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Mono-Osmylation of Dehydroamino Acid Dienes: Synthesis of Dehydroamino Acids Related to the Azinomycins

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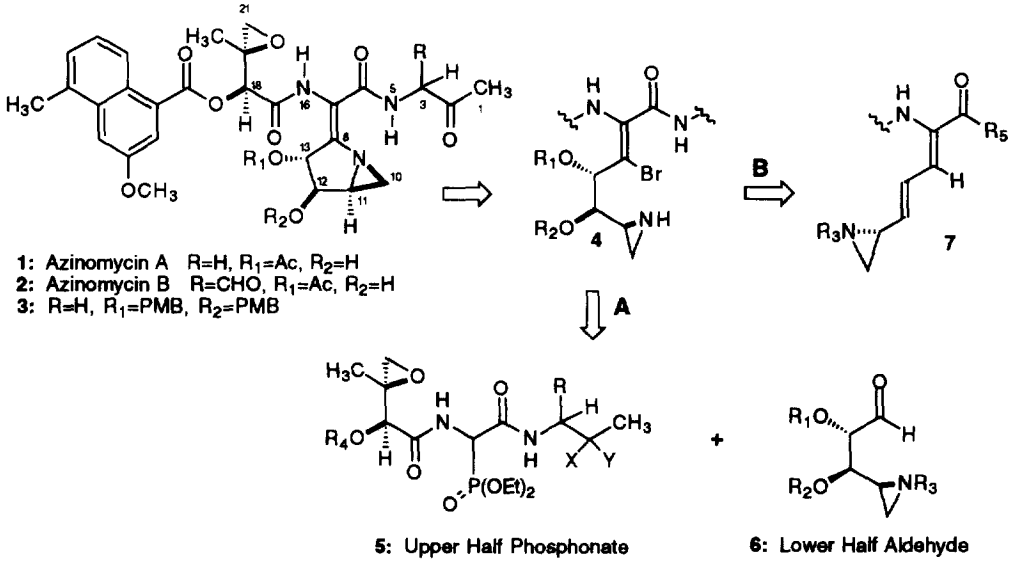
Abstract: Dehydroamino acid dienes **11A-C** were synthesized and subjected to the Sharpless asymmetric dihydroxylation, producing diols **13A-C**. Diol **13A** was further converted to the naphthoate derivative **18** and to the triacetate **19**.

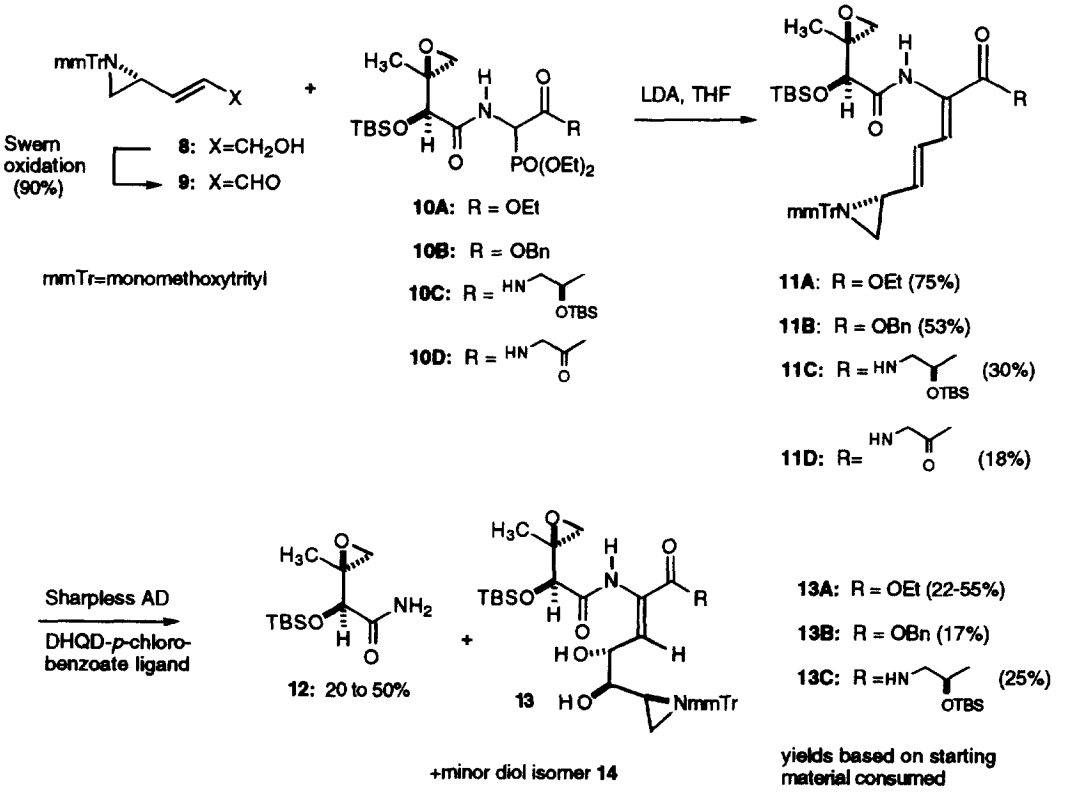
Azinomycins A (**1**) and B[1,2] (**2**) are potent antitumor antibiotics isolated from the fermentation broth of *Streptomyces griseofuscus*. As part of our efforts to elucidate the structure/activity relationships of these natural products, and to confirm their structures,[3] we are working toward the total synthesis of azinomycin A.[4] We have recently described the synthesis of several highly-functionalized analogs of the azinomycins, including 13-*O*-desacetyl-12-*O*, 13-*O*-bis-paramethoxybenzyl azinomycin A **3**, a hydroxyl-protected version of azinomycin A.[5] These analogs were synthesized according to disconnection A (Scheme 1), which makes



Scheme 1

use of a pre-formed "lower half" diol aldehyde **6**. Disconnection A suffers from a major drawback: the crucial Horner-Emmons reaction[6] that couples the upper and lower halves of the azinomycin skeleton is sensitive to the nature of the C12/C13 hydroxyl protecting groups, so that certain protecting group combinations (e.g., R_1, R_2 = trialkylsilyl or acetyl) were rendered unworkable. Having used the Sharpless asymmetric dihydroxylation (AD) for the synthesis of **6**, we were inspired to consider disconnection B by Sharpless's report[7] of selective mono-osmylation of the *distal* double bond of an α,β,γ,δ-unsaturated ester. Dehydroamino acid diene **7** requires two separate oxidative events, one at each olefin of the diene system, to provide a compound at the oxidation state of **4**. Our hope was that the AD could be used selectively to produce the allylic diol structure found in the azinomycins, which could then be brominated according to our earlier strategy. Our preliminary efforts along these lines are the subject of this communication.

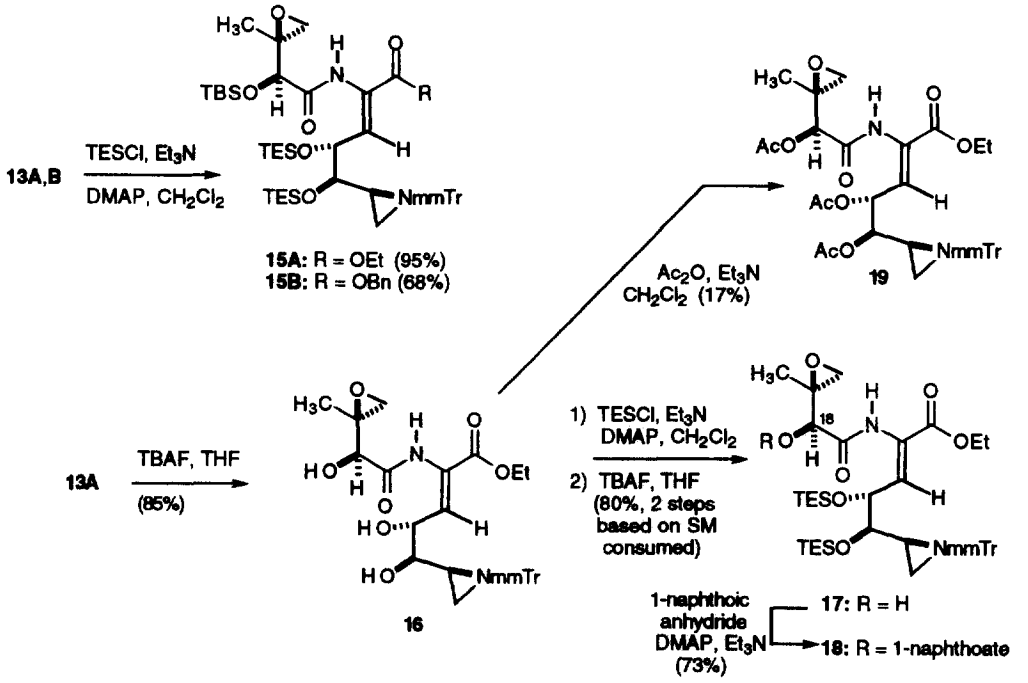
Dehydroamino acid dienes **11A-D** were synthesized via the Horner-Emmons condensation[6] of phosphonates **10A-D**[5,8] with aldehyde **8**[9] (Scheme 2). In the case of esters **10A** and **10B**, the reaction, when



Scheme 2

carried out at -30 °C, gave a 4:1 ratio of (Z,E) to (E,E) isomers by ^{1}H NMR analysis of the crude reaction mixture. The reaction of amide **10C** was more sluggish, and at room temperature gave approximately a 1:1 ratio. Upon chromatography on silica gel, the (E,E) isomers suffered decomposition to an unidentified aziridine-opened species, leaving pure (Z,E) isomers **11A-C** in the indicated yields. Keto-phosphonate **10D** underwent intramolecular condensation at a rate competitive with intermolecular reaction, so that product **11D** was formed in only 18% yield (-78 °C).

Dienes **11A-C** were subjected to osmylation conditions similar to those used by Sharpless, et. al., in their selective osmylation of diene esters.[7,10] In general, best results were obtained when the reaction was run on a small (<0.3 mmol) scale and run to approximately 50% conversion. Under these conditions diene **11A** gave up to a 55% yield of diol **13A** based on starting material consumed, separable from a minor diol isomer **14** (typically 3:1 to 7:1 ratio). The stereochemistry of the major isomer is presumed to be that shown based on the Sharpless mnemonic[11] and on our results with osmylations to produce aldehydes **6**. In all of these reactions, epoxy amide **12** was also produced in approximately the same yield as diol **13**. Compound **12** results from dihydroxylation of the proximal enamide double bond of the diene (or of the desired product diol), followed by hydrolysis of the resulting N-acyl hemiaminal. **12** becomes predominant at higher conversion ratios (>50%), indicating that although there is some selectivity for osmylation of the distal double bond, this selectivity is modest.



Scheme 3

Diols **13A** and **13B** were converted to the bis-TES protected derivatives **15A** and **15B** in excellent yield (Scheme 3). These derivatives were previously inaccessible since the Horner-Emmons condensation of phosphonates **10** with aldehydes **6** (R_1, R_2 = trialkylsilyl) failed.[12] In order to generate more advanced intermediates, diol **13A** was converted to triol **16**. Treatment of **16** with excess triethylsilyl chloride followed by mono-desilylation gave **17** in 80% yield for the two step sequence. The greater lability of the C18 silyl ether is consistent with previous observations on derivatization of other azinomycin analogs.[5] Esterification to the naphthoate derivative **18** proceeded in good yield. Triol **16** also underwent peracetylation to afford triacetate **19**. The major product in this reaction was derived from elimination of the C13 acetate.

We have shown that dehydroamino acid dienes undergo the asymmetric dihydroxylation reaction with limited regioselectivity. Triacetate **19** is our first derivative containing an allylic acetate which will allow us to investigate the bromination and cyclization stability of C13-acetylated derivatives. Our efforts at conversion of diols **13** to bicyclic aziridines will be reported in due time.

Acknowledgment. We wish to thank the National Science Foundation (CHE-8858059), the Office of Naval Research (N00014-88-K-0544), and BASF corporation (fellowship to J.E.T) for financial support of this work.

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2. Azinomycins: a) Nagaoka, K.; Matsumoto, M.; Oono, J.; Yokoi, K.; Ishizeki, S.; Nakashima, T. *J. Antibiot.* **1986**, *39*, 1527; b) Yokoi, K.; Nagaoka, K.; Nakashima T. *Chem. Pharm. Bull.* **1986**, *34*, 4554; c) Ishizeki, S.; Ohtsuka, M.; Irinoda, K.; Kukita, K.; Nagaoka, K.; Nakashima, T. *J. Antibiot.* **1987**, *40*, 60. Carzinophilin: d) Hata, T.; Koga, F.; Sano, T.; Kanamori, K.; Matsumae, A.; Sugawara, R.; Shima, T.; Ito,S; Tomizawa, S. *J. Antibiot., Ser. A, (Tokyo)* **1954**, 7, 107.
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6. a) Schmidt, U.; Lieberknecht, A.; Kazmaier, U.; Griesser, H.; Jung, G.; Metzger, J. *Synthesis* **1991**, 49; b) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1988**, 159.
7. Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570.
8. **10B** was synthesized by LiOH hydrolysis of **10A**, followed by DCC coupling with benzyl alcohol.
9. Derived from previously-described alcohol **8**; see reference 4c.
10. In a typical experiment, a mixture of **11A** (239 mg, 0.35 mmol), $K_2OsO_2(OH)_4$ (5.6 mg, .015 mmol), dihydroquinidine *p*-chlorobenzoate (32 mg, 0.069 mmol), $K_3Fe(CN)_6$ (270 mg, 0.82 mmol), K_2CO_3 (110 mg, 0.80 mmol), *t*-BuOH (3 ml), and water (3 ml) was stirred at 23 °C for 5.5 hr. Normal workup ($NaHSO_3$ quench, CH_2Cl_2 extraction) followed by silica gel chromatography gave (in order of elution) recovered **11A** (96 mg, 40 %), **12** (20 mg, 23%), **13A** (70 mg, 28%), and **13B** (10 mg, 5%). Yield of **13A** is 47% based on starting material converted.
11. Becker H.; Soler M. A.; Sharpless K. B. *Tetrahedron* **1995**, *51*, 1345-1376.
12. Coleman and co-workers have reported the successful condensation of *N*-methoxycarbonyl glycinyl phosphonates with aldehyde **6** (R_1 = Ac, R_2 = TBS, R_3 = Cbz); see Ref. 4d.

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