Pergamon

Tetrahedron Letters 42 (2001) 7801–7804

TETRAHEDRON LETTERS

Total synthesis of pamamycin-607†

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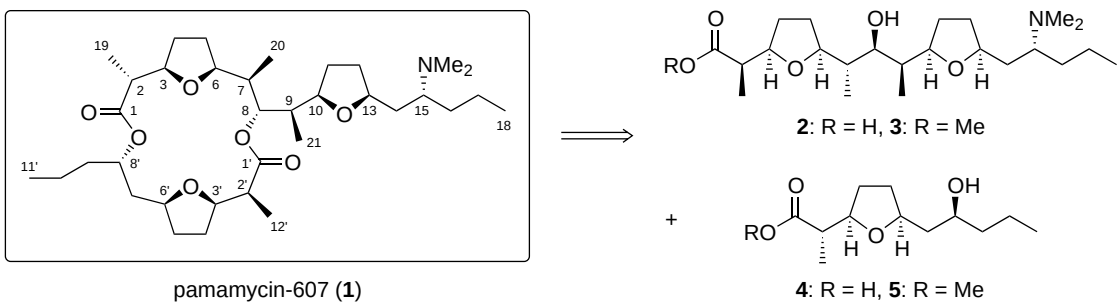
Received 23 July 2001; revised 3 September 2001; accepted 4 September 2001

Abstract—The macrodiolide antibiotic pamamycin-607 has been synthesized by coupling of the two hydroxy acid constituents using the Yamaguchi method. While the final lactonization with formation of the ester linkage between C(1) and the C(8′) oxygen proceeded with complete C(2) epimerization, the alternative ring closure involving the carboxylic acid of the smaller fragment and the hydroxyl group of the larger fragment yielded the target molecule.

The macrodiolide pamamycin-607 (**1**) isolated from various *Streptomyces* species displays pronounced antibiotic, autoregulatory, anionophoric and antifungal activities (Scheme 1).[1,2] Through the extensive application of sultone methodology,[3] we have been able to develop straightforward routes to the methyl ester **3** of the larger C(1)-C(18) fragment **2**, as well as to the methyl ester **5** of the smaller C(1′)-C(11′) fragment **4**.[4] Here we report the completion of the total synthesis[5,6] of **1** by coupling of the two hydroxy acid building blocks.

Concerned by reports on the sluggish acylation of the secondary alcohol present in the larger hydroxy acid **2**,[1c,7] we decided to execute the final macrolactonization with formation of the ester linkage between C(1) and the C(8′) oxygen. Next to avoiding potential reactivity problems during this critical intramolecular step, this end game strategy also offered the option to directly use methyl ester **3**[4b] for the intermolecular coupling process, while the smaller fragment methyl ester **5**[4a,d] had to be modified accordingly.

To this end, hydroxy ester **5** was first silylated, and the resulting silyl ether **6** was saponified to give the carboxylic acid **7** without any detectable epimerization (Scheme 2). A subsequent intermolecular Yamaguchi esterification[8] of **7** (1.65 equiv.) with **3** afforded the desired coupling product **8** in nearly quantitative yield when the acylation step was performed at 0.05 M concentration of **3** in toluene. The high efficacy of this fragment coupling shows that the Yamaguchi protocol works well even with a rather hindered secondary alcohol. Desilylation of **8** proceeded smoothly to yield the known hydroxy ester **9**.[1c] However, whereas hydrolysis of the methyl ester function in **9** succeeded with complete chemoselectivity leaving the internal ester unaffected, epimerization to give a 2:1 mixture of two



Scheme 1.

Keywords: antibiotics; epimerisation; macrodiolide; Yamaguchi lactonisation.

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† Dedicated to Professor Jürgen Fabian on the occasion of his 65th birthday.

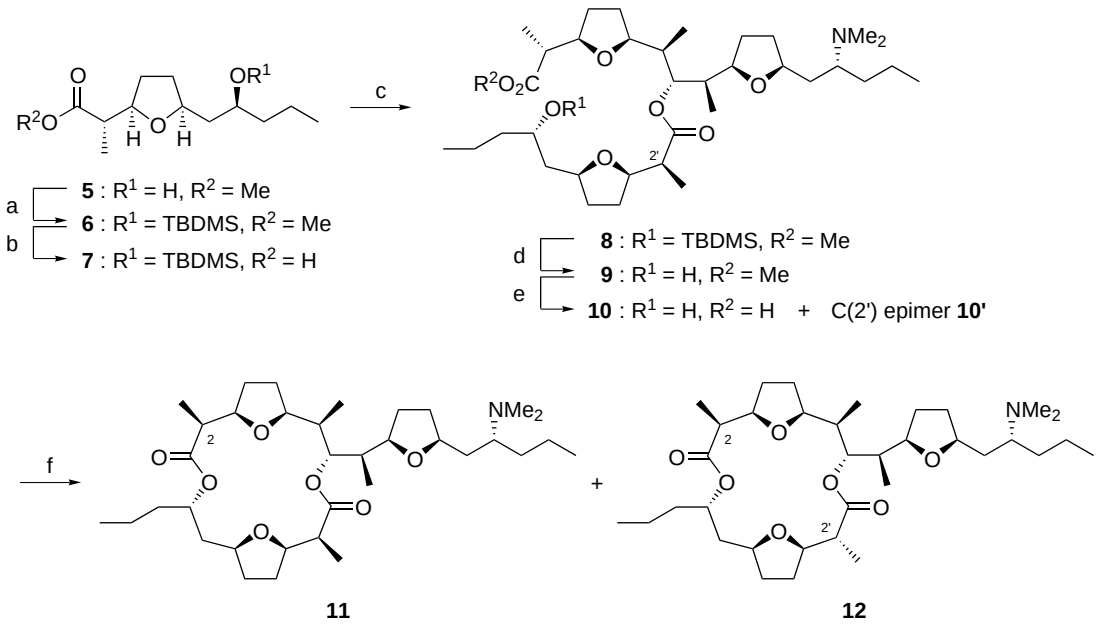
PII: S0040-4039(01)01665-3

hydroxy acids **10** and **10′** could not be avoided despite extensive variation of the reaction conditions. Reductive cleavage of this mixture with lithium aluminum hydride indicated that partial epimerization occurred at C(2′), while the configuration at C(2) was maintained.[9] All the more surprising was the result of the Yamaguchi macrolactonization[8,10] of the 2:1 *seco* acid mixture. To our disappointment, only 2-*epi*-pamamycin-607 (**11**)[11] and 2,2′-bis*epi*-pamamycin-607 (**12**)[12] were isolated in 28 and 17% yields, respectively, after mixed anhydride activation of the acid function and reflux in toluene under high dilution in the presence of DMAP. Attempted cyclization using modified Yamaguchi conditions at room temperature[13] did not afford **1** either.

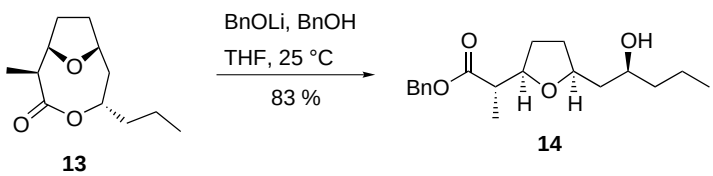
Thus, quite similarly to the recently communicated extensive epimerization during the Yamaguchi cyclization of a hydroxy acid precursor of **3** to give medium-ring lactone **13**,[4a] an inversion of configuration at C(2) is observed, and it is even complete in the case of the substrates **10** and **10′**. Again, either equilibration at the stage of the mixed anhydride coupled with a faster cyclization of the (2*S*) compound or formation of a ketene intermediate coupled with a stereoselective protonation of the enol or enolate resulting from a hydroxy ketene cyclization[14] could account for this unexpected result.

Encouraged by the efficient intermolecular Yamaguchi esterification of **3** to give **8**, we next focussed on the alternative sequence of events for fragment coupling involving lactonization with formation of the ester linkage between C(1′) and the C(8) oxygen. In order to prevent potential problems with methyl ester cleavage, we chose benzyl ester **14** instead of **5** as the smaller fragment surrogate. Upon treatment of lactone **13**, which is available in only two steps from an intermediate for the synthesis of **3**,[4a] with the lithium alkoxide of benzyl alcohol,[13a] coupling component **14** was readily obtained (Scheme 3).

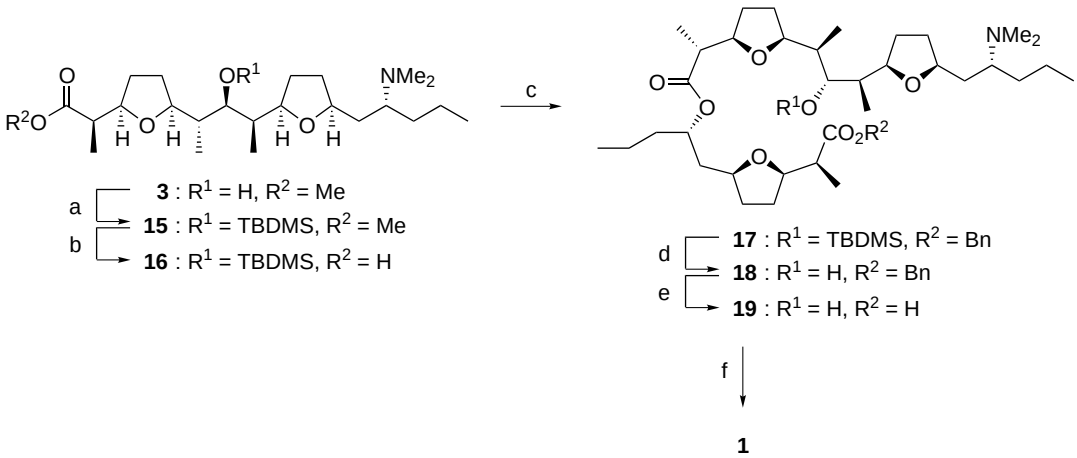
Silylation of methyl ester **3** followed by mild saponification of the silyloxy ester **15** yielded the larger fragment coupling component **16** as a single stereoisomer (Scheme 4). Subsequent intermolecular Yamaguchi esterification of **16** with **14** (1.1 equiv.) then provided the coupling product **17** in high yield. Desilylation of **17** using aqueous HF and reductive debenzylation of the resultant benzyl ester **18** proceeded uneventfully to give the desired *seco* acid **19**. To our delight, the final Yamaguchi macrolactonization of **19** performed at reflux in toluene under high dilution in the presence of DMAP afforded pamamycin-607 (**1**)[1h,i,15] as the major product in 42% yield. Most gratifyingly, modified Yamaguchi cyclization at 6.4×10^{-3} M concentration of



Scheme 2. (a) TBDMSCl, imidazole, DMAP, DMF, 25°C, 100%; (b) 1N KOH, MeOH, THF, 25°C, 99%; (c) (i) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 25°C, (ii) **3**, DMAP, toluene, 25°C, 98%; (d) aq. HF, MeCN, 25°C, 92%; (e) 0.2N LiOH, THF, MeOH, 25°C, 100%; (f) (i) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 25°C, (ii) DMAP, toluene, reflux, 28% **11**, 17% **12**



Scheme 3.



Scheme 4. (a) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 25°C, 90%; (b) 0.2N LiOH, THF, MeOH, 25°C, 81%; (c) (i) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 25°C, (ii) **14**, DMAP, toluene, 25°C, 88%; (d) aq. HF, MeCN, 25°C, 95%; (e) H_2, 10% Pd/C, THF, MeOH, 25°C, 98%; (f) 2,4,6-trichlorobenzoyl chloride, DMAP, 4 Å sieves, CH_2Cl_2, 25°C, 69%

19 at room temperature in dichloromethane[13a] even improved the yield of **1** to 69%.

In summary, starting from furan, racemic 1,2-epoxypentane and vinylsulfonyl chloride,[4] an enantioselective synthesis of pamamycin-607 (**1**) has been accomplished in only 28 steps and thus, our route to **1** compares favorably to the recently disclosed[5] alternative access to **1**.

Acknowledgements

Financial support of this work by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged. We thank the BASF AG and the ASTA Medica AG for generous gifts of chemicals, Professor U. Gräfe, Hans-Knöll-Institut für Naturstoff-Forschung, Jena, for a sample of a ca. 2:1 mixture of natural pamamycin-621A and pamamycin-607 and Professor M. Natsume, Tokyo University of Agriculture and Technology, for ^1H NMR and mass spectra of compounds **1**, **3** and **9**.

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9. After reduction of an analytical sample of the mixture of hydroxy acids **10** and **10′** with lithium aluminum hydride to give the corresponding diols and subsequent silylation using excess MSTFA, capillary GC analysis showed a single peak for the larger diol derivative, whereas two peaks (ca. 2:1) were found for the smaller diol derivative.
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11. Compound **11**: $[\alpha]_D^{25}=+11.4$ (*c* 0.95, CH_2Cl_2); ^{13}C NMR (125.8 MHz, acetone-d_6, excess CF_3CO_2D): δ 8.00 (q, C-19), 8.82 (q, C-12′), 9.63 (q, C-21), 10.16 (q, C-20), 13.98 (q, C-18), 14.26 (q, C-11′), 18.98 (t, C-10′), 20.34 (t, C-17), 27.78 (t, C-4′), 28.02 (t, C-5), 28.71 (t, C-4), 29.06 (t, C-16), 30.02 (t, C-11), 31.62 (t, C-12), 32.24 (t, C-5′), 34.38 (t, C-14), 36.58 (q, NCH_3), 36.93 (d, C-7), 38.07 (t, C-9′), 39.77 (t, C-7′), 41.36 (d, C-9), 42.02 (d, C-2), 42.20 (d, C-2′), 43.76 (q, NCH_3), 68.63 (d, C-15), 71.99 (d, C-8′), 75.26 (d, C-6′), 75.43 (d, C-8), 77.11 (d, C-6), 79.29 (d, C-3′), 79.98 (d, C-13), 80.23 (d, C-3), 81.04 (d, C-10), 174.67 (s, C-1), 174.90 (s, C-1′); NOESY (500 MHz, acetone-d_6, excess CF_3CO_2D) diagnostic NOE's observed between 2-H and 3-H, 2′-H and 3′-H, 19-H and 20-H. ^1H and ^{13}C signals were assigned by 2D NMR (COSY, HSQC, HMBC) spectra.
12. Compound **12**: $[\alpha]_D^{25}=+8.3$ (*c* 0.40, CH_2Cl_2); ^{13}C NMR (125.8 MHz, acetone-d_6, excess CF_3CO_2D): δ 7.91 (q, C-19), 9.61 (q, C-21), 9.98 (q, C-20), 13.98 (q, C-12′), 13.98 (q, C-18), 14.32 (q, C-11′), 18.92 (t, C-10′), 20.34 (t, C-17), 27.77 (t, C-5), 28.42 (t, C-4), 28.99 (t, C-16), 30.05 (t, C-11), 30.77 (t, C-4′), 31.57 (t, C-12), 31.62 (t, C-5′), 34.41 (t, C-14), 36.60 (q, NCH_3), 36.79 (d, C-7), 37.82 (t, C-9′), 40.88 (t, C-7′), 41.50 (d, C-9), 41.74 (d, C-2), 43.71 (q, NCH_3), 49.05 (d, C-2′), 68.60 (d, C-15), 72.30 (d, C-8′), 74.79 (d, C-8), 75.16 (d, C-6′), 76.56 (d, C-6), 80.06 (d, C-13), 80.22 (d, C-3), 81.06 (d, C-10), 82.34 (d, C-3′), 173.54 (s, C-1′), 174.88 (s, C-1); NOESY (500 MHz, acetone-d_6, excess CF_3CO_2D) diagnostic NOE's observed between 2-H and 3-H, 12′-H and 3′-H, 19-H and 20-H, 12′-H and 21-H. ^1H and ^{13}C signals were assigned by 2D NMR (COSY, HSQC, HMBC) spectra.
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14. Molecular modeling studies with MM2 (CS Chem3D Pro, version 5.0; CambridgeSoft Corporation, Cambridge, MA, USA) of the C(2) enol of **11** indeed suggest preferential protonation to give epimer **11**.
15. Pamamycin-607 (**1**): $[\alpha]_D^{25}=+17.8$ (*c* 0.60, CH_2Cl_2), $[\alpha]_D^{30}=+22.2$ (*c* 0.25, MeOH) (Ref. 1i: $[\alpha]_D^{33}=+22.8$ (*c* 0.26, MeOH)); ^{13}C NMR (125.8 MHz, acetone-d_6, excess CF_3CO_2D): δ 8.66 (q, C-12′), 9.76 (q, C-21), 10.36 (q, C-20), 13.96 (q, C-18), 14.04 (q, C-19), 14.32 (q, C-11′), 18.76 (t, C-10′), 20.31 (t, C-17), 27.92 (t, C-4′), 28.06 (t, C-5), 28.97 (t, C-16), 30.02 (t, C-11), 31.13 (t, C-4), 31.54 (t, C-12), 32.11 (t, C-5′), 34.23 (t, C-14), 36.47 (q, NCH_3), 37.82 (t, C-9′), 37.85 (d, C-7), 39.41 (t, C-7′), 41.50 (d, C-9), 42.08 (d, C-2′), 43.71 (q, NCH_3), 47.87 (d, C-2), 68.68 (d, C-15), 71.48 (d, C-8′), 75.17 (d, C-6′), 75.22 (d, C-8), 77.27 (d, C-6), 79.20 (d, C-3′), 79.96 (d, C-13), 81.05 (d, C-10), 83.16 (d, C-3), 173.70 (s, C-1), 174.95 (s, C-1′); NOESY (500 MHz, acetone-d_6, excess CF_3CO_2D) diagnostic NOE's observed between 19-H and 3-H, 2′-H and 3′-H. ^1H and ^{13}C signals were assigned by 2D NMR (COSY, HSQC, HMBC) spectra and match exactly those of the natural product **1** separated on an analytical scale by HPLC from a ca. 1:2 mixture of natural pamamycin-607 (**1**) and pamamycin-621A[1e,2] kindly provided by Professor U. Gräfe, Hans-Knöll-Institut für Naturstoff-Forschung, Jena.