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Efficient Method for Introducing Vineomycin-Fridamycin-Type Side Chain. Total Synthesis of Fridamycin E

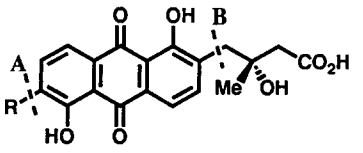
Takashi Matsumoto, Hideki Jona, Miyoko Katsuki, and Keisuke Suzuki*
Department of Chemistry, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223, Japan

Summary: An effective approach for introducing vineomycin-fridamycin-type side chain was developed. Tin-lithium exchange of arylstannane 5 followed by the reaction with chiral aldehyde 6 gave the desired adduct 7. Total synthesis of (R)-(+)-fridamycin E was accomplished.

Vineomycin[1]-fridamycin[2] antibiotics constitute a novel class of antitumor compounds with synthetically attractive structures: Three dissimilar components, *i.e.*, the anthraquinone, the C-glycosidated sugar, and the characteristic aliphatic side chain, are connected together through two C-C bonds (**A** and **B**, Figure 1). For the formation of aryl C-glycoside bond **A**, we developed a new method which proved to be effective in synthesizing the C-glycoside sector of these compounds.[3] In order to accomplish the total synthesis, we elected to investigate the approach for forming the bond **B**, that is, the connection of the chiral, non-racemic side chain to the aromatic moiety in regioselective manner.

In this communication, we wish to report an effective approach for the side chain connection and its successful application to the total synthesis of (*R*)-(+)-fridamycin E (**1**), one of the components of fridamycin antibiotics lacking the C-glycoside portion.[4, 5]

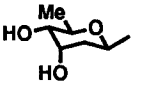
Figure 1



Fridamycin E (**1**) R = H

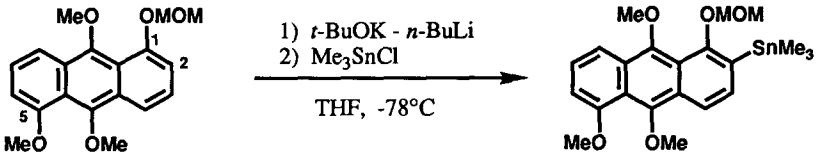
Fridamycin A (**2**) (≡Vineomycinone B 2) R =

Fridamycin B (**3**) R =



MOM-Ether **4**, prepared from 1,5-dihydroxy-9,10-anthraquinone (anthrarufin) in 4 steps,[3b] was treated with *t*-BuOK - *n*-BuLi (2.0 equiv. each / THF / -78 °C) for 10 min to effect the regioselective *ortho*-metallation at C(2).[6,7] Since excess base was required to complete the metallation, it was impractical to use this metallation mixture for the reaction with the electrophilic partner. Therefore, the reaction was once quenched with Me_3SnCl to afford arylstannane **5** in 86% yield.[8] It should be noted here that use of the magic base was

essential for the clean *ortho*-metallation, since the conventional conditions (*e.g.* *n*-BuLi-TMEDA)[9] were totally ineffective for this purpose.[7]



4 **5**

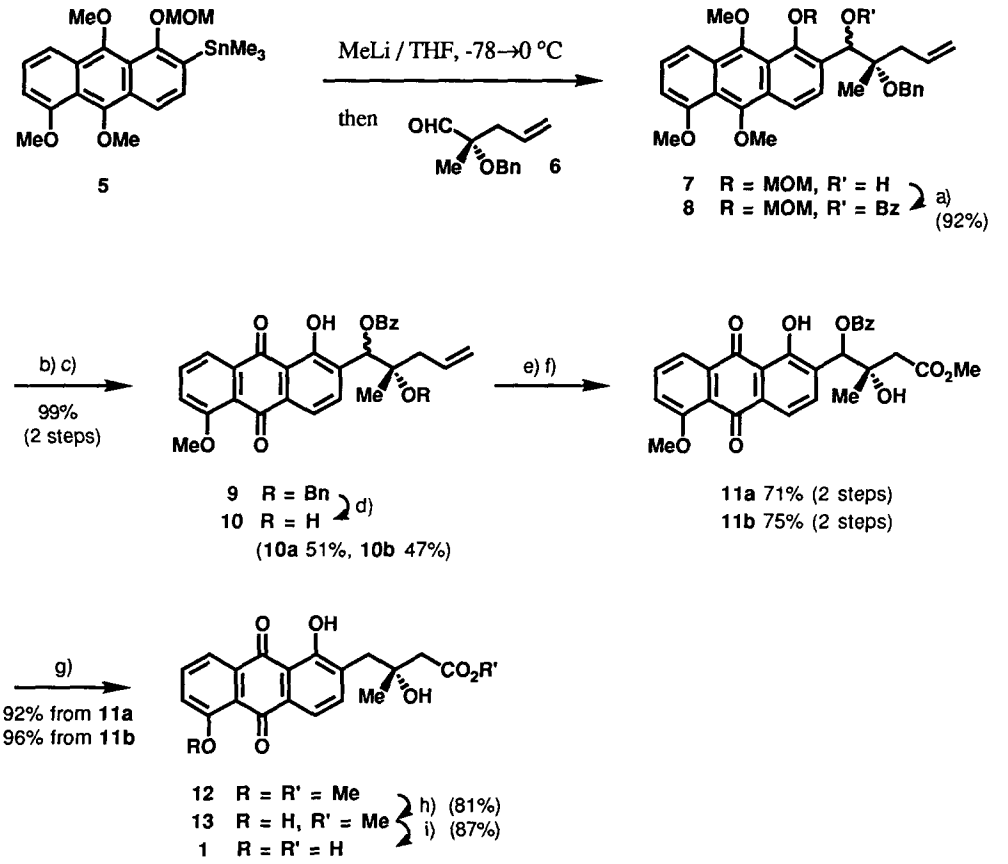
Arylstannane **5**, thus obtained, served as an equivalent of nucleophilic anthraquinone derivative. Tin-lithium exchange of **5** was carried out in toluene by adding MeLi (-78 → 0 °C)[10] and subsequent reaction with (*S*)-aldehyde **6**[11] at 0 °C for 15 min afforded the adduct **7** as a mixture of diastereomers. After benzoylation of **7**, the resulting anthracene **8** was oxidized with cerium(IV) ammonium nitrate to give the corresponding anthraquinone, the crude product of which was further subjected to acidic conditions to give **9**. Oxidative removal of the benzyl group was then effected by treatment with DDQ in two-phase system (CH_2Cl_2 - H_2O)[12] to afford *tert*-alcohol **10**. At this stage the two diastereomers were easily separated with silica-gel chromatography to give the less polar isomer **10a** (Rf: 0.40, $CHCl_3$ / Et_2O = 9/1) and the more polar isomer **10b** (Rf: 0.30).

Double bond of **10a** was cleaved with ozone (MeOH / -78 °C) and subsequent treatment with acetic anhydride and triethylamine gave methyl ester **11a** in 71% yield.[13] Similarly, **10b** was converted to the diastereomeric ester **11b** in 75% yield. Configurational assignment of these diastereomers was not attempted.

Catalytic hydrogenation of **11** with Lindlar catalyst in the presence of Hünig base in ethyl acetate quickly gave the desired methylene compound **12** in excellent yield from each diastereomers, **11a** and **11b**. The reaction proceeds most probably via the initial formation of the corresponding hydroquinone followed by the 1,6-elimination of the benzoyloxy group.[14] Other catalysts such as 10% Pd-C gave lower yield of **12** along with undefined over-reduction products. Treatment of **12** with boron tribromide effected clean deprotection of methyl ether to give triol **13**.[15] Finally, hydrolysis of methyl ester with *t*-BuOK - H_2O in 1,4-dioxane[16] cleanly furnished fridamycin E (**1**) as a yellow solid in 86% yield after recrystallization from methanol. All the physical data were in agreement with those reported.[2,17]

In summary, an effective approach for introducing vineomycin-fridamycin-type side chain was developed, which was applied to the total synthesis of fridamycin E. Total synthesis of vineomycins will be reported elsewhere.

Scheme 1[7]



Keys: a) BzCl, DMAP / Pyr, 10 hr; b) CAN / MeCN-H_2O, -20 °C → rt, 15 min; c) 3 N HCl / dioxane, rt, 4 hr; d) DDQ / CH_2Cl_2 - H_2O, rt, 22 hr; e) O_3 / CH_2Cl_2 - MeOH, -78 °C; f) Ac_2O, Et_3N / CH_2Cl_2, 0 °C, 1 hr; g) H_2, Pd-$CaCO_3$, $^iPr_2NEt$ / EtOAc, rt, 5 min; h) BBr_3 / CH_2Cl_2, -78 → -20 °C, 40 min; i) *t*-BuOK - H_2O / dioxane, rt, 10 hr.

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References and Notes

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3) a) T. Matsumoto, M. Katsuki, K. Suzuki, *Tetrahedron Lett.*, **29**, 6935 (1988); b) T. Matsumoto, M. Katsuki, H. Jona, K. Suzuki, *ibid.*, **30**, 6185 (1989).
4) The antibiotic activity against Gram-positive bacteria of fridamycin E is stronger than the other components with C-glycoside structures. See ref. 2.
5) Total synthesis of the enantiomer of **1** was reported: K. Krohn, W. Baltus, *Tetrahedron*, **44**, 49 (1988).
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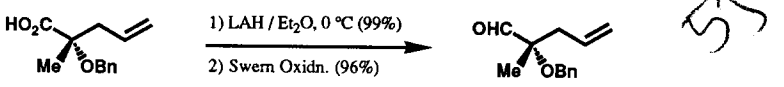
7) Use of two equivalents of both bases is essential for the completion of the metallation, see T. Matsumoto, H. Kakigi, K. Suzuki, *Tetrahedron Letters, in press.*
8) All new compounds were fully characterized by ^{1}H NMR (400 MHz), IR, and HRMS.
9) H. W. Gschwend, H. R. Rodriguez, *Org. React.*, **26**, 1 (1979).
10) For the successful tin-lithium exchange, use of toluene as the solvent was essential, since the alkyl anion attacked the C(9)/C(10)-position in ether or THF. MeLi gave better results than BuLi.
11) (*S*)-Aldehyde **6** was prepared from (*S*)-acid **14**, which is available in optically pure form. T. Sugai, H. Kakeya, H. Ohta, *J. Org. Chem.*, **55**, 4643 (1990).



14 **6**

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14) Use of sodium dithionite turned out to be less effective in terms of reproducibility in this case. Cf. K. Krohn, *Tetrahedron*, **46**, 291 (1990).
15) **13**: $[\alpha]^{28}_D$ -12° (c 0.80, $CHCl_3$); ^{1}H NMR δ ($CDCl_3$) 13.18 (s, 1H), 12.67 (s, 1H), 7.84 (dd, 1H, J 7.7, J_2 = 1.0 Hz), 7.81 (d, 1H, J = 7.7 Hz), 7.70 (d, 1H, J = 7.7 Hz), 7.68 (dd, 1H, J_1 = 8.1, J_2 = 7.7 Hz), 7.32 (dd, 1H, J_1 = 8.1, J_2 = 1.0 Hz), 3.8 - 4.0 (br, 1H), 3.72 (s, 3H), 3.10 (d, 1H, J = 13.7 Hz), 3.04 (d, 1H, J = 13.7 Hz), 2.59 (d, 1H, J = 16.2 Hz), 2.55 (d, 1H, J = 16.2 Hz), 1.31 (s, 3H); ^{13}C NMR δ ($CDCl_3$) 188.3, 187.8, 173.3, 162.7, 161.4, 139.7, 136.6, 134.6, 133.2, 131.8, 125.0, 119.4, 118.9, 116.1, 115.6, 71.8, 51.7, 44.4, 40.5, 27.3; IR (neat) 3540, 2970, 1730, 1630, 1600, 1580, 1430, 1375, 1320, 1260, 1080, 790 cm^{-1}; HRMS *m/z* 352.0976 (352.0946 calcd for $C_{20}H_{16}O_6$, M^+-H_2O).
16) P. G. Gassman, W. N. Schenk, *J. Org. Chem.*, **42**, 918 (1977).
17) **1**: $[\alpha]^{27}_D$ +8.9° (c 1.1, dioxane); mp. 164-165 °C (methanol); ^{1}H NMR δ (d_6-DMSO) 12.8 - 13.2 (br, 1H), 12.5 (s, 1H), 11.8 - 12.3 (br, 1H), 7.84 (dd, 1H, J_1 = 8.1, J_2 = 7.7 Hz), 7.83 (d, 1H, J = 7.9 Hz), 7.78 (dd, 1H, J_1 = 7.7, J_2 = 1.3 Hz), 7.73 (d, 1H, J = 7.9 Hz), 7.42 (dd, 1H, J_1 = 8.1, J_2 = 1.3 Hz), 3.08 (d, 1H, J = 13.1 Hz), 2.90 (d, 1H, J = 13.1 Hz), 2.41 (s, 2H), 1.19 (s, 3H); ^{13}C NMR δ (d_8-dioxane) 189.2, 188.7, 173.8, 163.1, 161.8, 140.2, 137.0, 135.5, 134.4, 132.6, 125.0, 119.3, 118.8, 117.2, 116.4, 71.9, 45.2, 40.7, 27.1; IR (KBr) 3440, 2940, 1700, 1630, 1605, 1580, 1430, 1375, 1315, 1270, 790 cm^{-1}; HRMS *m/z* 357.0973 (357.0973 calcd for $C_{19}H_{17}O_7$, M^++1).

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