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A stereocontrolled synthetic route to the C1–C18 subunit of pamamycin-607

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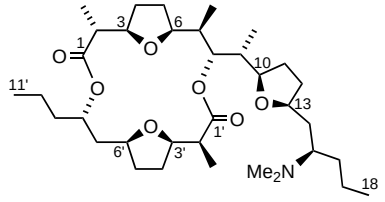
Abstract—The C1–C18 subunit **2** of the 16-membered macrodiolide pamamycin-607 has been synthesized stereoselectively using the Ag_2CO_3-mediated intramolecular iodoetherification for the two *cis*-2,5-disubstituted tetrahydrofurans, crotylation and cuprate epoxide opening for the hydroxyl and methyl substituents.

Pamamycin-607 is the lowest homolog of pamamycin family, isolated from *Streptomyces alboniger* and *Streptomyces aurantiacus* JA4570.[1] Its unique structural feature is the composition of 16-membered macrodiolide, and three *cis*-2,5-disubstituted tetrahydrofurans retaining *anti*- and *syn*-methyl substituents α to the rings.[2] It exhibits various biological activities such as antimicrobial, autoregulatory and anionophoric properties.[1,3] Noticeably, it possesses the promising potency against multiple antibiotic-resistant strains of *Mycobacterium tuberculosis*.[3f] Due to its intriguing structural and biological aspects as well as its purification difficulty, our efforts have been directed to a total synthesis of pamamycin-607. Herein we describe a stereoselective synthesis of the C1–C18 subunit **2** of pamamycin-607 **1**.[4]



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Based on the retrosynthetic analysis toward **2**, its two indispensable *cis*-2,5-disubstituted tetrahydrofurans were envisaged to be installed by iodocyclization of γ-triethylsilyloxyalkenes (Scheme 1).[5] Accordingly, alkenes **3** and **4** were chosen as the key intermediates, the double bonds of which were expected to be generated by Wittig olefination. The two requisite components for **4**, corresponding to aldehyde and phosphonium salt, could be derived from the common alkene **5**. In addition, the adjacent hydroxyl and methyl functional groups of **5** would be elaborated by Roush's crotylboronate methodology.[6]

The synthesis of **2** began with crotylation of the aldehyde, generated from the known alcohol **6**,[7] with (*E*)-crotylboronate **7** to afford alcohol **5** in 80% ee and 87% overall yield (Scheme 2). To attain not only the intended derivatization but also enantiomeric separation, **5** was subjected to esterification with *N*-Cbz-L-proline, dihydroxylation, oxidative cleavage and $NaBH_4$ reduction in sequence to furnish a 9:1 separable mixture of the desired alcohol **8** and its diastereomeric alcohol in 87% combined yield. Conversion of **8** into iodide **9** ($[\alpha]_D^{26}=+36.3$, $c=1.00$, $CHCl_3$) was carried out in 86% overall yield via a sequence of basic hydrolysis, protection as acetonide, debenzylation by dissolving metal reduction and iodination using iodine in the presence of Ph_3P and imidazole.[8] Acidic hydrolysis of **9** yielded labile diol, which was disilylated consecutively with TBDPSCl and TESOTf, and then reacted with Ph_3P to render phosphonium salt **10** in 83% overall yield. To prepare the coupling partner of **10** as aldehyde, **8** was oxidized under Swern conditions,[9] reacted with vinyl Grignard reagent and then hydrolyzed to give the craved allylic alcohol **12** ($[\alpha]_D^{27}=+19.8$, $c=1.16$, $CHCl_3$) in 53% overall yield along with 17% of the diastereomeric alcohol **11**. Subjection of alcohol **11** to Mitsunobu inversion[10] and basic hydrolysis produced a 3.3:1 mixture of **12** and the rearranged primary allylic

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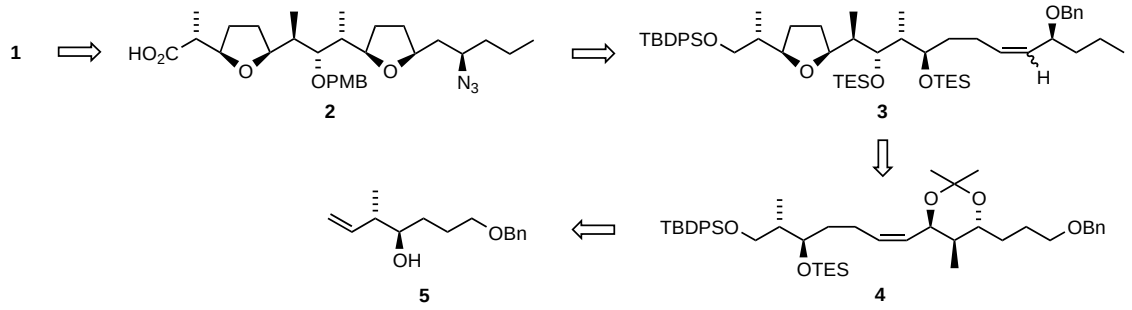
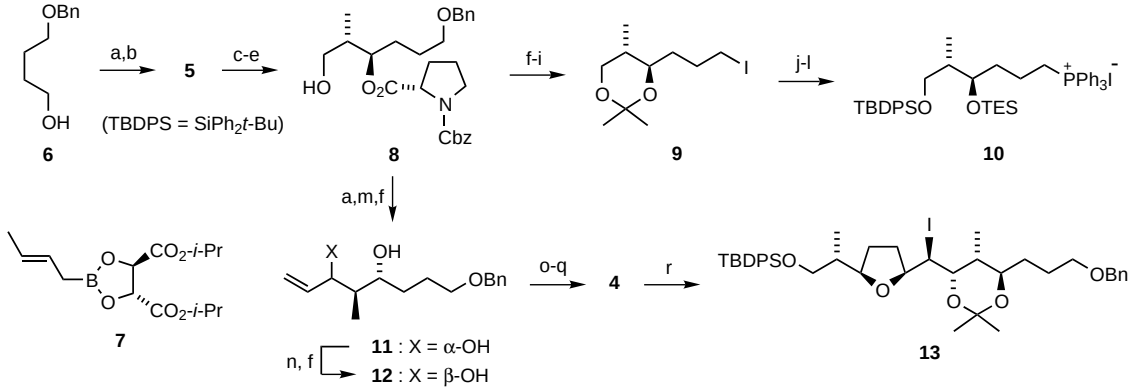


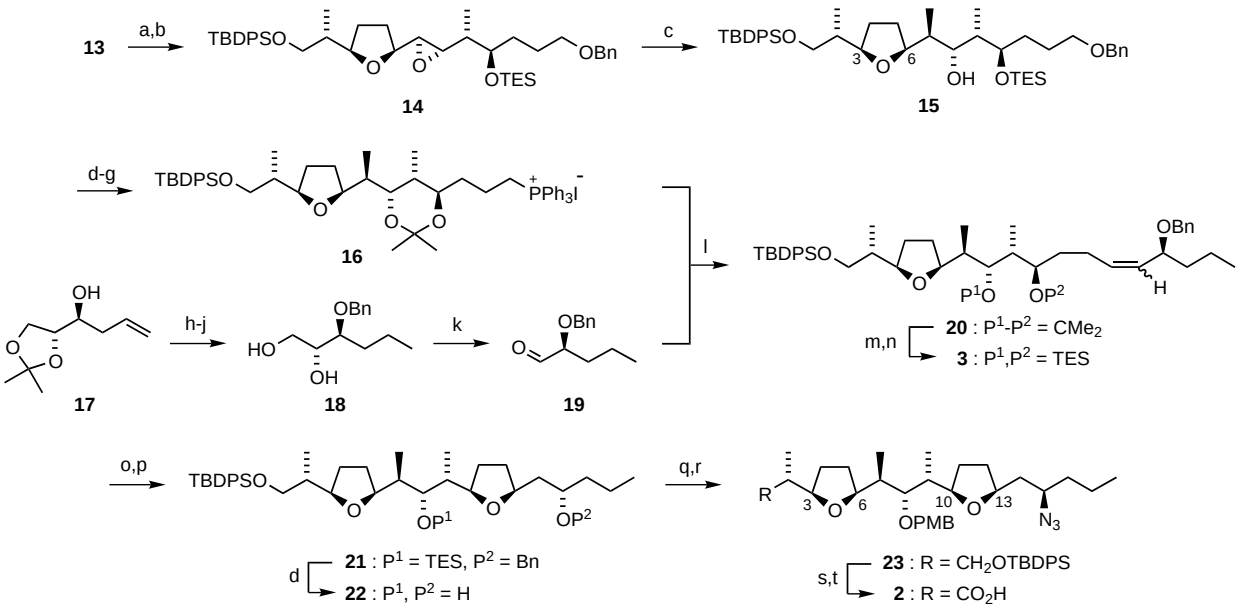
Scheme 1. Retrosynthetic analysis.



Scheme 2. (a) Swern oxidation; (b) **7**, 4 Å MS, PhMe, −78°C, then 2N NaOH, 0°C; (c) *N*-Cbz-L-proline, DCC, DMAP, CH_2Cl_2, rt; (d) OsO_4, NMO, aq. acetone, rt; (e) $NaIO_4$, aq. THF, rt, then $NaBH_4$, 0°C; (f) LiOH, aq. MeOH, rt; (g) PPTS, $Me_2C(OMe)_2$, PhMe, reflux; (h) Li, NH_3(l), THF, −78°C; (i) I_2, Ph_3P, imidazole, THF, 0°C; (j) conc. HCl, MeOH, 0°C; (k) TBDPSCl, DMAP, Et_3N, CH_2Cl_2, −15°C, then TESOTf, −15°C; (l) Ph_3P, K_2CO_3, MeCN, reflux; (m) CH_2=$CHMgBr$, Et_2O, −78°C; (n) $PhCO_2H$, Ph_3P, DEAD, THF, −20°C; (o) PPTS, $Me_2C(OMe)_2$, acetone, rt; (p) O_3, $NaHCO_3$, CH_2Cl_2, MeOH, −78°C, then Me_2S, rt; (q) **10**, *t*-BuLi, THF, −78 to −5°C, then aldehyde, 10°C; (r) I_2, Ag_2CO_3, Et_2O, rt.

alcohol in 84% combined yield. The aldehyde derived from **12** via acetonide protection and ozonolysis reacted with the ylid generated from **10** with *t*-BuLi to provide only *cis*-alkene **4** ($[\alpha]_D^{25}=-7.9$, $c=1.03$, $CHCl_3$) in 85% overall yield. With γ-triethylsilyloxyalkene **4** precursory to *cis*-2,5-disubstituted tetrahydrofuran in hand, extensive iodocyclization conditions were examined. Consequently, treatment of **4** with iodine in the presence of Ag_2CO_3 resulted in a remarkable stereoselectivity to give rise to *cis*-tetrahydrofuran **13** ($[\alpha]_D^{26}=-17.9$, $c=1.06$, $CHCl_3$) as a single stereoisomer in 94% yield,[11] the stereochemistry of which was corroborated by the NOE experiments of **15** (vide infra).

Since the left tetrahydrofuran of **2** was secured efficiently, it was necessary to introduce the second right ring. Conversion of **13** into epoxide **14** ($[\alpha]_D^{26}=-11.5$, $c=1.00$, $CHCl_3$) was accomplished in 87% overall yield by acidic deprotection, cyclization and silylation in sequence (Scheme 3). Cuprate reaction of **14** with lithium dimethylcuprate afforded the desired alcohol **15** ($[\alpha]_D^{26}=-6.8$, $c=1.13$, $CHCl_3$) in 78% yield along with 15% of its regioisomer. While the molecular arrangement of **15** was ascertained by its COSY spectrum, the NOE experiments between H-3 and H-6 (3% enhancement) evidenced the *cis* relationship of the tetrahydrofuranyl ring. When the secondary hydroxyl group of **14** was unprotected, the epoxide opening reaction yielded the wrong regioisomer as the major. Hydrogenolysis of **15** was implemented in 96% yield to unmask benzyl and triethylsilyl groups concurrently. The resulting triol was protected as 1,3-dioxane and subsequently transformed into phosphonium salt via iodide to furnish **16** in 90% overall yield. The aldehyde **19** required for the Wittig olefination with **16** was obtained from the known homoallylic alcohol **17**.[12] Hydrogenation of **17** followed by benzylation and acidic hydrolysis generated diol **18** ($[\alpha]_D^{25}=+14.6$, $c=1.37$, $CHCl_3$) in 70% overall yield. After oxidative cleavage of **18**, the produced aldehyde **19** was olefinated with the ylid derived from **16** to give a 10:1 mixture of *cis*- and *trans*-alkenes **20** in 88% combined yield. Acidic hydrolysis and the following silylation furnished γ-triethylsilyloxyalkenes **3** in 89% overall yield. Formation of the second *cis*-2,5-disubstituted tetrahydrofuran from **3** proceeded uneventfully under the cyclization conditions established in that of **4** and the ensuing reductive deiodination[13] of the iodo products rendered *cis*-tetrahydrofuran **21** ($[\alpha]_D^{24}=+10.7$, $c=1.50$, $CHCl_3$) as the only stereoisomer in 77% overall yield. Coincident deprotection of benzyl and triethylsilyl groups of **21** by hydrogenolysis provided diol **22** ($[\alpha]_D^{25}=-20.9$, $c=1.98$, $CHCl_3$) in 95% yield. The sterically less hindered hydroxyl group of **22** was chemoselectively con-



Scheme 3. (a) PPTS, MeOH, THF, rt, then K_2CO_3, rt; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, −78°C; (c) Me_2CuLi, Et_2O, 10°C; (d) H_2, $Pd(OH)_2/C$, EtOH, rt; (e) PPTS, acetone, rt; (f) I_2, Ph_3P, imidazole, THF, 0°C; (g) Ph_3P, K_2CO_3, MeCN, reflux; (h) H_2, 10% Pd/C, MeOH, rt; (i) NaH, BnBr, *n*-Bu_4NI, THF, 0°C; (j) 1N HCl, MeOH, rt; (k) $NaIO_4$, acetone, H_2O, 0°C; (l) *n*-BuLi, THF, −78 to −5°C, then **19**, 10°C; (m) PPTS, MeOH, THF, rt; (n) TESOTf, 2,6-lutidine, CH_2Cl_2, rt; (o) I_2, Ag_2CO_3, Et_2O, rt; (p) Ph_3SnH, Et_3B, THF, 0°C; (q) HN_3, Ph_3P, DEAD, PhH, 0°C; (r) PMBCl, *n*-Bu_4NI, DMF, 0°C, then KHMDS, 0°C; (s) *n*-Bu_4NF, THF; (t) Jones oxidation, 0°C.

verted into azido group under Mitsunobu conditions,[14] and the remaining one was protected as *p*-methoxybenzyl ether to give rise to azide **23** ($[\alpha]_D^{26} = -6.0$, $c = 1.38$, $CHCl_3$) in 86% overall yield, the stereochemistry of which was determined by the NOE experiments between H-3 and H-6 (3% enhancement), and between H-10 and H-13 (3% enhancement). Successive desilylation and Jones oxidation of **23** afforded the C1–C18 subunit **2** ($[\alpha]_D^{25} = +11.1$, $c = 1.40$, $CHCl_3$) in 85% overall yield.[11]

In summary, we have established a stereocontrolled synthesis of the upper subunit **2** for a total synthesis of pamamycin-607 using the developed stereoselective intramolecular iodoetherification in the presence of Ag_2CO_3, which is expected to be of general utility.

Acknowledgements

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11. The selected spectroscopic data are reported below. **13**: ^{1}H NMR (400 MHz, C_6D_6) δ 7.82–7.79 (4H, m), 7.33–7.07 (11H, m), 4.35 (2H, dd, $J=15.9$, 13.0 Hz), 4.33 (1H, dd, $J=11.2$, 4.2 Hz), 4.00 (1H, dd, $J=9.7$, 4.0 Hz), 3.82 (1H, dd, $J=11.2$, 1.5 Hz), 3.74 (1H, dd, $J=9.7$, 7.0 Hz), 3.63–3.54 (2H, m), 3.40–3.30 (2H, m), 3.23 (1H, dt, $J=7.4$, 4.2 Hz), 2.13–2.00 (2H, m), 1.93–1.84 (1H, m), 1.73–1.45 (7H, m), 1.29 (3H, s), 1.26 (3H, s), 1.19 (9H, s), 1.02 (3H, d, $J=6.8$ Hz), 0.85 (3H, d, $J=6.7$ Hz); ^{13}C NMR (100 MHz, C_6D_6) δ 139.5, 136.1, 134.5, 134.4, 129.9 (two peaks), 128.5, 128.1, 127.6, 101.6, 81.2, 75.5 (two peaks), 73.0, 70.4, 70.3, 67.1, 43.0, 41.2, 40.7, 32.3, 31.7, 29.2, 27.2, 26.9, 25.0, 23.8, 19.6, 14.1, 10.8; IR (neat) 1225, 1173, 1112, 1065, 1027 cm^{-1}; HRMS (EI) calcd for $C_{41}H_{57}IO_5Si$: 784.3020, found: 784.3062. **2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (2H, d, $J=8.6$ Hz), 6.84 (2H, d, $J=8.6$ Hz), 4.55 (2H, dd, $J=36.4$, 11.1 Hz), 4.19 (1H, td, $J=7.5$, 2.9 Hz), 3.92–3.82 (2H, m), 3.77 (3H, s), 3.77–3.68 (2H, m), 3.43–3.36 (1H, m), 2.54 (1H, p, $J=7.3$ Hz), 2.03–1.80 (5H, m), 1.75–1.30 (11H, m), 1.16 (3H, d, $J=7.1$ Hz), 0.91 (3H, t, $J=7.2$ Hz), 0.81 (3H, d, $J=6.9$ Hz), 0.80 (3H, d, $J=6.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 158.9, 131.7, 129.1, 113.6, 81.0, 80.3, 79.7, 79.5, 75.7, 74.0, 60.4, 55.2, 44.1, 41.3, 40.4, 39.2, 36.2, 31.3, 29.9, 29.7, 28.4, 19.2, 13.8, 13.0, 10.3, 9.5; IR (neat) 2101, 1712, 1248, 1062, 1039, 962 cm^{-1}; HRMS (EI) calcd for $C_{29}H_{45}N_3O_6$: 531.3308, found: 531.3312.
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