Total Synthesis of Pamamycin-607

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Pamamycins are 16-membered macrodiolides isolated from *Streptomyces alboniger* and *S. aurantiacus*.[1] They display autoregulatory, antibiotic, and anionophoric activities[2] (Figure 1). Pamamycin-607[1b−d] is especially interesting for its potent activity[2e] against gram-positive bacteria (including multiple antibiotic-resistant strains of *Mycobacterium tuberculosis*) as well as against phytopathogenic fungi.

Total synthesis of pamamycin-607 and other members of the family have not yet been communicated in the literature despite intense synthetic efforts,[3,4] and we wish to report here the results of our research which culminated in a total synthesis of pamamycin-607.

In retrosynthetic analysis (Scheme 1), the ester bond formation between the carboxylic acid **A** and the alcohol **E** would set the stage for the final macrodiolide cyclization required in the preparation of pamamycin-607 (**1**). The acid **A** may be obtained from the ester **D**, employing the key radical cyclization reaction[5] converting the β-alkoxyvinyl ketone **C** into the tetrahydrofuranyl ester **B**. The two tetrahydrofuran rings in **E** and **F** were also envisaged to arise from radical cyclization reactions of the intermediates such as **G** (in practice, two separate radical cyclization reactions are deemed necessary), which may be synthesized from the protected pentahydroxy intermediate **H**.

The PMB-protected 3-hydroxypropanal **2** was reacted with the (*Z*)-boron enolate prepared from the chiral imide **3**.[6] The imide

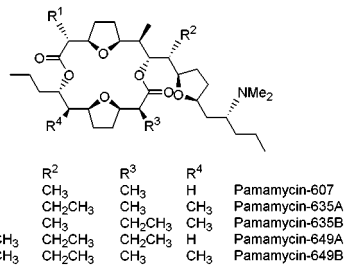
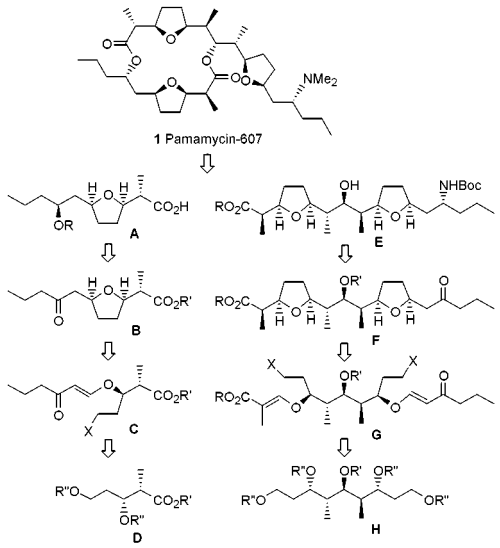
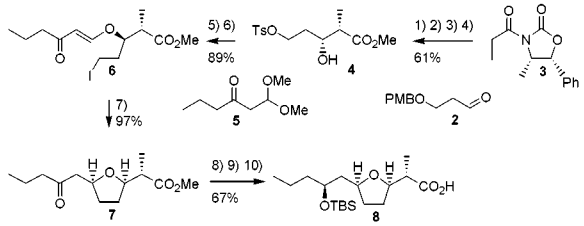


Figure 1.

Scheme 1



Scheme 2



1) 1.2 eq. *n*-Bu_2BOTf, 1.2 eq. TEA, DCM, -40 ~ 0 °C, 30 min; 1.1 eq. **2**, -78 ~ 0 °C, 5 h; 2) 0.2 eq. $Sm(OTf)_3$, MeOH-THF (1:1), r.t. 24 h; 3) H_2, Pd/C, MeOH, r.t. 4 h; 4) 1.0 eq. *p*-TsCl, 1.2 eq. TEA, DCM, 0 °C, 12 h; 5) 3.0 eq. **5**, 0.1 eq. TFA, Benzene, Reflux, 15 h; 6) 3.0 eq. NaI, Acetone, Reflux, 2 h; 7) 1.2 eq. Bu_3SnH, 0.02 eq. AIBN, Benzene (0.025 M), Reflux, 90 min (Syringe pump, 1 h); 8) 3.0 eq. SmI_2, 20 eq. MeOH, THF, 0 °C ~ r.t. 8 h; 9) 1.5 eq. TBSCl, 1.5 eq. Imidazole, DMF, r.t. 12 h; 10) 0.6 N NaOH, MeOH-H_2O (2:1), r.t. 11 h.

aldol was converted into the corresponding methyl ester, and the ester **4** was obtained via PMB-deprotection and tosylation. The reaction of **4** with the acetal ketone **5** under acidic conditions afforded the β-alkoxyvinyl ketone **6**[7] after subsequent iodide substitution. Radical cyclization of **6** in the presence of tributylstannane and AIBN under the standard high-dilution conditions proceeded efficiently to give the tetrahydrofuranyl ketone product **7** in high yield (Scheme 2). Samarium(II) iodide was the reagent of choice[8] for stereoselective reduction of the carbonyl group (8.5:1) in **7**, and the carboxylic acid **8** was prepared via TBS-protection of the hydroxy group and basic hydrolysis of the methyl ester moiety.

(1) (a) McCann, P. A.; Pogell, B. M. *J. Antibiot*. **1979**, *32*, 673−678. (b) Kondo, S.; Yasui, K.; Katayama, M.; Marumo, S.; Kondo, T.; Hattori, H. *Tetrahedron Lett*. **1987**, *28*, 5861−5864. (c) Kondo, S.; Yasui, K.; Natsume, M.; Katayama, M.; Marumo, S. *J. Antibiot*. **1988**, *41*, 1196−1204. (d) Natsume, M.; Kondo, S.; Marumo, S. *J. Chem. Soc., Chem. Commun*. **1989**, 1911−1913. (e) Natsume, M.; Yasui, K.; Kondo, S.; Marumo, S. *Tetrahedron Lett*. **1991**, *32*, 3087−3090. (f) Natsume, M.; Tazawa, J.; Yagi, K.; Abe, H.; Kondo, S.; Marumo, S. *J. Antibiot*. **1995**, *48*, 1159−1164. (g) Härtl, A.; Stelzner, A.; Schlegel, R.; Heinze, S.; Hülsmann, H.; Fleck, W.; Gräfe, U. *J. Antibiot*. **1998**, *51*, 1040−1046. (h) Kozone, I.; Chikamoto, N.; Abe, H.; Natsume, M. *J. Antibiot*. **1999**, *52*, 329−331.

(2) (a) Stengel, C.; Reinhardt, G.; Gräfe, U. *J. Basic Microbiol*. **1992**, *32*, 339−345. (b) Gräfe, U.; Stengel, C.; Möllmann, U.; Heinisch, L. *Pharmazie* **1994**, *49*, 343−346. (c) Natsume, M.; Honda, A.; Oshima, Y.; Abe, H.; Kondo, S.; Tanaka, F.; Marumo, S. *Biosci. Biotechnol. Biochem*. **1995**, *59*, 1766−1768. (d) Grigoriev, P. A.; Berg, A.; Schlegel, R.; Gräfe, U. *Bioelectrochem. Bioenerg*. **1996**, *39*, 295−298. (e) Pogell, B. M. *Cell. Mol. Biol*. **1998**, *44*, 461−463.

(3) (a) Walkup, R. D.; Park, G. *Tetrahedron Lett*. **1988**, *29*, 5505−5508. (b) Walkup, R. D.; Kim, S. W.; Wagy, S. D. *J. Org. Chem*. **1993**, *58*, 6486−6490. (c) Walkup, R. D.; Kim, S. W. *J. Org. Chem*. **1994**, *59*, 3433−3441. (d) Walkup, R. D.; Kim, Y. S. *Tetrahedron Lett*. **1995**, *36*, 3091−3094. (e) Mavropoulos, I.; Perlmutter, P. *Tetrahedron Lett*. **1996**, *37*, 3751−3754. (f) Arista, L.; Gruttadauria, M.; Thomas, E. J. *Synlett* **1997**, 627−628. (g) Mandville, G.; Girard, C.; Bloch, R. *Tetrahedron: Asymmetry* **1997**, *8*, 3665−3673. (h) Mandville, G.; Bloch, R. *Eur. J. Org. Chem*. **1999**, 2303−2307. (i) Solladié, G.; Salom-Roig, X. J.; Hanquet, G. *Tetrahedron Lett*. **2000**, *41*, 551−554. (j) Bernsmann, H.; Hungerhoff, B.; Fechner, R.; Fröhlich, R.; Metz, P. *Tetrahedron Lett*. **2000**, *41*, 1721−1724. (k) Calter, M. A.; Bi, F. C. *Org. Lett*. **2000**, *2*, 1529−1531. (l) Solladié, G.; Salom-Roig, X. J.; Hanquet, G. *Tetrahedron Lett*. **2000**, *41*, 2737−2740. (m) Bernsmann, H.; Fröhlich, R.; Metz, P. *Tetrahedron Lett*. **2000**, *41*, 4347−4351. (n) Bernsmann, H.; Gruner, M.; Metz, P. *Tetrahedron Lett*. **2000**, *41*, 7629−7633.

(4) A total synthesis was communicated by Professor Sung Ho Kang (Korea Advanced Institute of Science and Technology) at the CMDS Symposium 2000, November 9, 2000, Daejon, Korea. A communication appeared in the literature after submission of this manuscript: Germay, O.; Kumar, N.; Thomas, E. J. *Tetrahedron Lett*. **2001**, *42*, 4969−4974.

(5) Lee, E. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Applications, Vol. 2; Wiley-VCH: Weinheim, 2001; pp 303−333.

(6) For an example of asymmetric aldol reactions, see: Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc*. **1990**, *112*, 7001−7031.

(7) For an example of radical cyclizations of β-aminovinyl ketones, see: Lee, E.; Kang, T. S.; Chung, C. K. *Bull. Kor. Chem. Soc.* **1996**, *17*, 212−214.

(8) Keck, G. E.; Wager, C. A. *Org. Lett*. **2000**, *2*, 2307−2309.

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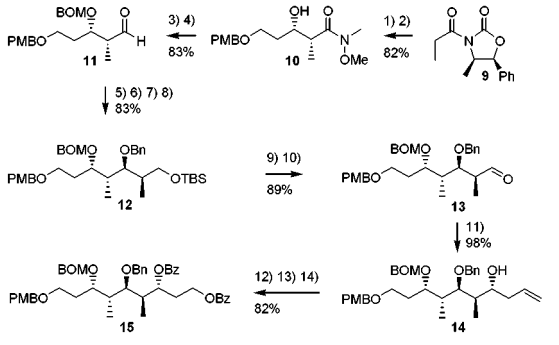
Scheme 3



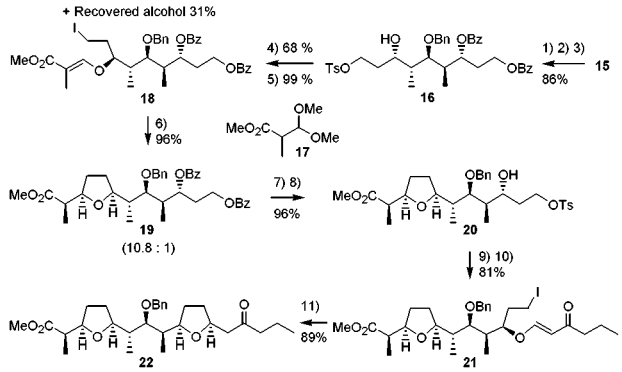
1) 1.2 eq. *n*-Bu_2BOTf, 1.2 eq. TEA, DCM, -40 ~ 0 °C, 30 min; 1.1 eq. **2**, -78 ~ 0 °C, 5 h; 2) 3.5 eq. MeNH(OMe).HCl, 3.5 eq. Me_3Al, THF, -20 °C ~ r.t. 3 h; 3) 3.0 eq. BOMCl, 3.0 eq. DIPEA, 0.1 eq. TBAI, DCM, r.t. 15 h; 4) 2.0 eq. DIBAL, THF, -78 °C, 1 h; 5) 1.1 eq. **3**, 1.2 eq. *n*-Bu_2BOTf, 1.2 eq. TEA, DCM, -40 ~ 0 °C, 30 min; **11**, -78 ~ 0 °C, 5 h; 6) 4.0 eq. $NaBH_4$, THF-H_2O (3:1), r.t. 3 h; 7) 1.2 eq. TBSCl, 1.5 eq. Imidazole, DCM, 0 °C, 1 h; 8) 1.2 eq. BnBr, 1.1 eq. NaHMDS, THF-DMF (5:1), 0 °C, 1 h; 9) 3.0 eq. TBAF, THF, r.t. 8 h; 10) 5.0 eq. SO_3.Pyr, 10 eq. TEA, DMSO-DCM (3:1), r.t. 3 h; 11) 1.5 eq. $H_2CCHCH_2SnBu_3$, 3.0 eq. $MgBr_2.Et_2O$, DCM, r.t. 3 h; 12) 0.05 eq. OsO_4, 3.0 eq. NMO, Acetone-H_2O (3:1), r.t. 90 min; 3.0 eq. $NaIO_4$, r.t. 30 min; 13) 5.0 eq. $NaBH_4$, EtOH, r.t. 1 h; 14) 6.0 eq. BzCl, 10 eq. Pyridine, 0.2 eq. DMAP, DCM, r.t. 24 h.

Synthesis of the northern part of **1** commenced with the reaction of **2** with the (*Z*)-boron enolate of the imide **9** (Scheme 3). The Weinreb amide **10** obtained from the aldol imide was transformed into the benzyloxymethyl derivative, and the aldehyde **11** was obtained via reduction with DIBAL. Reaction of **11** with the (*Z*)-boron enolate of the imide **3**, $NaBH_4$ reduction, protection of the primary hydroxy group with TBSCl, and benzylation of the secondary hydroxy group provided the protected tetrahydroxy intermediate **12** in stereoselective manner. Allylation of the aldehyde **13**, which was obtained from **12** via TBS-deprotection and oxidation, proceeded stereoselectively upon addition of allyltributylstannane in the presence of $MgBr_2-Et_2O$ complex.[9] The homoallylic alcohol **14** thus obtained was converted into the dibenzoate **15** via oxidative cleavage of the double bond, $NaBH_4$ reduction, and benzoylation.

The alcohol **16** was obtained from **15** via PMB-deprotection with ceric ammonium nitrate, tosylation of the primary hydroxy group, and BOM-deprotection. Reaction of **16** with excess methyl 3,3-dimethoxy-2-methylpropanoate (**17**) in the presence of an acid catalyst provided the desired β-alkoxymethacrylate derivative, which was converted into the iodide **18** via iodide substitution. Low-temperature radical cyclization reaction of **18** in the presence of triethylborane proceeded efficiently, producing a mixture of the tetrahydrofuranyl products favoring (10.8:1) the correct threo isomer **19**[10] (Scheme 4). The benzoate moieties in **19** were hydrolyzed, and the primary hydroxyl group was tosylated to provide the alcohol **20**. The reaction of **20** with the acetal ketone **5** proceeded uneventfully, and the β-alkoxyvinyl ketone **21** was obtained after iodide substitution. Radical cyclization reaction of **21** under the standard high-dilution conditions in the presence of tributylstannane and AIBN afforded the ketone **22** in high yield as expected.

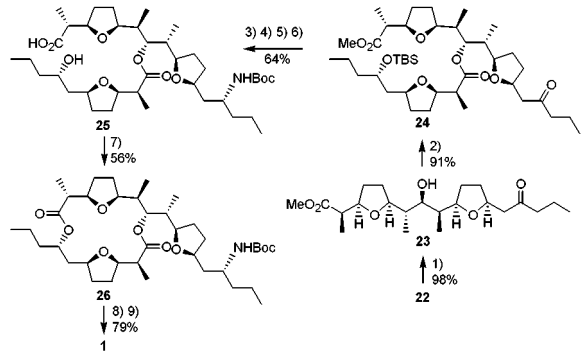
Debenzylation via hydrogenolysis provided the alcohol **23**, and the ester bond formation between **23** and the carboxylic acid **8** was achieved using Yamaguchi protocol,[11] yielding the ester **24** in high yield (Scheme 5). Reductive amination of the carbonyl group in **24** and subsequent Boc-protection proceeded stereoselectively, and TBS-deprotection and hydrolysis of the methyl ester moiety afforded the hydroxy carboxylic acid **25**. Dicyclohexylcarbodiimide was the reagent of choice for the crucial macrodiolide ring closure,[12] and the macrodiolide **26** was obtained in 56% yield. Pamamycin-607 (**1**)[13] was obtained via Boc-deprotection of **26** and reductive methylation of the free amino group.

Scheme 4



1) 2.0 eq. CAN, MeCN-THF (9:1), r.t. 30 min; 2) 1.0 eq. *p*-TsCl, 1.2 eq. TEA, DCM, 0 °C, 3 h; 3) conc. HCl-MeCN (1:5), r.t. 2 h; 4) 3.0 eq. **17**, 0.2 eq. *p*-TsOH, $CHCl_3$, Reflux, 12 h; 5) 3.0 eq. NaI, Acetone, Reflux, 2 h; 6) 1.2 eq. Bu_3SnH, 1.5 eq. Et_3B, Toluene (0.01 M), -78 °C, 1 h; 7) 5.0 eq. K_2CO_3, MeOH, r.t. 3 h; 8) 1.0 eq. *p*-TsCl, 1.2 eq. TEA, DCM, 0 °C, 8 h; 9) 3.0 eq. **5**, 0.1 eq. TFA, Benzene, Reflux, 15 h; 10) 3.0 eq. NaI, Acetone, Reflux, 2 h; 11) 1.2 eq. Bu_3SnH, 0.2 eq. AIBN, Benzene (0.02 M), Reflux, 3 h.

Scheme 5



1) H_2, Pd/C, MeOH, r.t. 8 h; 2) 1.1 eq. **8**, 1.2 eq. 2,4,6-$Cl_3PhCOCl$, 1.3 eq. TEA, THF, r.t. 2 h; **23**, 1.0 eq. DMAP, Benzene (0.1 M), r.t. 3 h; 3) 10 eq. NH_4OAc, 1.5 eq. $NaBH_3CN$, 4 A MS, *i*-PrOH, 0 °C, 8 h; 4) 5.0 eq. Boc_2O, 10 eq. TEA, DCM, r.t. 1 h; 5) conc. HCl, MeOH, r.t. 1 h; 6) 0.6 N LiOH, MeOH-H_2O (3:1), r.t. 5 h; 7) 10 eq. DCC, 10 eq. PPTS, 100 eq. Pyridine, $ClCH_2CH_2Cl$ (0.001 M), Reflux, 24 h (Syringe pump, 15 h); 8) 10% TFA, DCM, r.t. 1 h; 9) H_2 (50 psi), Pd/C, 20 eq. aq. CH_2O, 10 eq. AcOH, MeOH, r.t. 12 h.

In the present synthesis, the three *cis*-2,5-disubstituted tetrahydrofuran rings in **1** were stereoselectively introduced via radical cyclization reactions of β-alkoxyvinyl ketones and β-alkoxymethacrylates, and it provides another efficacious example of radical-mediated reactions in the construction of complex molecules.

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Supporting Information Available: Schemes for stereochemical assignment, selected experimental procedures and spectral data for **36** (the reduction product of **7**), **15**, **22**, and **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA016272Z

(9) For examples of stereoselective aldehyde allylation reactions using allylstannane in the presence of Lewis acids, see: Keck, G. E.; Abbott, D. E. *Tetrahedron Lett*. **1984**, *25*, 1883−1886. In our case, reactivity and stereoselectivity improved vastly in the presence of diethyl ether.

(10) Lee, E.; Choi, S. J. *Org. Lett.* **1999**, *1*, 1127−1128.

(11) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn*. **1979**, *52*, 1989−1993.

(12) Kageyama, M.; Tamura, T.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990**, *112*, 7407−7408.

(13) Pamamycin-607 (**1**) was obtained in 3.9% total yield from the imide **9** in 34 steps in the longest sequence: $[\alpha]^{25}_D$ +21.9 (*c* 1.38, MeOH).