Natural Product Synthesis

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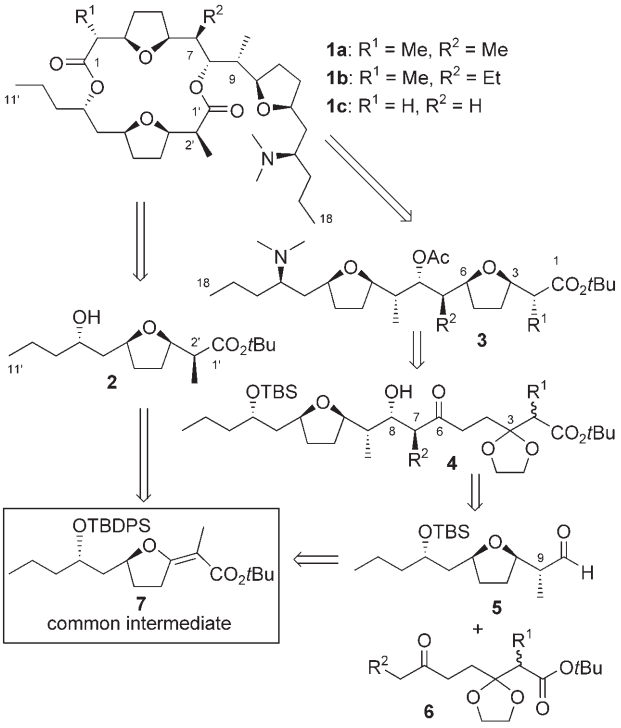
A Convergent Strategy for the Pamamycin Macrodiolides: Total Synthesis of Pamamycin-607, Pamamycin-593, and Pamamycin-621D Precursors**

*Steve Lanners, Hassan Norouzi-Arasi, Xavier J. Salom-Roig, and Gilles Hanquet**

Dedicated to Professor Guy Solladié

The pamamycins are a family of naturally occurring homologous macrodiolides and are isolated from various *Streptomyces* species.[1,2] Besides displaying autoregulatory, anionophoric, and antifungal activities, several members of this family have been shown to be highly active against Gram-positive bacteria including multiple antibiotic-resistant strains of *Mycobacterium tuberculosis*.[3] Owing to their complex structure, the pamamycins are attractive synthetic targets. Several total syntheses of the most prominent member, pamamycin-607 (**1a**, Scheme 1), have been reported,[4] and synthetic studies towards the pamamycins have been reviewed recently.[5] On the other hand, the promising biological properties of the pamamycins call for the development of general routes to these molecules to establish structure–activity relationships, improve the pharmacological properties, and probe their mode of action. Metz and coworkers described the synthesis of pamamycin-621A and pamamycin-635B by means of their sultone-based strategy.[6] Herein we describe the asymmetric total synthesis of pamamycin-607 (**1a**) from enantiomerically pure (*S*)-*p*-tolyl methyl sulfoxide as the only chiral starting material and illustrate the potential of our strategy for an analogous synthesis of pamamycin-621D (**1b**) and pamamycin-593 (**1c**) by the preparation of advanced precursors.

In a retrosynthetic sense, our approach is based on the disconnection of the two lactone linkages to afford the C1′–C11′ fragment **2** and the C1–C18 fragment **3** (Scheme 1). In the latter, the tetrahydrofuran ring and dimethylamino group can be further simplified to obtain **4**. An aldol disconnection of the C7-C8 bond leads to the precursors **5** and **6**. Although the convergence of our strategy is based on the assembly of three fragments (**2**, **5**, and **6**) of similar molecular weight, the observation that **2** and **5** only differ by the configuration α to the tetrahydrofuran ring allows a further simplification to a common intermediate **7**.



Scheme 1. Retrosynthetic analysis of Pamamycin-607. TBS = *tert*-butyldimethylsilyl.

We have previously reported the diastereodivergent synthesis of fragments **2** and **5** from (*S*)-*p*-tolyl methyl sulfoxide[7] by a diastereoselective reduction[8] of a suitably protected β,δ-diketosulfoxide.[9] We have also developed efficient conditions for the *E*–*Z* isomerization of the double bond of intermediate **7**[10] that enables us to access both **2** and **5** by diastereoselective hydrogenation of either of the double bond isomers.

Although one possible approach to ketones **6** relied on the ring opening of γ-caprolactone,[11] the most reliable and scalable route proved to be a five-step procedure starting from commercially available 4-pentenoic acid that afforded ketones **6a** and **6b** (Scheme 2) in 45 to 50% overall yield.[12] Ketone **6c** was obtained by Wacker oxidation of an intermediate of this sequence.[13,14]

[*] Dr. S. Lanners, Dr. H. Norouzi-Arasi, Dr. G. Hanquet
Laboratoire de Stéréochimie associé au CNRS
ECPM, Université Louis Pasteur
25, rue Becquerel, 67087 Strasbourg (France)
Fax: (+33) 3-9022-42742
E-mail: ghanquet@chimie.u-strasbg.fr
Dr. X. J. Salom-Roig
Institut de Biomolécules Max Mousseron (IBMM)
UMR 5247, Synthèses Stéréosélectives
Université Montpellier II
Place Eugène Bataillon, Montpellier (France)

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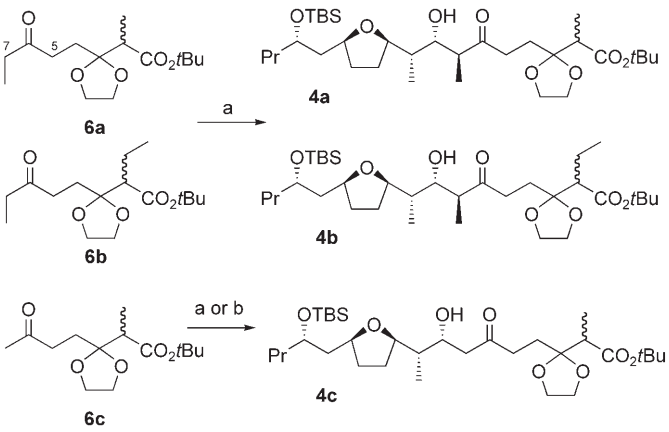
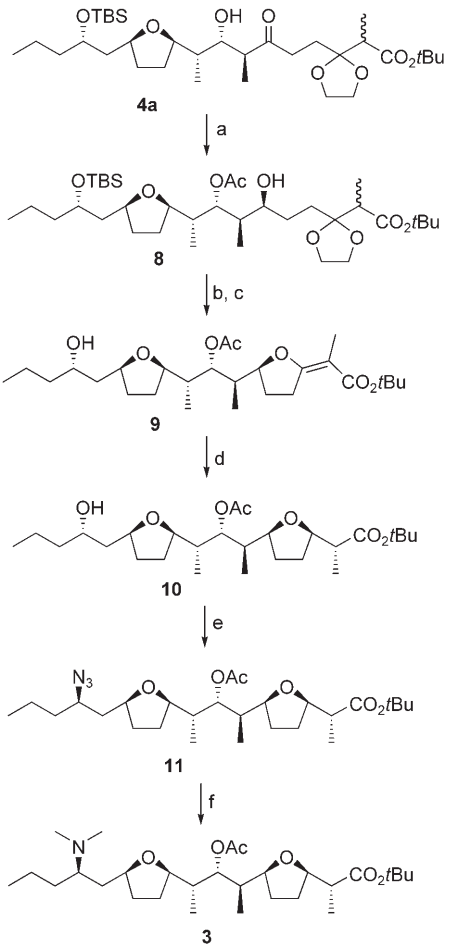


Scheme 2. Reagents and conditions: a) Chx_2BCl, Et_3N, Et_2O, 0 °C, then **5**, −78 → −23 °C, (**4a**, 52%; **4b**, 61%; **4c**, 48%); b) LiHMDS, THF, −78 °C, 63%. Chx = cyclohexyl, LiHMDS = lithium hexamethyldisilazanide, Pr = propyl.



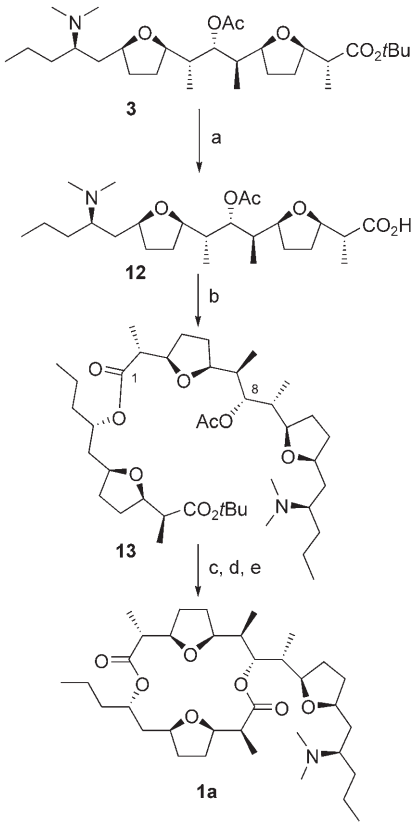
Scheme 3. Reagents and conditions: a) SmI_2 cat., MeCHO, THF, −10 °C, 59%; b) oxalic acid, CH_2Cl_2, H_2O; c) TBAF, THF, RT, 78% over two steps; d) H_2, 4 bar, Rh/Al_2O_3, MeOH, RT, 90%; e) HN_3, PPh_3, DIAD, toluene, RT, 72%; f) H_2, Pd/C, HCHO, AcOH, MeOH, RT, 85%. TBAF = tetrabutylammonium fluoride, DIAD = diisopropyl azodicarboxylate.

With precursors **2**, **5**, and **6** in hands, we examined the planned aldol coupling between aldehyde **5** and ketone **6a**. To obtain the desired 2,3-*anti*-3,4-*syn* relationship between the newly formed stereogenic centres in aldol adduct **4a**, we decided to use the Chx_2BCl/Et_3N system[15] to prepare the *E* enolate of **6a** selectively. We anticipated that enolization of **6a** might give rise to regioselectivity issues through competitive deprotonation at C5 and C7. Indeed, when the reaction is conducted in pentane as the solvent, **4a** is isolated as the minor product in a 1:4 ratio with respect to the aldol products derived from internal enolization. Fortunately, switching the solvent to diethyl ether inverted the regioselectivity. Aldol adduct **4a** could be isolated in good yields along with regioisomeric products (3:1 ratio with respect to all undesired products; Scheme 2). A detailed examination of the factors governing this unusual solvent effect will be published elsewhere.[12]

Similarly, the aldol coupling with ketone **6b** delivered the desired adduct **4b** in good yield. On the other hand, for methylketone **6c**, the same reaction conditions led to complete regioselectivity but with an important decrease in the diastereoselectivity (*syn*/*anti* = 6:4). Fortunately, diastereoselectivity was increased without affecting regioselectivity by using the lithium enolate,[16] and **4c** was isolated in 63% yield. Although **4a** was subsequently used to complete the total synthesis of pamamycin-607 (**1a**), the preparation of aldol adducts **4b** and **4c**—precursors of pamamycin-621D (**1b**) and pamamycin-593 (**1c**), respectively—illustrates the flexibility of our synthetic approach as far as the incorporation of different alkyl substituents (R^1, R^2) is concerned.

The subsequent elaboration of the C1–C18 fragment **3** required the 1,3-*anti* selective reduction of the ketone group of **4a** with concomitant differentiation of the two secondary hydroxy groups, a transformation that was achieved by using the samarium(II) iodide catalyzed Evans–Tishchenko conditions.[17] The use of acetaldehyde as a reducing agent converted **4a** into hydroxyacetate **8** (Scheme 3). Acid-catalyzed dioxolane deprotection and cyclization followed by TBS deprotection afforded the unsaturated intermediate **9**. A diastereoselective hydrogenation under Bartlett conditions[18] afforded intermediate **10**. The requisite configuration of the amine function was obtained by Mitsunobu inversion of the secondary alcohol by using hydrazoic acid, and the resulting azide **11** was reduced to the primary amine and methylated by Pd/C catalyzed hydrogenation in the presence of formaldehyde, thus completing the synthesis of the C1–C18 fragment **3**.

The final sequence of steps followed the order of esterifications established Metz and co-workers to avoid epimerization at C2.[4a] Deprotection of *tert*-butyl ester **3** by using trifluoroacetic acid (TFA) in dichloromethane and a first esterification between the resulting acid **12** and the small fragment **2** under Yamaguchi conditions[19] led to the seco ester **13** in good yield (Scheme 4). Unfortunately, attempted deprotection of the acetate group under a wide variety of conditions (KCN, MeOH; 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), toluene; LiOH, THF/water



Scheme 4. Reagents and conditions: a) TFA, CH_2Cl_2, RT, 88%; b) 2,4,6-Cl_3PhCOCl, Et_3N, THF, then **3**, DMAP, toluene, 74%; c) lipase type VII, DMF, H_2O; d) $MgBr_2$, CH_2Cl_2, 84% over two steps; e) 2,4,6-Cl_3PhCOCl, DMAP, CH_2Cl_2, 62%. DMAP = 4-(*N*,*N*-dimethylamino)-pyridine, DMF = *N*,*N*-dimethylformamide.

(2:1); 0.5 M NH_2NH_2, pyridine/AcOH (4:1); guanidine)[20] resulted either in the decomposition of the substrate, C1 ester cleavage, or intramolecular *trans* esterification between the resulting free alcohol at C8 and the C1 ester. The conditions of NH_3/MeOH/water afforded the desired product in only 27% yield. Reductive deacetylation by using diisobutylaluminum hydride (DIBAL-H) in toluene at −78°C improved the yield to 60%. Finally, the use of the enzymatic method described by Holmes and co-workers[21] followed by *tert*-butyl ester removal with $MgBr_2$ in dichloromethane delivered the isolated seco acid in 84% yield. The synthesis was completed in 62% yield by using a modified Yamaguchi macrolactonization under the conditions reported by Fleming and Ghosh.[22,23]

In summary, a short and highly stereoselective access to the larger fragment precursors **4a**, **4b**, and **4c** of pamamycins-607 (**1a**), -621D (**1b**), and-593 (**1c**) has been developed by means of an unprecedented solvent-modulated regio- and diastereoselective aldol reaction and application of β-keto-sulfoxide methodology (all 13 stereogenic centers of **1a** are derived from (*S*)-*p*-tolyl methyl sulfoxide). Starting from intermediate **4a**, a total synthesis of pamamycin-607 (**1a**) has been accomplished in only 11 steps. Thus, our route for the formation of **1a** compares favorably with the recently disclosed alternatives. The synthesis can be further shortened by the described replacement of **2** by **5** as the small fragment precursor.[24] The high convergence and flexibility of our strategy makes it suitable for the production of analogues. Herein we have shown how the incorporation of an alternative substituent at C2 and C7 (Scheme 1, R^1 and R^2) can be achieved. Similarly, a late-stage modification in the synthesis of **2** and **5**[7] should be a viable route for the introduction of alternative substituents at C9 and C2′. These modifications are complementary to those recently reported by Metz and co-workers,[6] and thus our efforts complete the available tools required for the preparation of the structurally and biologically intriguing pamamycin macrodiolides. The total synthesis of pamamycin-621D (**1b**) and -593 (**1c**) starting from precursors **4b** and **4c**, respectively, are in progress in our group.

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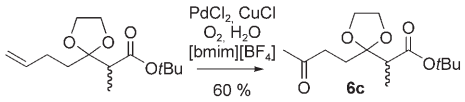

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