Total Synthesis

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Chirality Relay To Access Oxygenated Angular Aromatic Polyketides**

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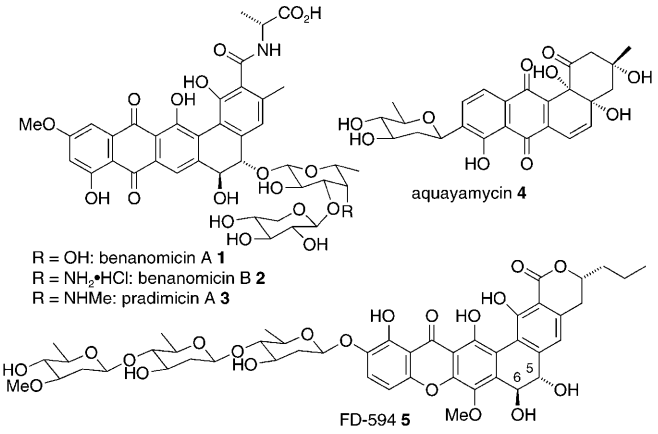
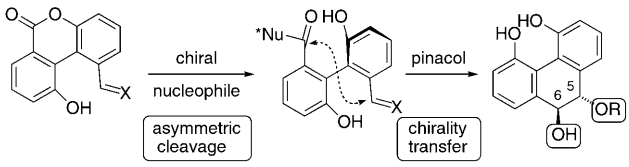
Aromatic polyketide natural products are an important source of therapeutic leads, such as the anthracyclines and tetracyclines. The development of synthetic strategies to access this class of natural products is therefore an important area of investigation. From a synthetic perspective, aromatic polyketides that incorporate oxygenated angular ring systems in their structure pose a significant challenge. Such compounds include the benzo[*a*]anthracene antibiotics **1**–**4**[1] and



the naphthoxanthene antibiotic FD-594 (**5**).[2] Notably, the benanomicin–pradimicin antibiotics **1**–**3** show significant antifungal and anti-HIV activity. FD-594 (**5**) displays antibacterial activity against some Gram-positive bacteria. A unique structural property of FD-594 is a novel solvent-dependent atropisomerism.[3] This dynamic stereochemical behavior is associated with the location of a *trans* diol at C5 and C6 within the polycyclic framework, which incorporates a biaryl ring system. A related structural arrangement is present in the benanomicin–pradimicin antibiotics (BpAs), represented by benanomicin A/B (**1**, **2**) and pradimicin (**3**). One hydroxy group of the *trans* diol in **1**–**3** is glycosylated with a disaccharide unit. From the standpoint of total synthesis, this glycosylation introduces a significant challenge as a result of the pseudo C_2 symmetry of the *trans*-diol system.

A number of synthetic approaches have addressed challenges associated with the BpAs.[4] In 2005, Suzuki and co-workers described a comprehensive solution to the synthesis of the BpAs.[5] Recently, this elegant synthetic strategy was extended to a total synthesis of the aglycone of FD-594.[6] The key elements of the Suzuki strategy are illustrated in Scheme 1. In the first step of a two-step process, asymmetric



Scheme 1. Strategy of Suzuki and co-workers based on asymmetric lactone cleavage and chirality transfer.

cleavage of a biaryl lactone with a chiral nucleophile by a procedure similar to that described by Bringmann et al.[7] affords a diastereomerically enriched biaryl intermediate. A modified pinacol coupling then transfers the biaryl axial chirality to the pseudo-C_2-symmetric *trans* diol. An important feature of the pinacol coupling is that the product diol emerges differentially protected, which enables selective glycosylation of the C5 hydroxy group to afford access to the benanomicin–pradimicin antibiotics.

The Suzuki synthesis of the benanomicin–pradimicin aglycone began with a three-step reaction sequence leading to biaryl lactone **8** (Scheme 2): A Yamaguchi esterification between carboxylic acid **6** and phenol **7** was followed by MOM-ether cleavage and palladium-catalyzed ring closure. During investigations into the enantioselective reduction of lactone **8** with chiral reducing agents, a diastereoselective lactone opening with L-valine was observed serendipitously. This result led to the screening of other chiral nucleophilic amines and the eventual identification of (*R*)-valinol as a highly selective nucleophile. The treatment of **8** with (*R*)-valinol gave a 91:9 mixture of diastereomeric atropisomers, which could be separated by chromatography. The major isomer was assigned the *M* (or minus) configuration on the

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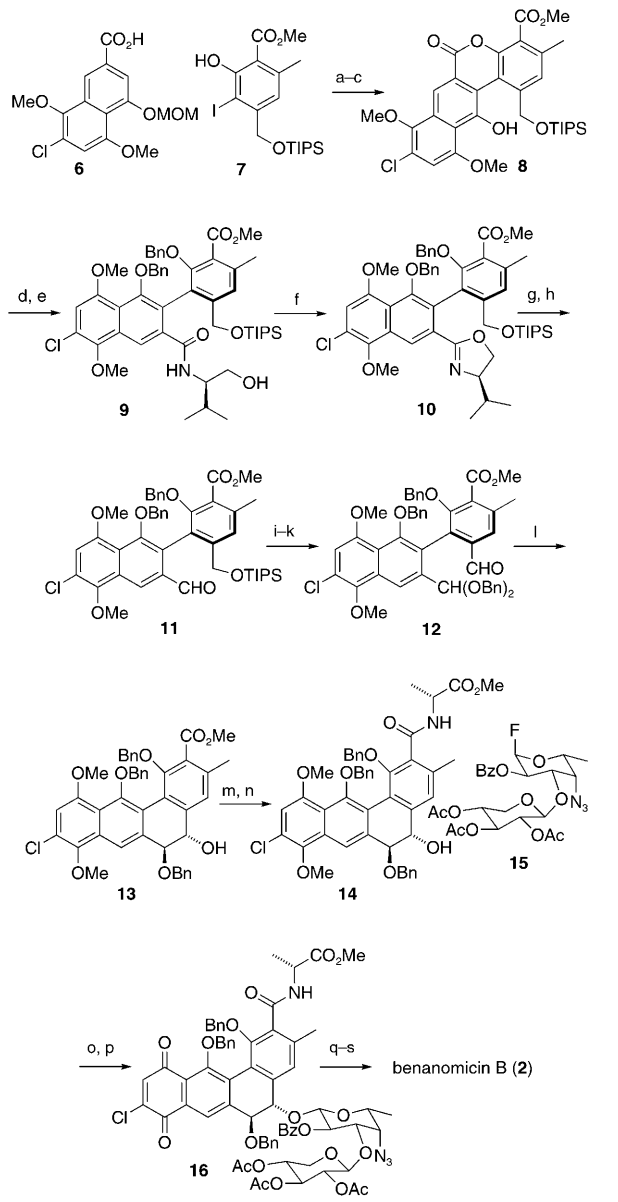

Scheme 2. Total synthesis of benanomicin B (**2**): a) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene (99%); b) CF_3CO_2H, CH_2Cl_2 (96%); c) $Pd(OAc)_2$ (30 mol%), PPh_3 (60 mol%), $tBuCO_2Na$, DMA, 110°C, 20 min (99%); d) (*R*)-valinol (2.6 equiv), CH_2Cl_2, 0°C, 43 h (90%, d.r. 91:9); e) BnBr, Cs_2CO_3, DMF, 0°C→RT (97%); f) I_2, PPh_3, imidazole, CH_2Cl_2, 0°C (100%); g) MeOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2; h) L-selectride, 0°C, then SiO_2, 17 h (96%, two steps); i) BnOTMS, TMSOTf, toluene, −15°C; j) nBu_4NF, THF, 0°C; k) MnO_2, CH_2Cl_2 (94%, three steps); l) SmI_2, $BF_3{\cdot}OEt_2$, MeOH, THF, −78°C, 1 min, then 0°C, 10 min. (95%, *trans*/*cis* > 99:1, > 99% *ee*); m) 5 M NaOH, EtOH, sealed tube, 100°C; n) D-Ala-OMe·HCl, BOP, Et_3N, DMF (84%, two steps); o) **14**, $[Cp_2HfCl_2]$/2 AgOTf, 4 Å molecular sieves, CH_2Cl_2, −78°C, 20 min, then −35°C, 11 h (72% β anomer, 9% α anomer); p) $Ce(NH_4)_2(NO_3)_6$, CH_3CN, H_2O, 0°C, 5 min; q) 1. (*E*)-(1,3-dimethoxybuta-1,3-dienyloxy)trimethylsilane, THF, 2 h; 2. SiO_2, 12 h; 3. K_2CO_3, CH_2Cl_2, THF, 3 h (74%, two steps); r) 5 M NaOH, MeOH; s) H_2, Pd/C, MeOH, 1 M HCl, DMF (53%, two steps). Bn = benzyl, BOP = benzotriazole-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, Bz = benzoyl, DMA = dimethylacetamide, DMAP = 4-dimethylaminopyridine, DMF = dimethylformamide, MOM = methoxymethyl, Tf = trifluoromethanesulfonyl, TIPS = triisopropylsilyl, TMS = trimethylsilyl.

basis of single-crystal X-ray analysis. Benzylation followed by cyclodehydration of the hydroxyamide provided the oxazoline **10**, which was converted into the requisite aldehyde **11** by N-methylation, reduction, and exposure to silica gel. In preparation for the key pinacol cyclization, acetal formation was followed by TIPS deprotection and oxidation to the aldehyde **12**.

Reaction conditions for the cyclization step were screened extensively, and it was found that the treatment of aldehyde **12** with SmI_2 in the presence of boron trifluoride etherate and MeOH yielded the desired protected diol (*S*,*S*)-**13** in greater than 99% *ee*. Without the addition of MeOH, yields were low and irreproducible. Saponification of the methyl ester, followed by coupling of the resulting carboxylic acid with D-alanine, gave **14**. Glycosylation with glycosyl fluoride **15**, which was activated by a combination of $[Cp_2HfCl_2]$ and AgOTf, was then followed by oxidation to quinone **16** in preparation for a Diels–Alder reaction to form the leftmost ring in the target. Finally, ester hydrolysis, acetate and benzoate cleavage, and hydrogenation provided the natural product benanomicin B (**2**).

Recently, Suzuki and co-workers applied the asymmetric-cleavage–chirality-transfer strategy (Scheme 1) to the total synthesis of the aglycone of FD-594 (Scheme 3).[6] The major transformations remained the same: In this case, the asymmetric cleavage of lactone **17** with an excess of (*S*)-valinol provided amide (*M*)-**18** as the major diastereomer (14:1). As expected, the use of (*R*)-valinol in the lactone-cleavage reaction reversed the stereoselectivity of the process to provide the *M* atropisomer as the minor diastereomer (1:18). Thus, the reaction proceeds under reagent control. A seven-step reaction sequence, similar to the sequence employed in the synthesis of benanomicin B, was required to advance amide **18** to dialdehyde **22**. As the xanthone carbonyl group interfered with the pinacol cyclization, temporary reduction to xanthene **22** was necessary. The cyclization of dialdehyde **22** was most successful with samarium iodide in THF at −78°C, with (*S*,*S*)-*i*Pr-pybox as an additive to minimize production of the undesired *cis* diol. Finally, **19** was converted into the FD-594 aglycone **20** in a six-step reaction sequence.

The Suzuki research group has demonstrated the scope of the asymmetric-cleavage–chirality-transfer strategy (Scheme 1) by completing the total synthesis of several benanomicin–pradimicin antibiotics[5b] and now the aglycone of FD-594.[6] This general synthetic strategy should provide access to nonnatural derivatives for investigations into the relationships between structure and biological activity within this fascinating class of natural products. Mechanistic details regarding the diastereoselectivity of the asymmetric cleavage of the biaryl lactones **8** and **17** by valinol would be interesting, given that (*R*)-valinol induced the same sense of axial chirality in the reaction with lactone **8** as induced by (*S*)-valinol in the reaction with the structurally related lactone substrate **17**.[8]

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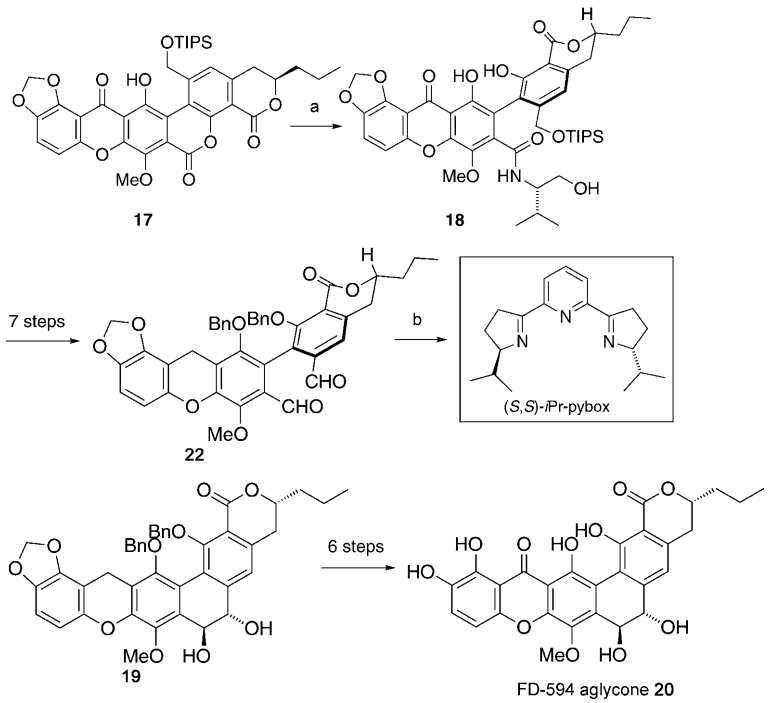

Scheme 3. a) (*S*)-valinol (3.2 equiv), THF, 26 °C, 20 min (d.r. 14:1); b) SmI_2, (*S*,*S*)-*i*Pr-pybox, THF, −78 °C, 0.5 h (72%).

[1] a) S. Gomi, M. Sezaki, S. Kondo, T. Hara, H. Naganawa, T. Takeuchi, *J. Antibiot.* **1988**, *41*, 1019–1028; b) T. Oki, M. Konishi, K. Tomatsu, K. Tomita, K. Saitoh, M. Tsunakawa, M. Nishio, T. Miyaki, H. Kasaguchi, *J. Antibiot.* **1988**, *41*, 1701–1704; c) T. Hasegawa, M. Kakushima, M. Hatori, S. Aburaki, S. Kakinuma, T. Furumai, T. Oki, *J. Antibiot.* **1993**, *46*, 598–605; d) K. Saitoh, Y. Sawada, K. Tomita, T. Tsuno, M. Hatori, T. Oki, *J. Antibiot.* **1993**, *46*, 387–393; e) M. Sezaki, S. Kondo, K. Maeda, H. Umezawa, M. Ohno, *Tetrahedron* **1970**, *26*, 5171–5190.

[2] Y. F. Qia, T. Okazaki, T. Ando, K. Mizoue, *J. Antibiot.* **1998**, *51*, 282–287.

[3] T. Eguchi, K. Kondo, K. Kakinuma, H. Uekusa, Y. Ohashi, K. Mizoue, Y. F. Qiao, *J. Org. Chem.* **1999**, *64*, 5371–5376.

[4] a) T. R. Kelly, Q. Li, V. Bhushan, *Tetrahedron Lett.* **1990**, *31*, 161–164; b) F. M. Hauser, W. A. Dorsch, D. Mal, *Org. Lett.* **2002**, *4*, 2237–2239; c) K. Krohn, S. Bernhard, U. Floerke, N. Hayat, *J. Org. Chem.* **2000**, *65*, 3218–3222.

[5] a) K. Ohmori, M. Tamiya, M. Kitamura, H. Kato, M. Oorui, K. Suzuki, *Angew. Chem.* **2005**, *117*, 3939–3942; *Angew. Chem. Int. Ed.* **2005**, *44*, 3871–3874; b) M. Tamiya, K. Ohmori, M. Kitamura, H. Kato, T. Arai, M. Oorui, K. Suzuki, *Chem. Eur. J.* **2007**, *13*, 9791–9823.

[6] R. Masuo, K. Ohmori, L. Hintermann, S. Yoshida, K. Suzuki, *Angew. Chem.* **2009**, *121*, 3514–3517; *Angew. Chem. Int. Ed.* **2009**, *48*, 3462–3465.

[7] G. Bringmann, M. Breuning, S. Tasler, *Synthesis* **1999**, 525–558.

[8] For a discussion of the principles behind the stereocontrol of the ring-opening reaction, see reference [7].