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Synthesis of deoxyfrenolicin and nanaomycin A

Abstract
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Disciplines
Chemistry | Organic Chemistry | Other Chemistry | Polymer Chemistry

Comments
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Synthesis of Deoxyfrenolicin and Nanaomycin A

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Deoxyfrenolicin and nanaomycin A have been synthesized. Key steps in the synthesis include a phthalide annulation reaction to produce a naphthoquinone, a tandem Diels–Alder/retro-Claisen reaction to produce the carbon skeleton, and a stereoselective reduction of a hemiketal.

The pyranquinone antibiotics are a diverse family produced by various species of Streptomyces. Some members of this family exhibit antifungal activity, anti-cancer activity, or anticoccidial activity. Their useful activity has made these compounds attractive synthetic objectives. Recently, total syntheses of nanaomycin D (1), nanaomycin A (2a), kalafungin, frenolicin, deoxyfrenolicin (2b), and the enantiomer of griseusin (3) have been achieved. Our synthesis of 1 and kalafungin was based on the addition of an alkoxyfuran to an activated naphthoquinone. While this strategy provided a valuable entry to the lactone-containing pyranquinones, it could not be extended to the synthesis of 2 and 3. Interestingly, however, the lactone-containing pyranquinones have been prepared from the corresponding acids (e.g., 1 has been synthesized from 2a). This transformation occurs under quite mild conditions and may be related to the biogenetic pathway. In a related study, we had observed that Diels–Alder adduct 5 was extremely unstable to base and that it underwent a facile retro-aldol reaction. In light of the above information, we reasoned that a hemiketal intermediate such as 4 might enable us to synthesize the entire class of compounds, provided that the hemiketal could be selectively reduced. The hemiketal, in turn, might be directly prepared by a Diels–Alder reaction followed by a retro-Claisen reaction. This plan has now been reduced to practice; the successful synthetic route is illustrated in Scheme I.

The cyanophthalide 6 was prepared by a modification of the Li procedure. Deprotonation of 6, followed by Michael addition with methyl vinyl ketone (MVK) and an intramolecular Claisen reaction, afforded a hydroquinone which could be oxidized with ceric ammonium nitrate (CAN) to quinone 7a. The yield of quinone from 6 was 66%. The best conditions for this annulation involved the addition of solid potassium tert-butoxide in portions to MVK in dry Me₂S0. These conditions represent a considerable improvement over our previously reported procedure that afforded 7a in only 25% yield. As expected, the Diels–Alder reaction of 7a yielded the ketene acetal derived from ethyl crotonate proceeded cleanly and rapidly at ambient temperature. The NMR of the unpurified product showed only three singlets for the 3-Me₂S0 group. The retro-Claisen reaction was also quite facile with 2 equiv of tetrabutylammonium fluoride in THF at 0 °C. The cis crotonate subunit that was liberated by the retro-Claisen reaction rapidly reacted with the neighboring phenol to produce 9a. This cyclization had previously been observed by both Yoshii and Uno. They avoided this cyclization by protecting the phenol. For our considerations, however, this cyclization was a desirable reaction. Oxidation of 9a with CAN in aqueous acetonitrile at ambient temperature produced the key hemiketal 10a in 71% yield from 7a. Both the proton and the carbon NMR spectra of 10a indicated that only one hemiketal was present. The structure of 10b (R = Pr) was determined by X-ray crystallography. It supports this structure which was initially

![Chemical Structure](image-url)

4. A variety of conditions were examined (H₂, Pd/C or Pt/C; Li, NH₂Et₂SiH, BF₃·OEt₂; Zn, HOAc). These experiments were done by Dr. James MacMillan.
Table I. Reduction of Hemiketals to Ethers

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>R¹</th>
<th>R²</th>
<th>% Yield</th>
<th>cis/trans Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OH</td>
<td>CH₃</td>
<td>CH₃</td>
<td>93</td>
<td>100:0</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>CH₃</td>
<td>i-Pr</td>
<td>70</td>
<td>100:0</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>Ph</td>
<td>CH₃</td>
<td>86</td>
<td>10:1</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>Ph</td>
<td>i-Pr</td>
<td>75</td>
<td>100:0</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>CH₃</td>
<td>CH₃</td>
<td>88</td>
<td>100:0</td>
</tr>
</tbody>
</table>

The reduction of a hemiacetal unit to an ether has been studied by several researchers. We studied this transformation in the context of converting a lactone to a cyclic ether. The reduction of a hemiketal to a cyclic ether would introduce a new stereogenic center. Although Kishi has reported an interesting example in the carbohydrate area, no studies on simpler alicyclic systems appear to have been reported. We initially examined the stereochemical consequences of this reduction on several model systems. The results are illustrated in Table I. The results show a strong preference for the production of an ether in which the two groups are cis. All results are consistent with axial delivery of hydride from Et₃SiH. This is opposite to the desired relative stereochemistry; however, the acid-catalyzed epimerization to the trans orientation has already been documented in related pyranonaphthoquinones.

The ionic hydrogenation conditions (triethylsilane, CF₃CO₂H) afforded a 95% yield of 11.

Scheme I

(11) ORTEP drawing of 10b.


(18) An authentic sample of 19 and its trans isomer was obtained from 2-methyl-4-valerolactone by (1) PhMgCl, THF, 0 °C; (2) LiAIH₄, THF, 0 °C; (3) TlCl, Et₃N, cat. DMAP, CH₂Cl₂; (4) NaH, THF, 0–25 °C. As expected by Cram's rule, the cis isomer predominated in a 3:1 ratio. The obtention of 19 is consistent with axial delivery of hydride (Et₃SiH) to an intermediate cation with the methyl group in an axial position to avoid A12 strain.

reaction is considered to proceed via a highly ordered transition state involving all three reactants; however, in this case the formation of dienol 12 followed by tautomerization to 11 is a distinct possibility and cannot be ruled out. The NMR spectrum of quinone 11 (R = CH₃, R' = Me) is identical with ours. Semmelhack had already reported the simultaneous cleavage of the methyl ether and
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partial epimerization with boron tribromide. While we obtained the desired phenol as a 2.0–2.5:1 ratio of trans/cis isomers, we also identified approximately 5% of a monobrominated product. This latter side product could be reduced by using 5% Pd/C in ethanol to the methyl ester of 2a. The methyl ester of 2a has been hydrolyzed to 2a by using dilute sodium hydroxide.15

The synthesis of deoxyfrenolicin began with the reaction of 6 with propyl vinyl ketone. Oxidation to quinone 7b, followed by Diels–Alder/retro-Claisen reaction to 9b and oxidation and reductive deoxygenation afforded 11b in 22% overall yield from 6. Quinone 11b is sterechemically homogeneous as evidenced by carbon NMR. Again, this isomer was produced by the reductive deoxygenation of the cis isomer. Quinone 11b was then reacted with BBr3 in hexanes. In this case only the trans isomer was obtained. Again, a small amount of brominated product was isolated. This could be converted to the methyl ester of deoxyfrenolicin with 5% Pd/C. The ester has been hydrolyzed to furnish deoxyfrenolicin.15

This route is the most direct and efficient route yet reported. It is extremely direct, generating the pyranonucleine nucleus in only seven steps. Additionally, these syntheses represent the first use of the Diels–Alder/retro-Claisen (DARC) strategy in natural products synthesis. The extension of this strategy to the synthesis of more complicated pyranonones such as lactoquinomycin is currently in progress.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Dichloromethane was distilled from phosphorus pentoxide. Infrared spectra were obtained on a Beckman IR-4250 spectrometer. Nuclear magnetic resonance spectra were determined on a Nicolet 300-MHz instrument. Carbon-13 NMR spectra were determined on a Nicolet 300-MHz 'H NMR (CDCl3) δ 0.74 (d, J = 7 Hz, 3 H), 1.08 (d, J = 7 Hz, 3 H), 1.22-1.39 (m, 1 H), 1.43-1.48 (m, 1 H), 4.55 (d, J = 2 Hz, 1 H), 7.17-7.33 (m, 5 H); MS, m/e 176, 190, 1044 cm; MS, m/e 117, 147, 162; HRMS, m/e calc 162.1045, found 162.1041.

2-Dimethyl-3,4-dihydro-1H-2-benzopyran (19): 300-MHz 'H NMR (CDCl3) δ 0.97 (d, J = 6 Hz, 3 H), 1.06 (d, J = 6 Hz, 3 H), 1.56 (d, J = 6 Hz, 3 H), 2.63-2.82 (m, 2 H), 3.78-3.88 (m, 1 H); IR (film) 3600-3400, 1640, 1600 cm-'.

Ethyl 1,2-benzofuran-3-ylacetate (19a). To a solution of hydroquinone (50.0 mg, 0.232 mmol) in 1 mL of methylene chloride was added ceric ammonium nitrate (2.92 g, 5.34 mmol) and then acidified with excess 2N HCl. The resulting brown solution was diluted with 19 mL of methylene chloride and acidified with excess 2N HCl. The resulting yellow solution was poured into 500 mL of ice water and extracted eight times with 50-mL portions of diethyl ether. The organic extracts were combined, washed with water, and dried. The solvent was removed in vacuo and the residue chromatographed on 175 g of silica gel, eluting with 2.51 hexanes/ethyl acetate to afford 1.74 g (66%): 300-MHz 'H NMR (CDCl3) δ 2.65 (s, 3 H), 4.05 (s, 1 H), 6.86 (s, 1 H, J = 7.2 Hz), 7.16 (s, 1 H, J = 7 Hz), 7.82 (d, 1 H, J = 8.1 Hz), 8.14 (s, 1 H, J = 13.6 Hz); HRMS, m/e calc 360-3400, 1640, 1600 cm.'
residue flash chromatographed on silica gel eluting with 2.71 hexane/ethyl acetate to afford 613 mg (77%) of 9a, yellow needles from ethyl acetate/hexanes: mp 103–104.5 °C; 300 MHz 1H NMR (CDCl3) δ 1.27 (t, 3 H, J = 6.9 Hz), 1.69 (s, 3 H), 2.68 (dd, 1 H, J = 13.9, 7.6 Hz), 2.87 (dd, 1 H, J = 7.6, 7.2 Hz), 3.25 (dd, 1 H, J = 16.8 and 7.2 Hz), 3.89 (dd, 1 H, J = 16.8 and 6.8 Hz), 4.01 (s, 3 H), 4.15 (q, 2 H, J = 6.9 Hz), 5.24 (m, 1 H), 6.75 (d, 1 H, J = 7.5 Hz), 7.30–7.50 (m, 2 H), 11.35 (s, 1 H); IR (film) 3005, 1730, 1310, 1220, 1150, 1050 cm⁻¹; 13C NMR 32.50, 38.38, 41.09, 56.22, 60.64, 78.87, 105.40, 114.75, 115.08, 116.26, 118.56, 124.94, 128.62, 146.79, 154.03, 157.72, 170.40, 201.11 ppm; MS, m/e 344, 298, 286, 264, 242, 229, 201; HRMS, m/e calcd 344.12599, found 344.12592.

trans-Ethyl [1-Hydroxy-9-methoxy-1-methyl-5,10-dioxo-3,4,5,10-tetrahydronaphtho[2,3-c]pyran-3-yl]acetate (10a). To a solution of 9a (613 mg, 1.78 mmol) in 40 mL of acetonitrile containing 3.87 (s, 1 H), 3.4, 2.5, and 2.5 Hz), 2.87 (m, 1 H), 7.28 (br d, 1 H, J = 18.1, 10.5, and 7.2 Hz), 2.60 (dd, 1 H, J = 15.6 and 7.5 Hz), 2.70 (dd, 1 H, J = 15.6 and 7.5 Hz), 2.83 (apparent dt, 1 H, J = 18.1, 2.5, and 2.5 Hz), 3.93 (m, 1 H), 4.00 (s, 3 H), 4.19 (q, 2 H, J = 7.2 Hz), 4.87 (m, 1 H), 7.28 (br d, 1 H, J = 8.4 Hz), 7.64 (t, 1 H, J = 7.8 Hz), 7.73 (dd, 1 H, J = 7.8 and 0.9 Hz); IR (film) 2980, 1730, 1660, 1585, 1520 cm⁻¹; MS, m/e 344, 298, 270, 257, 240; HRMS, m/e calcd 344.12592, found 344.1255.

Acknowledgment. We thank the National Institutes of Health (Grant GM 34342) for financial assistance. M.T.M. thanks the CSIC for a postdoctoral fellowship.

Supplementary Material Available: Experimental conditions and spectral data for compounds in the deoxyfrenolicin series (7b, 9b, 10b, and 11b) (7 pages). Ordering information is given on any current masthead page.

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Stereospecific Arylation of Alkenylsilanes with Arylpalladium Acetates

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Alkenyltrimethylsilanes (E)- and (Z)-RCH=CHR2CH2SiMe3, R = H, Ph, n-C8H17, and CH2=CHCH2CH2CH2 CH2=CHCH2CH2CH2CH2=CH2, stereospecifically reacted at 40 °C or room temperature with in situ generated phenylpalladium acetate to produce R(Ph)C=CHR2CH2SiMe3 and RCH=CHR2SiMe3 with inversion of their geometry. The arylation of CH2=CHR2CH2SiMe3 with arylpalladium acetates gave (E)-ArCH=CHR2CH2SiMe3 (Ar = PhH, X = H, 4-Me, 4-MeO, 4-Br, 4-I, 4-ETOCO, and 4-NO2) in good yields. Stereospecific transformations of alkenylsilanes by a variety of electrophiles have been developed and utilized in organic synthesis. However, little is known concerning the arylation of alkenylsilanes with transition-metal organometallics or salts whose catalysis has an important role in C–C coupling of main group organometallics with carbon-based electrophiles.

Reactions of (E)-PhCH=CHR2CH2SiMe3 or (Z)-PhCH=CHR2CH2SiMe3 with palladium salts have been reported to give (E)-PhCH=CHR2CH2SiMe3 intermediates through an addition–elimination mechanism. Palladium-catalyzed reactions of CH2=CHR2CH2SiMe3 with aryl iodides yield aryl-desilylated products, ArCH=CHR2CH2SiMe3. Recently

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