

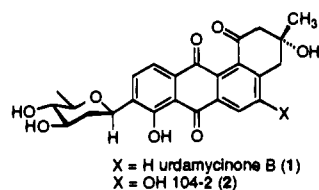
## Total Synthesis of the Angucycline Antibiotics Urdamycinone B and 104-2 via a Common Synthetic Intermediate

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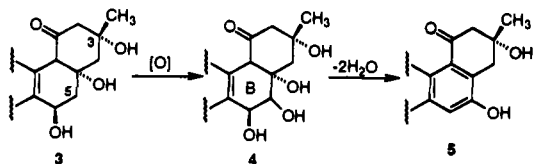
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The angucycline family of antibiotics is a large group of biologically active secondary metabolites of microbial origin.<sup>1–3</sup> Urdamycin B, a group member isolated from *Streptomyces fradiae*, is composed of a trisaccharide attached through a C-glycoside linkage to an angular quinone ring system.<sup>4</sup> Careful acid hydrolysis of urdamycin B led to the loss of two sugars and the isolation of the aglycon urdamycinone B (1).<sup>2a</sup>

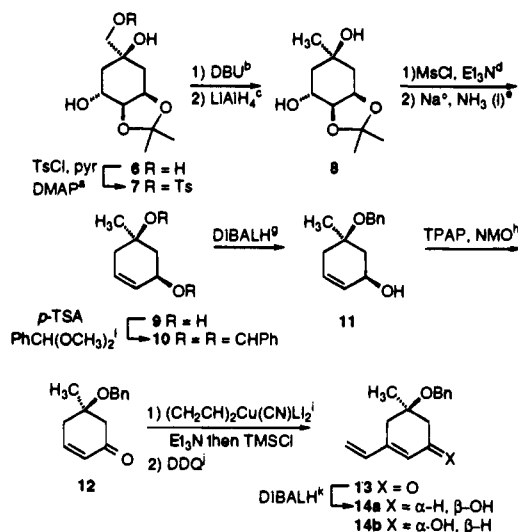


To investigate the midstage steps of the biosynthesis of angucycline antibiotics, blocked mutant strains of the urdamycin producer *S. fradiae* were prepared.<sup>5</sup> From these mutant strains five new metabolites including 104-2 (2) were isolated and identified. To account for the production of 104-2 (2), Rohr and co-workers postulated two shunt pathways. The first proposal entailed direct C5 oxidation of urdamycinone B (1) to 104-2 (2) by an unspecific oxygenase. The second proposal, outlined below, proceeds via selective C5 hydroxylation of urdamycinone B (1) to produce a hypothetical ring B triol (3). Subsequent dehydration of 3 would then account for the production of 4. Herein we report a total synthesis of urdamycinone B (1) and of the shunt metabolite 104-2 (2). The latter is conceptually similar to the biosynthetic pathway outlined below (3 → 4 → 5).



Our synthetic strategy relied on a Diels–Alder cycloaddition between diene **14a** and bromojuglone **17** to assemble the carbon framework common to **1** and **2**.<sup>3e</sup> We first outline in Scheme

### Scheme 1<sup>a</sup>



<sup>a</sup> (a) CH<sub>2</sub>Cl<sub>2</sub>, 0–20 °C, 71%. (b) PhH, 20 °C, 99%. (c) Et<sub>2</sub>O, 0–20 °C, 100%. (d) CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 98%. (e) THF, –78 °C, 83%. (f) CH<sub>2</sub>Cl<sub>2</sub>, 4 Å molecular sieves, 20 °C, 72%. (g) CH<sub>2</sub>Cl<sub>2</sub>, 0–20 °C, 99%. (h) CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 100%. (i) Et<sub>2</sub>O, –78 to 0 °C. (j) PhH, 0–20 °C, 72% for two steps. (k) CH<sub>2</sub>Cl<sub>2</sub>, –78 °C, 89%.

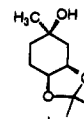
1 the synthesis of diene **14a** starting from known triol **6**, which is easily obtained from (–)-quinic acid using a previously described two-step procedure.<sup>6,7</sup> Tosylation of **6**<sup>8,9</sup> followed by epoxide formation and reduction afforded diol **8**<sup>8</sup> in 71% overall yield. Mesylation of **8** gave rise to the corresponding secondary mesylate, which upon reductive fragmentation afforded diol **9**<sup>8a</sup> as a colorless oil in 83% yield.<sup>10</sup> Protection of the more hindered tertiary alcohol of **9** was accomplished by a two-step sequence. First, the *cis*-1,3-diol was engaged as a cyclic benzylidene (**10**)<sup>8</sup> under standard reaction conditions. Treatment of a solution of **10** in dichloromethane with diisobutylaluminum hydride resulted in selective cleavage of the less hindered secondary ether, affording the desired benzyl ether **11**<sup>8a</sup> in 72% overall yield. Ley oxidation of **11** produced enone **12**<sup>8a</sup> in quantitative yield.<sup>11</sup> Conjugate addition of a higher-order vinyl cuprate to **12** followed by trapping of the intermediate enolate with trimethylsilyl chloride and DDQ oxidation of the resultant silyl enol ether afforded **13**.<sup>8a,12</sup> Reduction of dienone **13** with diisobutylaluminum hydride yielded a 9:1 mixture of diastereomers. The major isomer was assigned the *cis* configuration (**14a**) on the basis of a single-crystal X-ray analysis of the minor *trans* alcohol (**14b**).<sup>13</sup>

(7) Trost, B. M.; Romero, A. G. *J. Org. Chem.* **1986**, *51*, 2332–2342.

(8) (a) The structure assigned to each new compound is in accord with its infrared and high-field (200 or 400 MHz) <sup>1</sup>H NMR spectra as well as appropriate parent ion identification by high-resolution mass spectrometry. (b) In addition, an analytical sample of this new compound, obtained by recrystallization or liquid chromatography, gave C and H combustion analysis within 0.4%.

(9) In addition to **7** a second monotosylate, corresponding to sulfonation of the tertiary alcohol, as well as a ditosylate, corresponding to sulfonation of the primary and tertiary alcohols, were isolated in 10 and 16% yields, respectively.

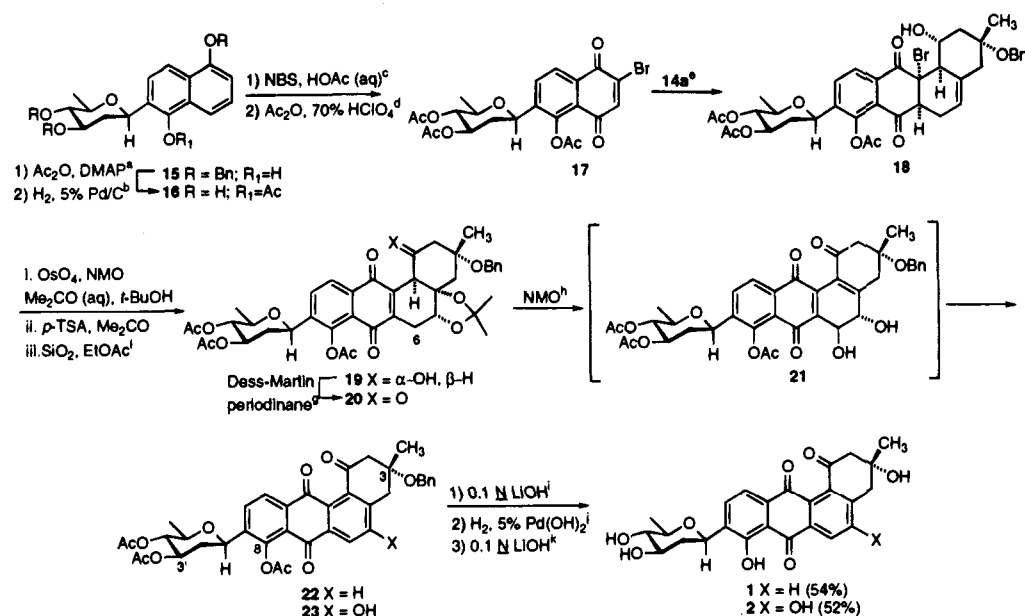
(10) Deoxygenation to provide **i** in 17% yield accounted for the remaining material balance.



(11) Griffith, W. P.; Ley, S. V. *J. Chem. Soc., Chem. Commun.* **1987**, 1625–1627.

(12) (a) Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Morettic, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641–2643. Reviews: (b) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005–5038. (c) Lipshutz, B. H. *Synlett* **1990**, 119–128.

- (1) Review: Rohr, J.; Thiericke, R. *Nat. Prod. Rep.* **1992**, *9*, 103–137.  
(2) Total synthesis: (a) Yamaguchi, Y.; Okuma, T.; Horiguchi, A.; Ikeura, C.; Minami, T. *J. Org. Chem.* **1992**, *57*, 1647–1649. (b) Krohn, K.; Khanbabaee, K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 99–100. (c) Matsumoto, T.; Sohma, T.; Yamaguchi, H.; Kurata, S.; Suzuki, K. *Synlett* **1995**, 263–266.  
(3) (a) Guingant, A.; Barreto, M. M. *Tetrahedron Lett.* **1987**, *28*, 3107–3110. (b) Katsuura, K.; Sniekus, V. *Can. J. Chem.* **1987**, *65*, 124–130. (c) Gordon, D. M.; Danishefsky, S. J.; Schulte, G. M. *J. Org. Chem.* **1992**, *57*, 7052–7055. (d) Krohn, K.; Khanbabaee, K. *Liebigs Ann. Chem.* **1994**, 1109–1112. (e) Larsen, D. S.; O'Shea, M. D. *Tetrahedron Lett.* **1993**, *34*, 1373–1376. (f) Andrews, F. L.; Larsen, D. S. *Tetrahedron Lett.* **1994**, *35*, 8693–8696. (g) Kim, K.; Reibenspies, J.; Sulikowski, G. *J. Org. Chem.* **1992**, *57*, 5557–5559.  
(4) (a) Drautz, H.; Zahner, H.; Rohr, J.; Zecek, A. *J. Antibiot.* **1986**, *39*, 1657. (b) Henkel, T.; Ciesiolka, T.; Rohr, J.; Zecek, A. *J. Antibiot.* **1989**, *42*, 299.  
(5) Rohr, J.; Schonewolf, M.; Udvarnoki, G.; Eckardt, K.; Schumann, G.; Wagner, C.; Beale, J. M.; Sorey, S. D. *J. Org. Chem.* **1993**, *58*, 2547–2551.  
(6) For a related reaction sequence starting from (–)-quinic acid, see: Billen, G.; Karl, U.; Scholl, T.; Stroech, K. D.; Steglich, W. In *Natural Products Chemistry 3*; Atta-Ur-Rahman, Le Quesne, P. W., Eds.; Springer-Verlag: Berlin, Heidelberg, 1988; pp 305–315.

Scheme 2<sup>a</sup>

<sup>a</sup> (a) pyridine, 20 °C, 100%. (b) EtOH, 20 °C, 99%. (c) 70 °C, 94%. (d) EtOAc, 0 °C, 92%. (e) PhH, reflux, 72%. (f) 67% for three steps. (g)  $\text{CH}_2\text{Cl}_2$ , 20 °C, 100%. (h)  $\text{CH}_2\text{Cl}_2$ , 20 °C, 72%. (i) THF, 0–20 °C. (j) EtOAc–MeOH (1:1), 0 °C. (k) THF, 0–20 °C.

Following completion of the diene component **14a** we turned our attention to the preparation of bromoquinone **17** and its subsequent cycloaddition with **14a**. We have previously described the preparation of  $\beta$ -*C*-naphthylglycoside **15**.<sup>14</sup> Acetylation of **15** followed by removal of the benzyl protecting groups sets the stage for oxidation of naphthol **16**.<sup>8a</sup> Oxidation of **16** utilizing conditions described by Gruenwell provides the corresponding bromoquinone, which was subsequently peracetylated to afford **17**.<sup>8a,15</sup> A solution of **17** and diene **14a** in benzene was brought to reflux and maintained for 10 h to afford cycloadduct **18**<sup>8a</sup> in 72% yield.<sup>16</sup> Dihydroxylation<sup>17</sup> of **18** followed by direct acetonide formation and silica gel induced dehydrobromination provided quinone **19**<sup>8a</sup> in 67% yield. Dess–Martin oxidation of **19** then furnished ketone **20**<sup>8a</sup> in quantitative yield.<sup>18</sup> Treatment of a solution of **20** in dichloromethane with 1 equiv of *N*-methylmorpholine *N*-oxide (NMO) resulted in the production of anthraquinones **22**<sup>8a</sup> and **23**<sup>8a</sup> as yellow solids in 27 and 72% yield, respectively. Anthraquinone **23** is proposed to arise through oxidation of the C6 position and  $\beta$ -elimination of the acetonide group to produce intermediate carbinol **21** (not isolated), which upon dehydration affords **22**.<sup>19,20</sup> while base-induced loss of acetone and water accounts for the production of the minor product **23**. The generation of **23**, under these conditions, via oxidation of **22** appears unlikely. Finally, anthraquinone **22** was also obtained directly for **18** in 88% yield via a periodinane oxidation.<sup>18</sup>

With anthraquinones **22** and **23** in hand, the remaining obstacle to completing the synthesis of urdamycinone B (**1**) and 104-2 (**2**) was the removal of protecting groups. In this regard the propensity of the C3 oxygen substituent, located  $\beta$  to the C1 keto group, to undergo  $\beta$ -elimination was of concern.<sup>1,2b</sup> Indeed attempts to remove all three acetyl groups employing 3 equiv of lithium hydroxide in aqueous tetrahydrofuran resulted in elimination of the C3 benzyloxy group accompanying deacetylation. To circumvent this problem, a three-step procedure was developed. First removal of the C8 acetyl group was effected using 1 equiv of lithium hydroxide followed by hydrogenolysis of the C3 benzyl ether and finally removal of the remaining C3' and C4' acetyl groups. This three-step deprotection procedure produced urdamycinone B (**1**) from **22** in 54% yield,<sup>21</sup> while anthraquinone **23** afforded 104-2 (**2**) in 52% yield. The spectral data of synthetic and natural urdamycinone B (**1**) were identical in all respects, as were those of synthetic and natural 104-2 (**2**) (i.e., <sup>1</sup>H and <sup>13</sup>C NMR, IR, and CD).

In conclusion, we have completed the total synthesis of urdamycinone B (**1**) and 104-2 (**2**). The former synthetic sequence proceeds in 18 steps and provides **1** in 6.7% overall yield, while the latter proceeds in 22 steps and provides **2** in 5.6% overall yield. The application of this convergent strategy to the total synthesis of other angucycline antibiotics is currently under investigation.

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**Supporting Information Available:** Experimental procedures and spectral data for all compounds (18 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(13) Unpublished results of Kyungjin Kim and Dr. Joseph Reibenspies, Texas A&M University, Department of Chemistry.

(14) Boyd, V. A.; Drake, B. E.; Sulikowski, G. A. *J. Org. Chem.* **1993**, *58*, 3191–3193.

(15) (a) Heinzman, S. W.; Gruenwell, J. R. *Tetrahedron Lett.* **1980**, *21*, 4305–4308. (b) Jung, M. E.; Hagenah, J. A. *J. Org. Chem.* **1983**, *48*, 5359–5361.

(16) A second Diels–Alder adduct which rapidly decomposes was isolated in ~13% yield. The structure of this second isomer has not been determined.

(17) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973–1976.

(18) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.

(19) (a) Andres, C. J.; Spetseris, N.; Norton, J. R.; Meyers, A. I. *Tetrahedron Lett.* **1995**, *36*, 1613–1616. (b) Bittner, S.; Lempert, D. *Synthesis* **1994**, 917–919. (c) Tsuji, N.; Kobayashi, M.; Terui, Y.; Tori. *Tetrahedron* **1976**, *32*, 2207–2210.

(20) We propose the oxidation of **20** to proceed via the corresponding quinone methide; see: Boyd, V. A.; Reibenspies, J.; Sulikowski, G. A. *Tetrahedron Lett.* **1995**, *36*, 4001–4004.

(21) In the case of urdamycinone B (**1**),  $\beta$  elimination accompanied the deprotection of the C3' and C4' acetyl groups to the extent of 22%.