integrated with results from the ongoing 2D ^1H NMR studies.

In conclusion, it is clear that the ^1H-detected HMQC method provides a valuable approach to exploring the NMR of spin $^1/_2$ metals where resolvable coupling to proton is present. In complex cases the dispersion in two dimensions helps in resolving both ^1H and metal spectra, and by appropriately adjusting the preparation delay in the pulse sequence, sites interacting with different couplings can be selected providing a further means of editing the spectrum.

Acknowledgment. This research was supported by grants from the National Institutes of Health AM 18778 (I.M.A.) and AM 20357 (D.C.) and by AHA (82-1099). We thank Dr. Donald G. Davis for valuable discussions.

Registry No. ^{113}Cd, 14336-66-4; Cd-EDTA, 16950-14-4.

Total Synthesis of (−)-Tirandamycin A[1]

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Received November 19, 1984

The unusual skeletal array contained in the antibiotic tirandamycin A (**1**)[3] has stimulated considerable effort toward its construction. Thus far, these synthetic endeavors have focused on the preparation of tirandamycic acid,[4] a degradation product of **1**.[5] We now wish to describe a synthesis of the antibiotic itself which utilizes the simple concept that the unsaturated lactone **2** should afford the bicyclic ketal **3** upon addition of methyllithium followed by acid treatment. A threo- and "Cram"-selective aldol condensation involving the vinylogous urethane **4** expedites the formulation of this lactone.[6]

Vinylogous urethane **4**[7] (2.0 equiv) was deprotonated (LDA/THF) and treated with the aldehyde **5**[8] (1.0 equiv) to afford the lactone **6**,[9] mp 150 °C, in 75% yield after chromatography and crystallization (Scheme I). The thiomethyl group, having played its pivotal role as the agency of threo and "Cram" stereoselection,[9] was then desulfurized (Bu_3SnH/AIBN)[10] to give the lactone **7**, mp 93 °C, after chromatography and crystallization in 90% yield. Compound **7** was then converted into lactone **2** in the following manner. Reductive methylation of **7** (1.0 equiv) was accomplished by its addition to a solution of lithium (5.0 equiv) in NH_3 until the blue color was discharged.[11] THF was then added to the mixture to give a 0.25 M suspension based on **7**. The ammonia was then removed (0.2 torr) and the resulting mixture treated with methyl iodide (6.0 equiv). Filtration of this mixture through silica gel gave an oil. Elimination of the pyrrolidine residue was carried out by the addition of *m*-CPBA (1.1 equiv) to a mixture of this oil (1.0 equiv) and $NaHCO_3$ (1.5 equiv), in CH_2Cl_2, followed after 2 h by DBU (1.2 equiv). The lactone **2**, mp 38 °C, was isolated by chromatography in 70% yield from **7**.

We were gratified at this stage to discover that reaction of **2** (1.0 equiv) with CH_3Li (1.0 equiv) followed by standard workup and treatment of the resultant oil (0.05 M in THF) with hydrochloric acid (1.5 equiv, 0.7 M) gave the bicyclic ketal **3**, mp 54 °C, in 93% yield.[12] As luck would have it, however, our plan to oxidize **3** directly into the aldehyde enone **8** by using chromium trioxide 3,5-dimethylpyrazole,[13] while successful in terms of chemical yield, caused some stereochemical corruption of the product.[14] Hence, we took a somewhat longer route to a similar end.

Epoxidation of **3** (1.0 equiv) with *m*-CPBA (1.05 equiv) in CH_2Cl_2 gave a single epoxide **9**, mp 137 °C. Ring opening of **9** (1.0 equiv) with PhSeNa (10.0 equiv) in ethanol followed by chromatography gave the selenide **10**, mp 104 °C.[15] Finally, elimination of the selenide residue of **10** (1.0 equiv) by oxidation with *m*-CPBA (1.05 equiv) in CH_2Cl_2 containing $NaHCO_3$ (2.0 equiv) followed by chromatography and crystallization gave the diol olefin **11**, mp 124 °C. In this manner, a 95% overall yield for the transformation of **3** into **11** was realized.

At this juncture we commenced elongation of the side chain of **11** into the unsaturated ester enone **12**. Thus, **11** (1.0 equiv) in CH_2Cl_2 (0.5 M) was reacted with PCC (7.0 equiv) to afford the aldehyde enone **8** contaminated with approximately 20% of the corresponding aldehyde containing the unrearranged tertiary allylic alcohol residue. Under these reaction conditions, complete conversion of **11** into **8** was not possible without epimerization of the methyl group adjacent to the aldehyde moiety.[16] As a result, the mixture containing **8** (1.0 equiv) was reacted with (carbethoxyethylidene)triphenylphosphorane (5.0 equiv) in benzene (0.4 M) to yield the corresponding unsaturated ester **12**, together with its unrearranged tertiary allylic alcohol analogue.[17] These esters were readily separable by chromatography, and, thus, that ester containing the tertiary allylic alcohol residue was subsequently treated with PCC in CH_2Cl_2 to afford **12**. In this fashion, **12** (oil), as a single compound, was obtained from **11** in 89% yield.

The epoxide residue was then introduced by treatment of the enone portion of **12** (1.0 equiv) with *t*-BuO_2H (3.0 equiv) and DBU (3.0 equiv) in THF solution at 22 °C to give compound **13**, mp 130–131 °C, in 95% yield.[18] Both the ester and ketone residues of **13** (1.0 equiv) were then reduced with DiBAL-H (3.0 equiv) to afford, in 90% yield, the diol epoxide **14**, oil.[19] PCC (5.0 equiv) oxidation of **14** (1.0 equiv) gave the unsaturated

(1) We dedicate this manuscript to the memory of Professor R. V. Stevens.
(2) Merck and Co. postdoctorate fellow.
(3) See: Reusser, F. In "Antibiotics: Mechanism of Action of Antibacterial Agents"; Hahn, F. E., Ed.; Springer-Verlag: New York, 1979; Vol. V, Part I, p 361 and references cited therein.
(4) (a) Ireland, R. E.; Wuts, P. G. M.; Ernst, B. *J. Am. Chem. Soc.* **1981**, *103*, 3205. (b) Zielger, F. E.; Thottathil, J. K. *Tetrahedron Lett.* **1981**, *22*, 4883. (c) DeShong, P.; Ramesh, S.; Perez, J. J.; Bodish, C. *Ibid.* **1982**, *23*, 2243. (d) DeShong, P.; Ramesh, S.; Perez, J. J. *J. Org. Chem.* **1983**, *48*, 2117. (e) Kelly, T. R.; Arvanitis, A. *Tetrahedron Lett.* **1984**, *25*, 39. (f) Ziegler, F. E.; Wester, R. T. *Ibid.* **1984**, *25*, 617. (g) Martin, S. F.; Gluchowski, C.; Campbell, C. L.; Chapman, R. C. *J. Org. Chem.* **1984**, *49*, 2512.
(5) Duchamp, D. J.; Branfman, A. R.; Button, A. C.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 4077 and references cited therein.
(6) Schlessinger, R. H.; Poss, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 357.
(7) The vinylogous urethane **4** was prepared by thiomethylation of methyl acetoacetate followed by reaction with pyrrolidine. Compound **4**, bp 125–130 °C (3×10^{-6} torr) as well as all other new compounds cited in this manuscript gave satisfactory ^1H NMR (300 and 400 MHz), ^{13}C NMR, IR, and mass spectra. Those intermediates that were stable (e.g., **4**, **2**, **3**, **11**, **13**, and **21**) gave correct elemental analyses.
(8) This aldehyde was first described by Nagaoka et al. (Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873) who obtained this material by oxidation of its corresponding alcohol $[\alpha]_D$ −22.8° (*c* 3.73, $CHCl_3$) under Swern conditions. The aldehyde **5**, $[\alpha]_D$ −60.5° (*c* 1.46, CH_2Cl_2), in these laboratories, was also obtained by Swern oxidation of the same alcohol $[\alpha]_D$ −23.2° (*c* 1.28, $CHCl_3$). The latter substance, however, was obtained by a somewhat shorter route than that previously described.
(9) The mechanism of this interesting threo- and "Cram"-selective aldol condensation reaction has now been studied in some detail and will be published in the near future.
(10) For a leading reference, see: McIntosh, J. M.; Schram C. K. *Can. J. Chem.* **1977**, *55*, 3755.
(11) Under these reaction conditions, between 80% and 90% of 1 equiv of **7** could be added before the reaction color was discharged.
(12) These conditions are similar to those given, for a different rearrangement, in ref 4b.
(13) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057.
(14) This oxidation caused epimerization of the methyl group adjacent to the aldehyde residue under a variety of reaction conditions.
(15) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.
(16) Dauben W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682. Buffered PCC (NaOAc) produces a mixture of methyl group epimers and other products.
(17) These homologation conditions are those employed by Ireland (ref 4a).
(18) The usual epoxidation conditions, as described by Yang et al. (Yang, N. C.; Finnegan, R. A. *J. Am. Chem. Soc.* **1958**, *80*, 5845), which use Triton B as the base, were not effective for this epoxidation.
(19) This reduction yields a single compound with the assigned stereochemistry based on its ^1H NMR spectrum.

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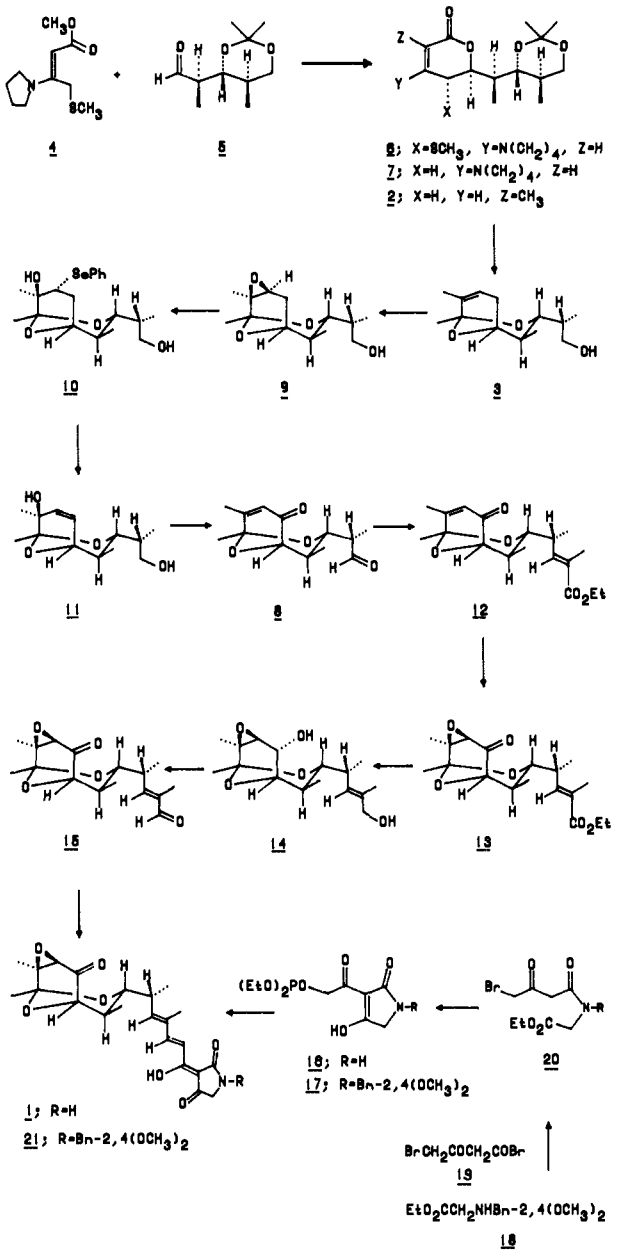
Scheme I



aldehyde ketone **15** (oil) in essentially quantitative yield. The latter substance was normally used without purification in the next synthetic step.

We now faced the introduction of the 3-acyltetramic acid portion of tirandamycin A. Boeckman and Thomas have described a reagent, **16**, which, as its dianion, undergoes an Emmons reaction with aldehydes. Unfortunately, the reaction conditions (THF/40 °C/24 h) defined by these authors for the condensation of the dianion of **16** and tiglic aldehyde were too vigorous for use with the sensitive unsaturated aldehyde **15**.[20a] Therefore, we set out to prepare an *N*-benzyl derivative of this reagent, the 3-acyltetramic acid phosphonate **17**, believing that it would exhibit greater reactivity toward unsaturated aldehydes.

The 2,4-dimethoxy-*N*-benzylglycine derivative **18** was prepared in the usual manner,[21] and reacted in CH_2Cl_2 solution at −40 °C with the acid bromide **19**[22] to give the amide **20** (thick oil) in 95% yield. Treatment of **20** (1.0 equiv) with $(EtO)_2POK$ (2.1 equiv) in THF solution (15 h) gave **17** (thick reddish oil) in 82% yield.[23] The dianion of **17** (1.0 equiv) was prepared in THF (0.5 M) using *t*-BuOK (2.1 equiv), and the resulting bright red solution added to freshly prepared **15** (0.5 equiv) dissolved in sufficient THF to bring the ultimate concentration of the reaction mixture to 0.4 M. After it was stirred for 12 h at 0 °C, the mixture was quenched with 5% HCl, extracted with CH_2Cl_2, and the extract chromatographed on silica gel to afford the Emmons adduct **21** (oil) in 80% yield from the diol epoxide **14**. The 2,4-dimethoxybenzyl residue was removed from **21** on treatment with TFA (neat, 0.1 M concentration of **21**) for 20 min at 22 °C. Chromatography of the reaction product as its sodium salt on Merck 7734 silica gel with CH_2Cl_2/MeOH, 9:1, gave tirandamycin A (**1**) as a yellow solid, mp 124-127 °C, in 85% yield.[24]

Acknowledgment. We thank D. Graves for help in the preparation of aldehyde **5**. Financial support from the NIH, Merck, and the Sherman Clarke Fund are gratefully acknowledged.

(20) (a) Boeckman, R. K., Jr.; Thomas, A. J. *J. Org. Chem.* **1982**, *47*, 2823. (b) DeShong, P.; Lowmaster, N. E.; Baralt, O. *Ibid.* **1983**, *48*, 1149.

(21) (a) Fugger, J.; Tien, J. M.; Hunsberger, I. M. *J. Am. Chem. Soc.* **1955**, *77*, 1843. (b) Lee, V. J. Ph.D. Dissertation, University of Illinois, Urbana, IL, 1975.

(22) (a) Tabei, K.; Kawashima, E.; Kato, T. *Chem. Pharm. Bull.* **1979**, *27*, 1842. (b) Murakami, K.; Takasuka, M.; Motokawa, K.; Yoshida, T. *J. Med. Chem.* **1981**, *24*, 88.

(23) For examples of the reaction of the sodium salt of this species, see: Sturtz, G. *Bull. Soc. Chim. Fr.* **1964**, *31*, 2340.

(24) We thank Professors DeShong and Rinehart for kindly providing us with samples of naturally occurring tirandamycin A. Naturally occurring **1** as supplied to us by Professor DeShong exhibited a mp of 123-127 °C. Tirandamycin A is reported by Rinehart et al. (Rinehart, K. L., Jr.; Lee V. J. *J. Antibiot.* **1980**, *33*, 408) to have a mp of 124-127 °C. All samples of tirandamycin A, both naturally occurring and synthetic, were crystallized from benzene. Rotations for new compounds are as follows: **6** $[\alpha]_D$ −67.4° (*c* 2.28, CH_2Cl_2), **7** $[\alpha]_D$ +69.0° (*c* 1.98, CH_2Cl_2), **2** $[\alpha]_D$ +26.1° (*c* 2.03, CH_2Cl_2), **3** $[\alpha]_D$ −75.9° (*c* 2.50, CH_2Cl_2), **9** $[\alpha]_D$ −7.1° (*c* 1.9, CH_2Cl_2), **10** $[\alpha]_D$ −39.1° (*c* 2.04, CH_2Cl_2), **11** $[\alpha]_D$ +195.6° (*c* 2.05, CH_2Cl_2), **12** $[\alpha]_D$ −174.4° (*c* 1.50, CH_2Cl_2), **13** $[\alpha]_D$ +34.0° (*c* 0.95, CH_2Cl_2), **14** $[\alpha]_D$ +20.6° (*c* 0.80, CH_2Cl_2), **21** $[\alpha]_D$ −5.7° (*c* 0.40, CH_2Cl_2), **1** $[\alpha]_D$ −8.4° (*c* 0.19, $CHCl_3$), for synthetic tirandamycin A prepared in these laboratories. A rotation of $[\alpha]_D$ −8.0° ($CHCl_3$) has been reported by Rinehart for naturally occurring tirandamycin A; see ref 5. Rotations for the aldehydes **8** and **15** were not obtained due to their marginally stable nature. Direct spectroscopic comparison between synthetic and natural tirandamycin A was made on the following instruments: ^1H NMR spectra, Brucker WH-400; ^{13}C NMR spectra, G.E. QE-300; Nominal and high-resolution mass spectra, VG-7035; IR spectra, Perkin-Elmer 299B. In all cases these spectra were essentially identical. Tirandamycin A, as its sodium salt, is reported to have a rotation of $[\alpha]_D$ +51.0° (EtOH) by: Meyer, C. E. *J. Antibiot.* **1971**, *24*, 558. Recently, Professor P. DeShong (Pennsylvania State University) completed a total synthesis of **1** using the reagent **17**.

Diastereoselective [3 + 2]-Type Heterocyclic Synthesis via [2-(Acetoxymethyl)-3-allyl]tri-*n*-butylstannane

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Received October 19, 1984

A [4 + 2] cycloaddition using carbonyl groups as acceptors for the synthesis of six-membered oxygen heterocycles permits easy access to this class of compounds with exceptional control of stereochemistry.[1] Developing analogous cycloaddition-like methods (eq 1) for the synthesis of five-membered heterocycles

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may provide similar benefits for these important classes of compounds. Unfortunately, the simplest solution to this problem using a palladium-catalyzed trimethylenemethane cycloaddition[2] failed. To resolve the impasse, we felt that a bifunctional conjunctive

(1) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F. *J. Am. Chem. Soc.* **1984**, *106*, 2456. See also earlier references of this group.

(2) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2315, 2326.

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