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HIGHLY CONVERGENT APPROACH TO THE SYNTHESIS OF THE EPOXY-AMIDE FRAGMENT OF THE AZINOMYCINS

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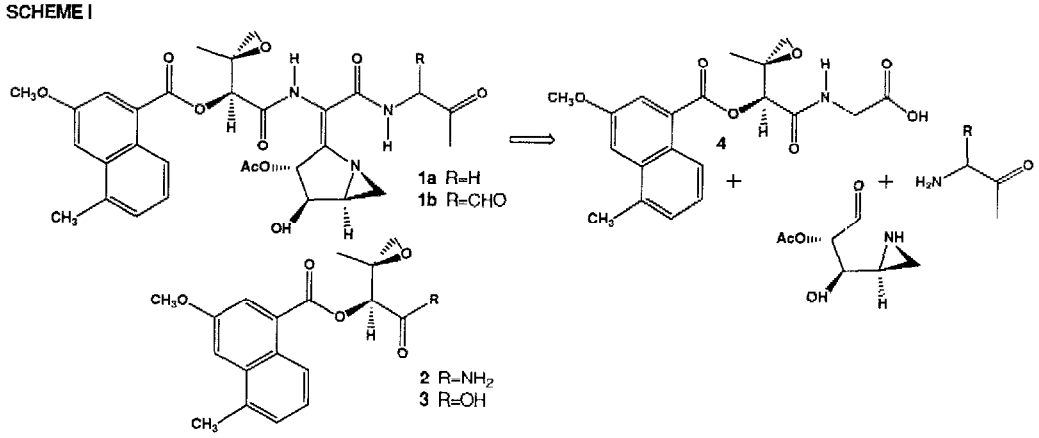
Summary: *An efficient synthesis of the α-acyl amide fragment of the azinomycin antibiotics has been accomplished using the Passerini three-component condensation Good diastereoselectivity was observed for a variety of isocyanide precursors.*

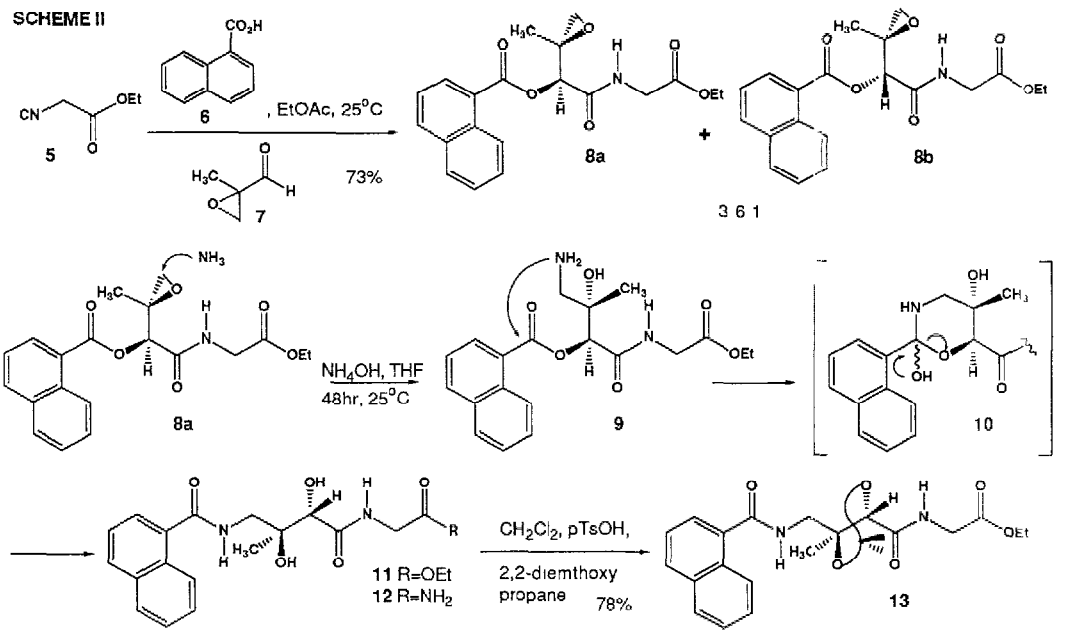
Azinomycins A (**1a**) and B (**1b**) were isolated from *Streptomyces griseofuscus* S42227 by Nagaoka *et al* [1] in 1986. These potent metabolites exhibit activity against a wide variety of tumors and are not structurally related to any other series of compounds. Shibuya[2] has synthesized the inactive metabolite **2** from a carbohydrate precursor and has established the absolute stereochemistry as shown. We recently reported[3] on the synthesis of acid **3** utilizing a Sharpless kinetic resolution to introduce the allylic epoxide, and subjected a synthetic intermediate in this route to the known ammonium hydroxide rearrangement resulting in addition of ammonia to the terminal carbon of the epoxide followed by acyl transfer via a six-membered ring intermediate [4] This transformation is of interest since it ties together some of the difficulties associated with the structural assignment of carzinophilin, a *Streptomyces sahachiroi* metabolite[5] which is identical to azinomycin B by comparison of spectral data.[6]

SCHEME I



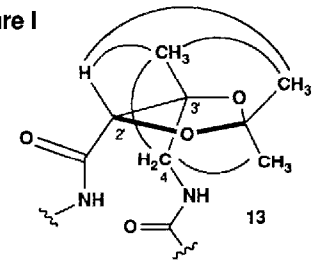
Retrosynthetic analysis of the azinomycins (Scheme I) led us to identify the acylated glycine derivative **4** as a potential precursor for introduction of the dehydroamino acid moiety. While condensation of glycine with the previously prepared acid **3** should afford this target, the presence of an α-acyl amide suggested that a Passerini condensation[7] might afford the desired connectivity in a more convergent fashion. The question of diastereoselectivity was more difficult to predict since additions of isocyanides to glycidal derivatives has not been extensively studied.[8] Application of the Felkin-Ahn model would suggest that the undesired erythro product might be favored, however, electron-electron repulsion and steric arguments are complicated since the reaction is carried out in an acidic media with a sterically unhindered nucleophile.

SCHEME II



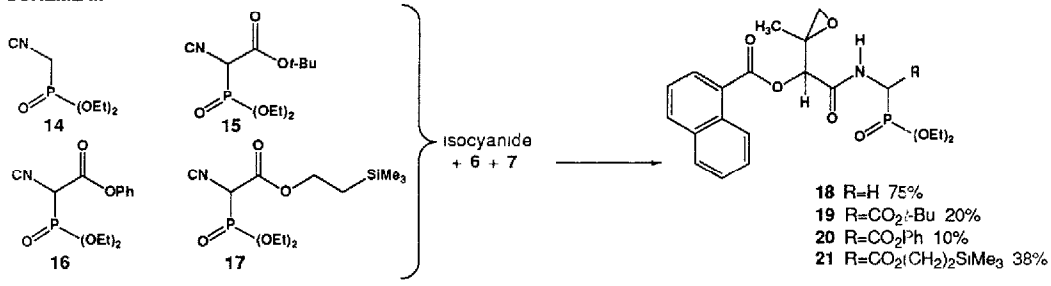
An ethyl acetate solution containing freshly distilled ethyl isocyanoacetate (1 equiv.), 1-naphthoic acid (1.5 equiv.), and 2-methylglycidal[9] (2 equiv), was allowed to stir at room temperature for 24 hr (Scheme II). Aqueous workup (satd. $NaHCO_3$) followed by silica gel chromatography afforded a 73% combined yield of diastereomers **8a** and **8b** in a 3.6:1 ratio. Examination of the stereochemical outcome of the reaction was facilitated by the ammonium hydroxide rearrangement to give a vicinal diol which could be converted to a cyclic ketal. This rearrangement is known to proceed with maintenance of stereochemical integrity. Thus, major diastereomer **8a** was reacted with ammonium hydroxide in THF at room temperature over a 48 hr period, affording ester **11** (57% yield) and amide **12** (29% yield) via epoxide ring opening and acyl transfer (**9**-**10**).[10] Diol **11** was subsequently converted to its isopropylidene derivative (**13**). NOE difference in combination with 2D NOESY experiments established the *syn* relationship of the C2' hydrogen and C3' methyl substituents (Figure I). This relationship was confirmed by the observation of a second series of crosspeaks relating both of these substituents to one of the isopropylidine methyls. Likewise, the C4' methylene showed strong crosspeaks with its geminal methyl group at C3' and the remaining isopropylidene methyl

Figure I



In order to facilitate the homologation of the Passerini products, isocycanomethylphosphonate (**14**)[11] and α-isocyano-α-phosphonoacetates (**15-17**) were condensed with 1-naphthoic acid and racemic 2-methyl glycidal under similar conditions to afford **18** and **19-21,** respectively. Yields reported reflect the limited stability and/or purity of the isocyanide precursors rather than the efficiency of the Passerini condensation. The yields tend to be high (i.e. **18**) when the isocyanide can be purified (Al_2O_3, hexanes-EtOAc) Phosphonates **19-21** contain an additional stereocenter which complicates analysis of the ^1H NMR, but the diastereoselectivity generally obtained approximates that for **8a/8b** (3.6:1). This value can be quantitated for product **18** as 3.5:1.

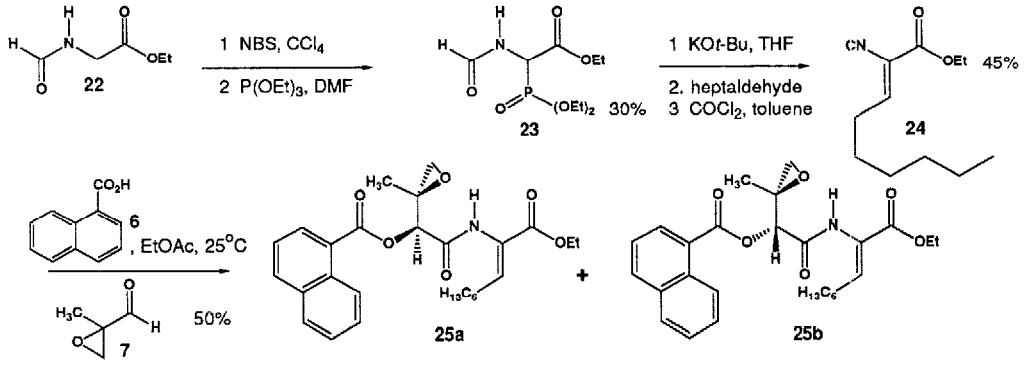
SCHEME III



A vinyl isocyanide was also a good substrate for the Passerini reaction. Bromination of formamide 22 followed by Arbuzov reaction afforded phosphonate **23** Wittig condensation and formamide dehydration using phosgene generated the *Z* vinyl isocyanide **24** (*Z*/*E*, 11:1), a stable intermediate which could be readily purified using silica gel chromatography. Condensation with **6** and **7** afforded dehydroamino acid derivatives **25a** and **25b** in 60% yield (based on **24**). The diastereomeric ratio was 3.7:1 by ^1H NMR analysis The stereochemistry of **25a** and **25b** are tentatively assigned by analogy to **8a** and **8b**.

The Passerini reaction provides a highly convergent approach to the α-acyl amide fragment of the azinomycins via the condensation of vinyl or phosphonate isocyanides. This strategy shows great potential in generating intermediates useful in probing structure/activity relationships of these novel antitumor antibiotics Condensation of vinyl isocyanide to generate **25a** constitutes the first synthesis of the dehydro acylamide portion of the azinomycins

SCHEME IV



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References

1. Nagaoka, K.; Matsumoto, M.; Oono, J.; Yokoi, K.; Ishizaki, S.; Nakashima, T. *J. Antibiot.* **1986**, *39*, 1527; Yokoi, K.; Nagaoka, K ; Nakashima, T. *Chem. Pharm. Bull.* **1986**, *34*, 4554.
2. Shibuya, M.; Terauchi, H. *Tetrahedron Lett.* **1987**, *28*, 2619.
3. England, P.; Chun, K-H.; Moran, E.J.; Armstrong, R.W. *Tetrahedron Lett.* **1990**, *31* 2669.
4. This elegant transformation has been described by Shibuya on **2** (Ref. 2). The rearranged product has been independently synthesized· a) Garner, P.; Park, J.J.; Rotello, V. *Tetrahedron Lett* 1985, *26*, 3299; b) Shibuya, M. *Tetrahedron Lett.* **1983**, *24*, 1175.
5. Isolation: Hata, T ; Koga, F.; Sano, Y ; Kanamori, K.; Matsumae, A.; Sugawara, R.; Shima, T.; Ito, S.; Tomizawa, S. *J. Antibiot , Ser A (Tokyo),* **1954**, *7*, 107 Proposed structures: Lown, J.W.; Hanstock, C.C. *J Am Chem. Soc* **1982**, *104*, 3213; Onda, M.; Konda, Y.; Hatano, A ; Hata, T.; Omura, S. *J Am Chem. Soc.* **1983**, *105*, 6311.
6. Submitted for publication. The ^{13}C and ^{1}H NMR of metabolites from *S. sahachiroi* (carzinophilin) and *S. griseofuscus* S42227 (azinomycins B) are superimposable. FAB-MS are also in accord with structure **1b**
7. Passerini, M. *Gass. Chim Ital.* **1921**, *51*, 126; Lumma, W C. *J. Org. Chem.* **1981**, *46*, 3668.
8. A report in the abstracted literature describes the condensation of cyclohexyl isocyanide, acetic acid, and oxirane carboxaldehyde-2-methyl: CA:98, 179116. Ptashnikov, Y.L. *deposited document* **1981**, VINITI 575-82/547-50.
9. Payne, G.B. *J. Am Chem. Soc.* **1959**, *81*, 4901.
10. An additional 13% of unreacted **8a** was recovered.
11. Rachon, J.; Schollkopf, U *Liebigs Ann Chem.* **1981**, 99.

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