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Stereoselective synthesis towards the C8–C18 subunit of pamamycin-607 induced by a chiral sulfoxide group

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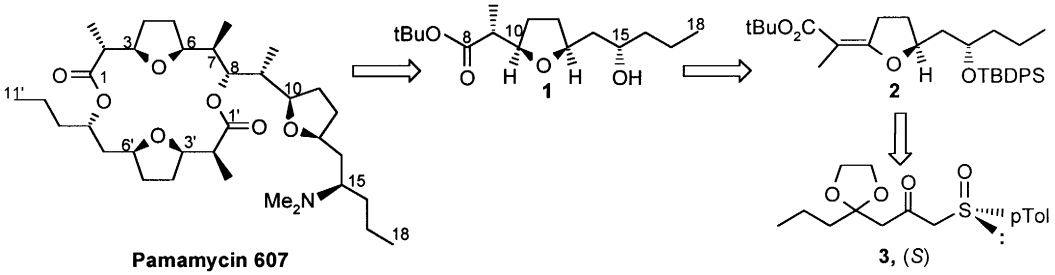
Abstract

A close precursor of the C8–C18 subunit of pamamycin-607 was prepared by asymmetric synthesis from ethyl butyryl acetate via a chiral β,δ-diketosulfoxide.

Pamamycin-607 is a member of a group of molecules isolated from *Streptomyces*[1] which has a remarkable range of biological activities including autoregulatory activity, antibiotic properties and anionophoric behavior.[2] Structure elucidation of pamamycin-607[3] showed three *cis*-2,5-disubstituted tetrahydrofuran units bearing *syn* and *anti* stereocenters α to the ring.



Scheme 1.

Several groups are involved in the total synthesis of pamamycin-607 but only the synthesis of the C1′–C11′[2b,4] and C1–C14[5] subunits have been published so far. The group of Walkup has already reported the synthesis of the C1′–C11′ fragment in racemic[4a] and optically active form[4b,2b] as well as the synthesis of the C1–C14 portion[5] from an enzymatically resolved allene derivative. The group of Perlmutter has recently reported the synthesis of the enantiomerically enriched 8′-*epi* C1′-C11′fragment[4c] from an optically active α-hydroxyacid. Finally the group of Bloch[4d] published a synthesis of the C1′–C11′ part from an enantiomerically pure 7-oxabicyclo[2,2,1] hept-5-ene derivative also obtained

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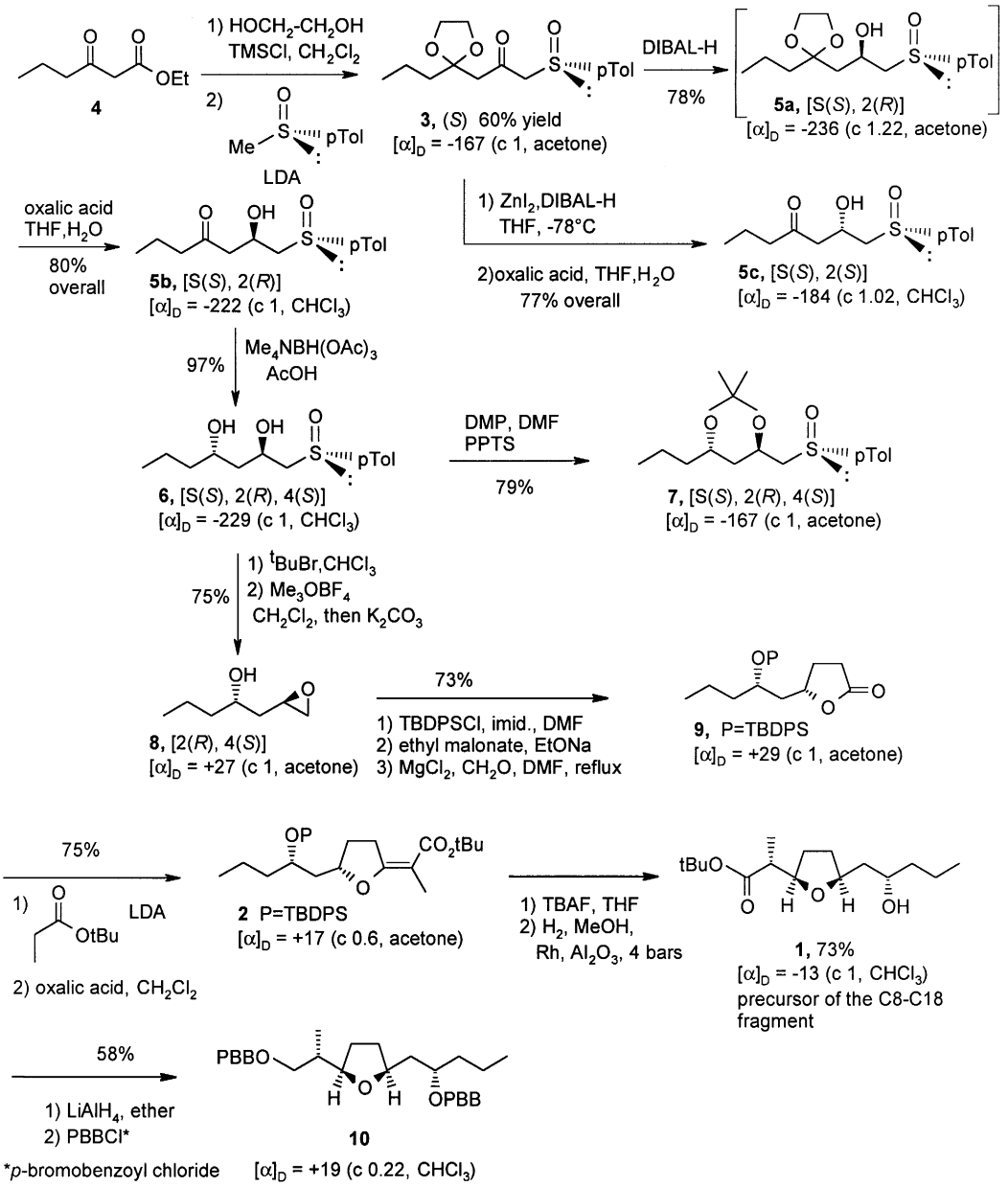
by enzymatic resolution. Very recently Bloch[4e] reported the synthesis of the C8–C18 fragment by the same method. This publication prompted us to report our own results and describe a novel, efficient, stereocontrolled approach to a close precursor **1** of the subunit C8–C18 starting from the intermediate **2** readily made by asymmetric synthesis from the chiral β,δ-diketosulfoxide **3** (Scheme 1).



Scheme 2.

The β-ketosulfoxide **3** was obtained from ethyl butyryl acetate **4** after carbonyl protection and condensation with two equivalents of (−)-(*S*)-methyl-*p*-tolylsulfoxide anion[6] in 60% isolated yield. DIBAL-H reduction afforded, as expected from our previous results,[7] the corresponding [S(*S*),2(*R*)]-β-hydroxysulfoxide **5a**[8a] (de>95%). We purified only an analytical sample for identification and hydrolyzed

the remaining crude reduction product with oxalic acid to give **5b** in an overall yield after the two steps of 80%. Only one diastereomer was observed in the 200 MHz ^{1}H NMR. The other diastereomer [S(*S*),2(*S*)]-**5c**[8b] was prepared by reduction with ZnI_2/DIBAL-H to confirm the absolute configuration and the diastereoselectivity.[7] The protection of the δ-carbonyl group as a dioxolane[9] avoided side-reactions in the reduction of β,δ-diketosulfoxides,[7] improved yields (33% yield for the direct reduction of the β,δ-diketosulfoxides because of product decompositon) and made the purification easier. After deketalization, the resulting [S(*S*),2(*R*)]-β-hydroxy-δ-keto-sulfoxide **5b** was reduced using Evans' method[10] giving *anti*-[S(*S*),2(*R*),4(*S*)]-β,δ-dihydroxy-sulfoxide **6** (de>95%), isolated by crystallization in 97%. Stereochemical assignment of the *anti* configuration was confirmed by ^{13}C NMR of the corresponding acetonide **7**.[11] Sulfoxide reduction to the corresponding sulfide, methylation at sulfur and intramolecular sulfonium elimination afforded in 75% yield the [2(*R*),4(*S*)]-β-hydroxy epoxide **8**.[12] Protection of the alcohol as its *t*-butyldiphenylsilyl ether, regioselective nucleophilic epoxide opening with ethyl malonate anion followed by smooth decarboxylation with magnesium chloride hexahydrate led to the butyrolactone **9** (73% yield). Finally reaction of **9** with *t*-butyl propionate enolate gave a hemiketal which, after acidic dehydration, provided the expected intermediate **2** in 75% yield in the more stable *E* configuration.[13]

Then compound **2** was deprotected with tetrabutylammonium fluoride and stereoselectively hydrogenated on the less hindered face with rhodium on alumina; a known process for this type of furan derivative (Scheme 2).[14] The target molecule **1** was obtained pure in 73% yield[15] after chromatography. Direct hydrogenation of silylated **2** led only to starting material even under more drastic conditions. In the case of the benzyl ether of **2**, we observed competitive hydrogenation of the aromatic ring giving a cyclohexylmethyl ether.[16]

The configuration of product **1** was confirmed by chemical correlation with the known compound **10** by ester reduction with lithium aluminum hydride followed by acylation with *p*-bromobenzoyl chloride (Scheme 2). All the characteristics of **10** are in agreement with those described by Walkup. [4a]

In conclusion, it has been demonstrated that the important intermediate **1** for the total synthesis of pamamycin-607 can be obtained in high ee in 14 steps and in 11% overall yield from ethyl butyryl acetate using (−)-(*S*)-methyl-*p*-tolylsulfoxide as the chiral auxiliary.

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8. ^{1}H NMR (200 MHz, $CDCl_3$): (a) [*S*(*S*),2(*R*)]-**5b**: δ 0.89 (t, 3H, J=7 Hz, H-7); 1.57 (sext.; 2H, J=7 Hz, H-6); 2.39 (t, 2H, J=7 Hz, H-5); 2.43 (s, 3H, benzylic CH_3); 2.64 (d, 2H, H-3, J=6 Hz); 2.86 (AB of ABX, 2H, H-1, J_{AX}=9.5 Hz, J_{BX}=2.5 Hz, J_{AB}=13.5 Hz); 4.10 (b s, 1H, OH); 4.69–4.57 (m, 1H, H-2, X of ABX); 7.35 (B of $(AB)_2$, 2H, arom.; J_{AB}=8 Hz, $\Delta\nu$=36

Hz); 7.53 (A of $(AB)_2$, 2H, arom.; J_{AB}=8 Hz, $\Delta\nu$=36 Hz); (b) [*S*(*S*),2(*S*)]-**5c**: 0.90 (t, 3H, H-7, J=7.3 Hz); 1.58 (sext, 2H, H-6, J=7.3 Hz); 2.40 (t, 2H, H-5, J=7.3 Hz); 2.41 (s, 3H, CH_3 arom.); 2.78 (AB of ABX, 2H, H-3, J_{AX}=7.3 Hz, J_{BX}=4.9 Hz, J_{AB}=17.5 Hz, $\Delta\nu$=37.7 Hz); 2.93 (AB of ABX, 2H, H-1, J_{AX}=7.5 Hz, J_{BX}=4.4 Hz, J_{AB}=12.9 Hz, $\Delta\nu$=24 Hz); 3.98 (d, 1H, OH, J=2.7 Hz); 4.55–4.50 (m, 1H, H-2, X of ABX); 7.32 (B of $(AB)_2$, 2H, H arom.; J_{AB}=8.22 Hz, $\Delta\nu$=41.5 Hz); 7.53 (A of $(AB)_2$, 2H, H arom.; J_{AB}=8.22 Hz, $\Delta\nu$=41.5 Hz); (c) (2*E*,6*S*,8*S*)-**2**: δ 0.67 (t, J=7 Hz, 3H); 1.06 (s, 9H); 1.52 (s, 9H); 1.73 (t, J=1.3 Hz, 3H); 1.10–1.80 (m, 7H); 1.99–2.21 (m, 1H); 2.74–2.91 (m, 1H); 3.02–3.16 (m, 1H); 3.96–4.04 (m, 1H); 4.41–4.54 (m, 1H); 7.32–7.48 (m, 6H); 7.66–7.73 (m, 4H); ^{13}C NMR: δ 169.0, 136.0, 134.7, 134.2, 129.6, 127.6, 98.8, 79.8, 79.1, 70.7, 42.5, 39.6, 31.2, 30.6, 28.6, 27.2, 19.6, 17.7, 14.0, 11.8; (d) (2*R*,3*R*,6*S*,8*S*)-**1**: δ 0.92 (t, 3H, H-11, J=7 Hz), 1.06 (d, 3H, H-12, J=7 Hz), 1.45 (s, 9H, CH_3), 1.85–1.23 (m, 8H), 2.06–1.87 (m, 2H), 2.48–2.32 (m, 1H), 2.91 (b s, 1H, OH), 3.87–3.77 (m, 1H), 4.02–3.88 (m, 1H), 4. 23–4.08 (m, 1H); ^{13}C NMR: δ 167.1, 165.3, 97.2, 82.3, 79.6, 68.6, 41.2, 39.4, 30.7, 28.9, 28.5, 19.1, 14.7, 14.2.

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