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A SYNTHESIS OF THE TETRAMIC ACID SUBUNIT OF STREPTOLYDIGIN: A REACTIVITY DEFINITION OF THIS SUBUNIT AS AN EMMONS REAGENT

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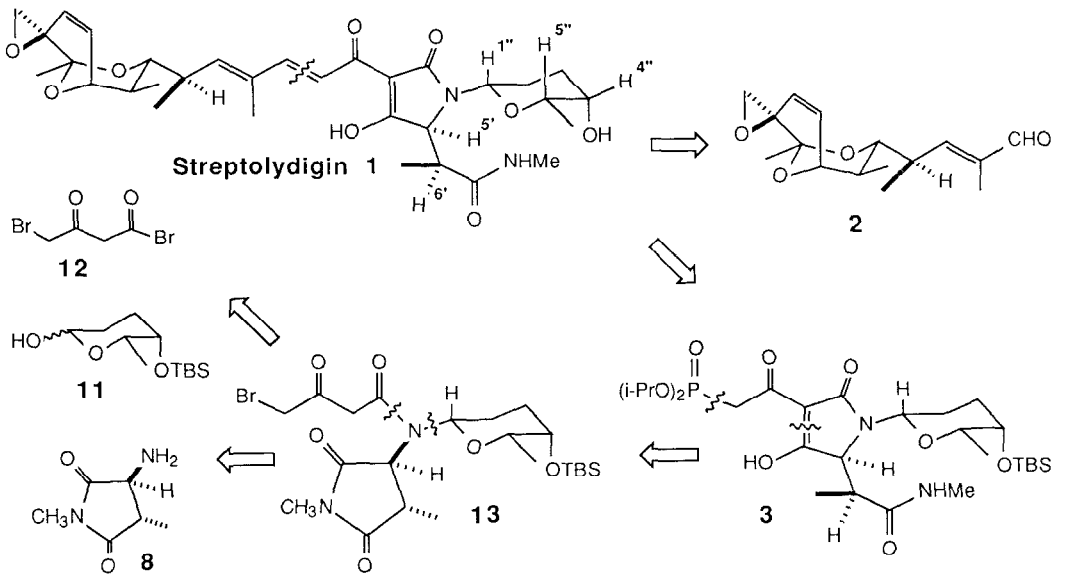
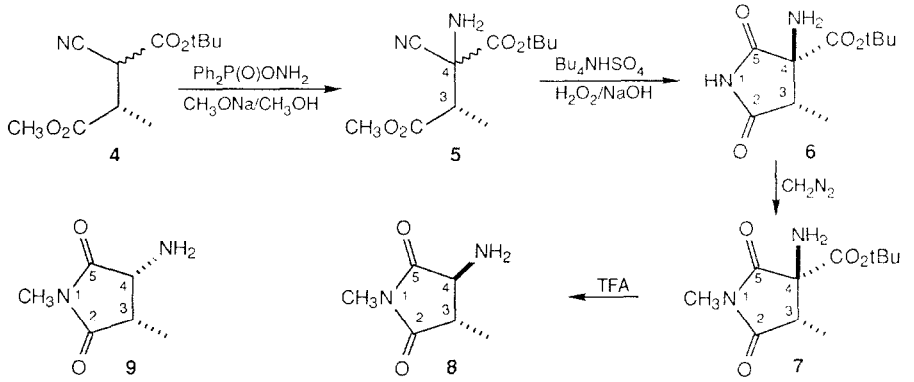
Summary: *A practical and brief construction of the tetramic acid-derived Emmons reagent **3** is described. The reactivity of this substance with aldehydes has been examined with respect to its use in a synthesis of the antibiotic streptolydigin.*

We are engaged in an effort to prepare the antibiotic streptolydigin (**1**)[2] by joining the unsaturated aldehyde **2** with the tetramic acid-derived Emmons reagent **3**. Herein, we recount a brief construction of the tetramic acid subunit **3**, and describe its olefination characteristics with aldehydes.[3] Shown below is our approach to both **1** and **3** outlined in *retro*-synthetic fashion.



The synthesis of **3** commenced with a Mitsunobu coupling of *t*-butyl cyanoacetate and methyl lactate to give **4** as a mixture of diastereomers.[4] Treatment of **4** with the aminating reagent $Ph_2P(O)ONH_2$ in the presence of CH_3OH/CH_3ONa afforded the corresponding amine **5** (70%

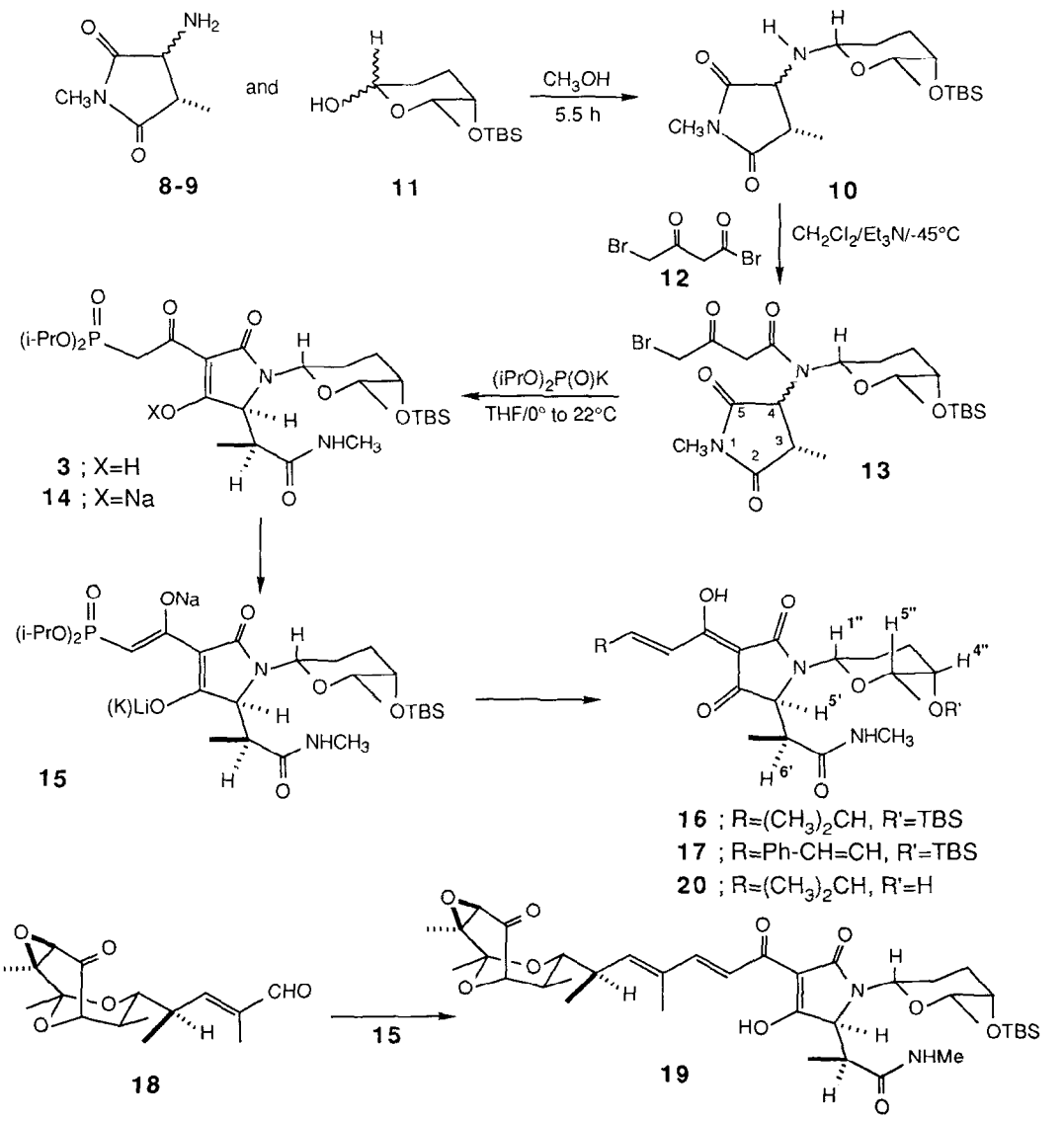
yield), also as a mixture of diastereomers.[5] Hydration of the nitrile portion of **5** with concomitant imide formation was accomplished in methylene chloride solution using basic hydrogen peroxide under phase transfer conditions (Bu_4NHSO_4).[6] Optically pure **6**, mp 175-176°C, $[\alpha]_D$ -43.8° (c 0.815, CH_2Cl_2) was separated from its optically impure C-4 diastereomer by filtration chromatography in 55% absolute yield. **6** was then converted into its N-methyl analogue **7**, mp 52.5-53°C, $[\alpha]_D$ -42.7° (c 1.13, CH_2Cl_2) through the agency of diazomethane (90% yield). Reaction of **7** with trifluoroacetic acid followed by filtration through basic alumina (activity grade II) afforded the amino-imides **8** and **9** as a 2:1 mixture of *trans* and *cis* isomers, respectively (87% yield).[7]



The 2:1 mixture of amino-imides **8** and **9** was used in the next two steps on the assumption that glycosylation and acylation of the amine residue would allow us to epimerize the amino center into the *trans* compound. Thus, the glycosylamine **10**, as a 2:1 mixture of *trans* to *cis* isomers was prepared (quantitative yield) by simply mixing the amino-imides **8** and **9** with the C-4 hydroxyl protected L-(-)-rhodinose derivative **11**[8] in methanol (0.5 M) for 5.5 h.[9] The 9 Hz coupling constant observed between the axial anomeric proton (4.00 ppm, $CDCl_3$) and the axial proton of the adjacent methylene group present in **10** indicated an equatorial positioning of the amino group on the rhodinose ring.[10] Without purification, **10** was acylated with the acid bromide **12** (CH_2Cl_2/Et_3N/ -45°C) to afford (80% yield) a 1.3:1 mixture of C-4 isomers, **13**, (each a mixture of β-keto amide tautomers). Treatment of **13** with $(iPrO)_2P(O)K$ in THF solution (0°C, 3 h, 22°C, 5 h) gave rise to **3** (>90% yield of crude material) which appeared (^1H NMR) to be a single compound with respect to the five stereogenic centers contained within it. **3** exists as a tautomeric mixture ($CDCl_3$) and as one tautomer ($CDCl_3$) as its mono-sodium salt, **14**.[11,12]

Our purpose in preparing the tetramic acid-derived Emmons reagent **3** was to test its feasibility as a synthon for reaction with the aldehyde **2**. It was our finding that **3** was most easily characterized, and stored, as its mono-sodium salt **14**; hence, either lithium diisopropylamide or potassium *t*-butoxide (1 eq) was used to generate what we believe to be the dianion species **15**. We first examined the reaction of isobutyraldehyde with **15** (THF, 0.1 M, 0°C, 2 h) and found that a single olefination adduct, **16**, was readily formed in 70% yield.[12] *Trans*-cinnamaldehyde also readily formed a single olefination adduct, **17**, in 55% yield, but *trans*-2-hexenal failed to afford any

detectable yield of olefination adduct. Most importantly, the unsaturated aldehyde **18**[13] gave ca. a 20% yield of the olefination product **19.**[14] Portentous as the latter result might be, we are nevertheless pursuing the preparation of aldehyde **2** in the hope of combining it with the Emmons reagent **3** to consummate the synthesis of streptolydigin.



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REFERENCES AND FOOTNOTES

1. National Science Foundation Predoctorate Fellow, Sherman Clark Fellow.

2. Rinehart, K. L., Jr.; Beck, J. R.; Borders, D. B.; Kinstle, T. H.; Krauss, D. *J. Am. Chem. Soc.* **1963**, *85*, 4038.

3. An Emmons reagent very similar to **3** has been prepared, *via* a different and interesting route, by Boeckman, R. K., Jr.; Potenza, J. C.; Enholm, E. J. *J. Org. Chem.* **1987**, *52*, 469. Olefination reactions of this reagent were not reported in this manuscript.

4. Kurihara, T.; Sugizaki, M.; Kime, I.; Wada, M.; Mitsunobu, O. *Bull. Chem. Soc. Jpn.* **1981**. *54*, 2107.

5. Boche, G.; Bernheim, M.; Schrott, W. *Tetrahedron Lett.* **1982**, *23*, 5399.

6. Cacchi, S.; Misiti, D.; La Torre, F. *Synthesis,* **1980**, 243.

7. We evaluated the ee of compounds **5**, **6**, **7**, **8**, and **9**, with respect to the C-3 methyl group by $Eu(tfc)_3$ (either C_6D_6 or $CDCl_3$) and by examination of the Mosher amide. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

8. Schlessinger, R. H.; Graves, D. D. *Tetrahedron Lett.* preceding Letter.

9. For other examples, see Kagan, F.; Rebenstorf, M. A.; Heinzelman, R. V. *J. Am. Chem. Soc.* **1957**, *79*, 3541. A different means of constructing a similar glycosylamine is described in reference 3.

10. As further proof of the structure of **10**, it was converted,*via* the action of methyl oxalyl chloride (CH_2Cl_2/Et_3N) followed by desilylation (Bu_4NF/THF), into (-)-methyl ydiginate (reference 3 and references cited therein). The axial anomeric proton, in this instance appears at 5.01 ppm (dd J_1=10.8, J_2=3). The ^1H NMR (300 MHz) spectrum of (-)-methyl ydiginate prepared in this manner was identical to one of synthetic material given us by Dr. E. J. Enholm (reference 3). We thank Professor Boeckman and Dr. Enholm for this spectrum.

11. A rearrangement similar to that found in the conversion of **13** into **3** has been reported by Cartwright, D.; Lee, V. J.; Rinehart, K. L. Jr. *J. Am. Chem.Soc.* **1978**, *100*, 4237. **3** proved unstable to chromatography, even using Bio-Sil A (100-200 mesh) as an adsorbent. As its mono-sodium salt, **3** could be stored for long periods, and from its ^1H NMR (300 MHz) spectrum it was estimated to be 95% pure.

12. The reaction protocol described herein is the culmination of an extensive examination of the behavior of reagent **15** towards aldehydes. The adduct **16**, $[\alpha]_D$ +51.6° (c 0.96, $CHCl_3$, as sodium salt) was desilylated (Bu_4NF/THF) to give its corresponding hydroxyl analogue, **20**. The ^1H NMR (300 MHz, $CDCl_3$) spectrum of this substance was compared, where appropriate, to the ^1H NMR (300 MHz, $CDCl_3$) spectrum of a sample of streptolydigin kindly provided us by Professor K. L. Rinehart. We thank Professor Rinehart for his generosity. Adduct **20**, ppm 4.85 (d, J=1, proton 5'), 3.04 (q, J=7, proton 6'), 2.87 (d, J=5, N-CH_3 group), 5.55 (dd, J_1=12, J_2=3, proton 1"), 3.40 (s, proton 4"), 3.61 (q, J=7, proton 5"). Natural streptolydigin (**1**) ppm 4.84 (s, proton 5'), 3.05 (q, J=7, proton 6'), 2.87 (d, J=5, N-CH_3 group), 5.56 (dd, J_1=12, J_2=2, proton 1"), 3.40 (brs, proton 4"), 3.63 (partially obscured q, proton 5").

13. Schlessinger, R. H.; Bebernitz, G. R.; LIn, P.; Poss, A. J. *J. Am. Chem. Soc.* **1985**,*107*, 1777.

14. **19** could not isolated in pure form; and thus, its structure should be viewed as tentative.

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