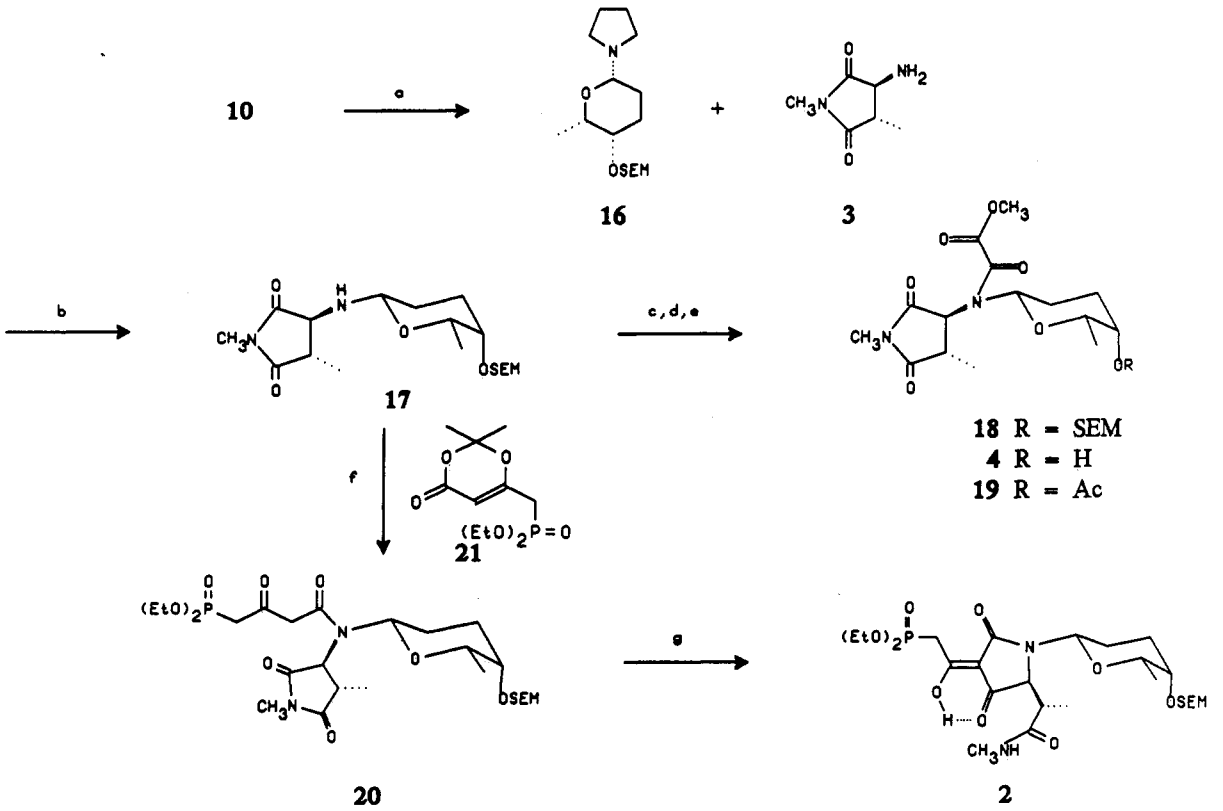
(25) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 731.

Scheme III[a]



[a] Reagents: (a) DCC (1 equiv), DMAP (catalytic), Et_2O, 0 → 23 °C, 19 h; (b) LDA (2.2 equiv), Me_3SiCl (2.2 equiv), −78 → 60 °C, 2 h then HCl; (c) *i*-BuOCOCl (1 equiv), Et_3N (1 equiv), PhH–Et_2O (1:1), −10 C, 1.5 h, then CH_3NH_2 (excess), 0 °C, 1.5 h; (d) O_3, CH_2Cl_2, −78 °C, then DMS; (e) PDC (3 equiv), CH_2Cl_2, 23 °C, 18 h; (f) anhydrous HCl (saturated) Et_2O, 23 °C, 18 h.

Scheme IV[a]



[a] Reagents: (a) pyrrolidine (as solvent), BF_3·Et_2O (catalytic), 23 °C, 0.5 h; (b) CSA (1 equiv), CH_3CN, 23 °C, 18 h; (c) $ClCOCO_2CH_3$ (1.25 equiv), Et_3N (3 equiv), CH_2Cl_2; 23 °C, 5 min; (d) Me_3SiI (excess), $CHCl_3$, −78 → −60 °C, 8 min; (e) Ac_2O (excess), pyridine, 23 °C, 12 h; (f) xylenes, 135 °C, 3.5 h; (g) KO-*t*-Bu (1.0 equiv), THF, 23 °C, 18 h.

cyclic intermediates. Such a derivative was the sensitive β-pyrrolidino-L-rhodinopyranoside **16**[24] which was obtained in 90% yield upon treatment of the acetates **10** with excess pyrrolidine in the presence of BF_3·Et_2O (catalytic) as shown in Scheme IV. The large coupling constant (J = 10.4 Hz) exhibited by the proton at the anomeric center unequivocally established the presence of the β-glycosyl linkage in **16**.

The key coupling of **3** and **16** was then effected (Scheme IV) without further purification of **16** by treatment of a solution of **16** in anhydrous CH_3CN at 25 °C with amino imide **3** in the presence of camphorsulfonic acid. An aminal exchange reaction ensued to produce the required β-glycosyl amine **17** in nearly quantitative yield.[26] High-field ^1H NMR decoupling experiments unequivocally established the presence of the expected large coupling constant (J = 10.4 Hz) for the proton at the anomeric center, consistent with the presence of a β-glycosidic linkage in **17**. Under acidic conditions, exclusive formation of the β-*N*-glycoside is most probably due to thermodynamic control. Dipole–dipole interactions are known to destabilize the α-glycoside isomer when nitrogen bears a positive charge as would be the case for **17** in acidic media. This phenomenon, referred to as the reverse anomeric effect, has been observed previously.[27]

(26) This process presumably occurs via exchange of **3** and pyrrolidine through the related acylic iminium ion.

In order to confirm the structure and absolute stereochemistry of glycosyl amine **17**, which contains all the stereochemistry required for conversion to **2** and ultimately **1**, we converted **17** to (-)-methyl ydiginate, a derivative of a primary degradation product of natural streptolydigin. Thus, treatment of **17** with methyl chlorooxalate cleanly afforded the 4'-*O*-SEM-protected (-)-methyl ydiginate **18** in 81% yield. Cleavage of the SEM ether was effected by treatment with Me_3SiI at -78 °C to afford (-)-methyl ydiginate (**4**) (74%) which was identical with that derived from natural streptolidigin by comparison of IR and ^1H NMR spectra.[28] Further confirmation of stereochemistry and absolute configuration was obtained upon acetylation of **4** (quantitative yield) to (-)-methyl 4'-*O*-acetylydiginate **19** (mp 157-159 °C, $[\alpha]^{23}_D$ -23.9° (*c* 0.590 CH_3OH)), which was identical in all respects (^1H NMR, IR, and optical rotation) with **19** (mp 157-159 °C, $[\alpha]^{32}_D$ -25° (*c* 1.13, CH_3OH)) derived from natural streptolydigin.[28,29]

Preparation of the required tetramic acid synthon **2** was then completed along the lines of our earlier studies.[5] Acylation of **17** to the highly polar and somewhat sensitive β-keto amide **20** proceeded smoothly in 53% yield upon treatment of **17** with dioxenone **21**[30] at 135 °C in xylenes, presumably via the intermediacy of the acyl ketene.[31] Final closure to the tetramic acid was effected by treatment of β-keto amide **20** with *t*-BuOK in THF at 25 °C for 18 h followed by acidification (HCl) affording **2** as a highly polar oil after chromatography on Biosil A. Nonnucleophilic bases and aprotic media proved to be best for the former transformation. The highly polar enolic nature of tetramic acid **2** complicated characterization by spectral methods, however, **2** exhibited UV absorption (λ_{max} 285 nm) characteristic of tetramic acids, and possessed IR, ^1H NMR, and field desorption mass spectra consistent with structure **2** and similar to related substances prepared previously in our laboratories.[5,7]

We are currently examining the Horner-Emmons reactions of **2**, and the application of **2**, using the aforementioned strategy, to the construction of streptolydigin (**1**) itself.

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(28) We thank Dr. Donald Borders, Lederle Laboratories, for helpful discussions, and for provision of copies of the IR and NMR spectra and other pertinent characterization data for **4** and **19**.
(29) The reported melting point for (-)-methyl 4'-*O*-acetylydiginate (**19**)[10b] is in error. The correct melting point, reported herein, is recorded in the related dissertation: Borders, D. B., Ph.D. Dissertation, University of Illinois, Urbana-Champaign, IL 1963.
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(33) McClarin, J. A.; Dressel, L. A.; Legg, I. J. *J. Am. Chem. Soc.* **1976**, *98*, 4150.

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Catalytic Reductions of Alkyl Halides Using Soluble Polyethers and Tri-*n*-butyltin Chloride as Cocatalysts

Summary: Alkyl and aryl halides can be reduced by suspensions of sodium borohydride in toluene to yield hydrocarbons in high yield by using as cocatalysts tri-*n*-butyltin chloride and polyether phase-transfer catalysts.

Sir: Phase-transfer catalysis has developed into a useful procedure in organic synthesis.[1] Recently, we have begun to study phase-transfer-catalyzed reactions under solid-liquid conditions using both conventional crown ether and polymeric catalysts including poly(ethylene glycol) derivatives and polyethylene-bound crown ether catalysts. In this communication, we describe a new procedure using either of these sorts of catalysts by which carbon-halogen bonds are reduced to carbon-hydrogen bonds using tri-*n*-butyltin chloride as a cocatalyst and a suspension of sodium borohydride as the source of the hydride.

A variety of methods exist for replacement of carbon-bonded halogen by hydride. As an outgrowth of our recent work in solid-liquid phase-transfer-catalyzed reactions,[2] we chose to examine possible procedures by which toluene suspensions of sodium borohydride could be used to effect such a process. While complex hydrides which are soluble in organic solvents are known to nucleophilically substitute hydride for halide,[3] sodium borohydride in the presence of benzo-15-crown-5 (**1**) was only a modestly effective reagent for this reaction under the conditions we used. However, suspensions of sodium borohydride in the presence of a crown ether like **1** along with tri-*n*-butyltin chloride were more reactive alkyl halide reducing agents. Apparently **1** acts as a phase-transfer catalyst to form tri-*n*-butyltin hydride from tri-*n*-butyltin chloride in toluene. The tri-*n*-butyltin hydride so formed reduces the alkyl halide. Since the product of the tin hydride reduction of an alkyl or aryl halide is a tin halide, the overall reaction shown in eq 1 used the crown ether and tri-*n*-butyltin

$$\underset{X=Cl,\ Br}{R-X} \xrightarrow[\text{excess } NaBH_4,\ C_6H_5CH_3,\ 110\ ^\circ C]{5\%\ \mathbf{1},\ \mathbf{2},\ \text{or}\ \mathbf{3},\ 5\text{-}10\%\ (n\text{-}Bu)_3SnCl} R-H \qquad (1)$$

chloride as cocatalysts. A polyethylene-bound crown ether (**2**) and poly(ethylene glycol) dimethyl ether (**3**) were also used as phase-transfer catalysts for reaction 1 although both were less active than **1**. Table I lists some representative results from these studies.

In situ formation of tin hydrides has been reported previously using alcoholic solutions of triorganotin halides and hydride reducing agents.[6-8] Ethereal solutions of the more reactive hydride source $LiAlH_4$ have also been used with catalytic amounts of dialkyltin dihalides.[9] While the

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(4) The polyethylene derivative of benzo-15-crown-5 was prepared as previously described.[2]
(5) The poly(ethylene glycol) dimethyl ether had a M_r of 1000 and was obtained from Aldrich Chemical Co.
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(8) The alcohol solvent used in these reactions also destroys the BH_3 byproduct from reduction of the tin halide by $NaBH_4$.
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