Pergamon

Tetrahedron Letters 41 (2000) 2737–2740

TETRAHEDRON LETTERS

Diastereodivergent synthesis of the C8–C18 precursor and C1′–C11′ subunit of pamamycin 607 induced by a chiral sulfoxide group

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Received 16 December 1999; accepted 9 February 2000

Abstract

A key step in obtaining the C8–C18 and C1′–C11′ fragments of pamamycin 607, which differ by the *syn*- and *anti*-configuration of one chiral center α to the tetrahydrofuran ring, was the chelation controlled *E*–*Z*-isomerization of the substituted vinyl tetrahydrofuran intermediate **3a** which has so far been obtained only in the more stable *E*-configuration.

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.

Several groups are involved in the total synthesis of pamamycin 607 but only syntheses of the C1′–C11′,[2b,4] C1–C14[5] and recently the C8–C18[4e] subunits have been published so far.

We have very recently reported[6] a stereoselective synthesis of a precursor of the C8–C18 moiety **1** with a *syn*-stereocenter α to the ring from the β-ketosulfoxide **4** via the intermediate **3a**-(*E*) (Scheme 1).

The C1′–C11′ fragment **2**, which is epimeric at C2′ (an *anti*-configuration α to the ring) should be obtained, by analogy with the synthesis of **1**, from **3a**-(*Z*) (Scheme 1).

In a previous report,[6] we described the synthesis of the enantiomerically pure **3a**-(*E*) from lactone **6** readily made from enantiomerically pure β-hydroxy epoxide **5**, obtained from the β-ketosulfoxide **4**-(*S*) (Scheme 2).

The transformation of the more stable *E*-isomer **3** into the *Z*-isomer was then investigated and we now report the results of the isomerization of **3a**-(*E*) to **3a**-(*Z*), the key step of our strategy. The idea was to equilibrate these two isomers and displace the equilibrium in favor of **3**-(*Z*) by chelation of a Lewis acid between the furanic and ester oxygens.

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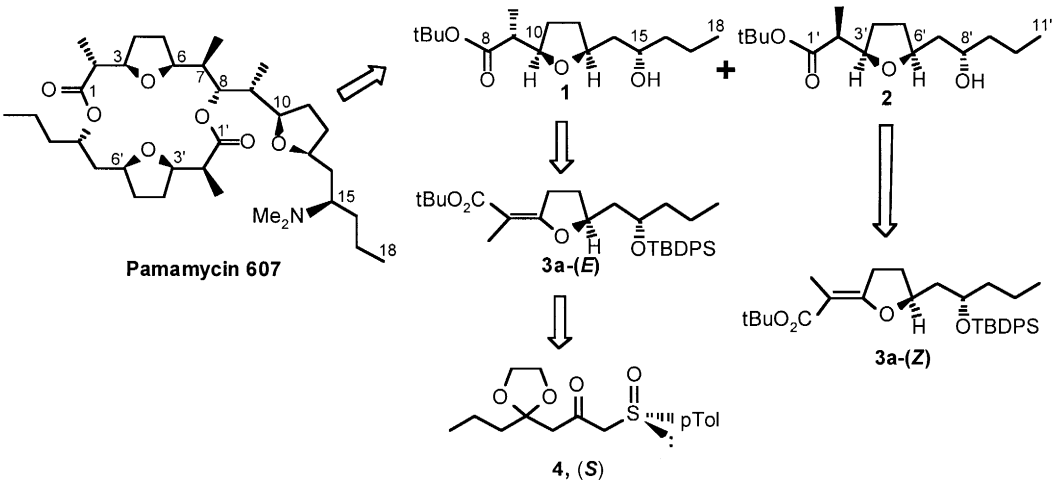
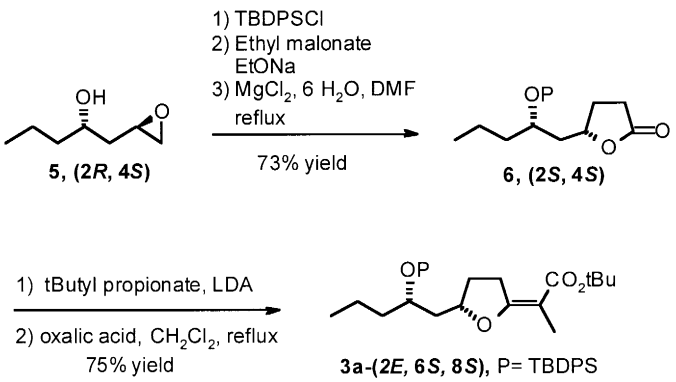
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00251-3

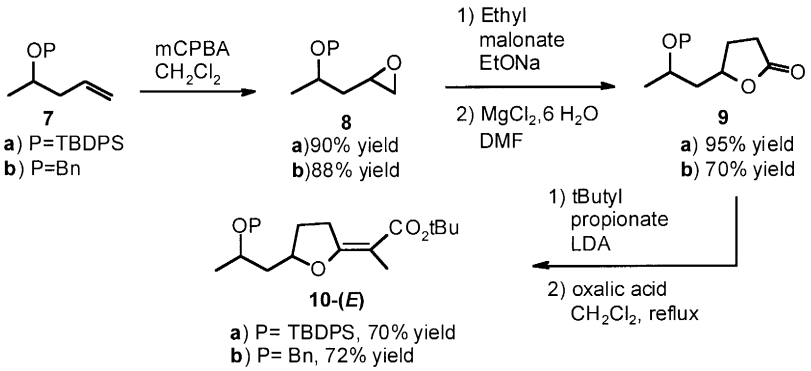


Scheme 1.



Scheme 2.

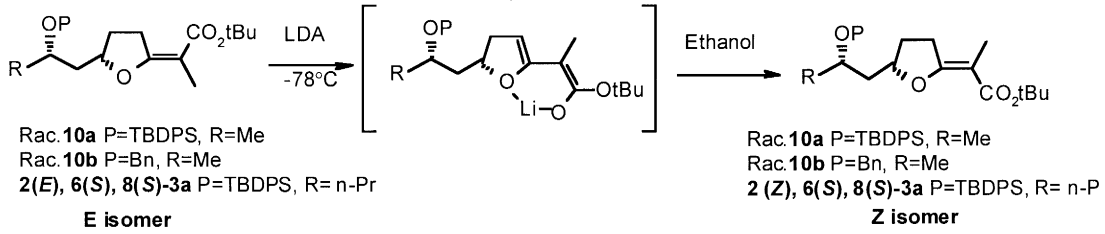
This study was first carried out on racemic analogues of **3** easily prepared by the sequence described in Scheme 3, from racemic 4-hydroxypent-1-ene **7** by epoxidation of the double bond giving epoxide **8**, which was opened with ethyl malonate anion, followed by intramolecular lactonization and decarboxylation in the presence of magnesium chloride. Finally, aldol condensation of *t*-butyl propionate enolate with the lactone **9** followed by acidic dehydration gave **10**-(*E*). The *E* double bond in **10** was formed during



Scheme 3.

the cationic acidic dehydration of the hemi-ketal formed in the aldol condensation of *t*-butyl propionate to the lactone.[7]

After several attempts with different Lewis acids which gave mixtures of **10**-(*E*) and **10**-(*Z*), the equilibration in favor of the *Z*-isomer was successful with LDA (2 equiv.) at −78°C in ether alone or in the presence of lithium chloride (3 equiv.) through ester enolization (Scheme 4). The reaction mixture was then quenched at −78°C by adding ethanol. The results are listed in Table 1.



Scheme 4.

Table 1
Isomerization of **3**-(*E*) to **3**-(*Z*) and analogues with LDA/ether at −78°C

Substrate	Base	Reaction time	*Z*/*E* ratio[a]	**(*Z*)-isomer** Isolated yield[b]
Racemic **10a**-(***E***)	LDA (2eq)	1h	80/20	71%
P=TBDPS	LDA, (2eq) + LiCl, (3eq)	45 min	93/7	86%
Racemic **10b**-(***E***)	LDA, 2eq	1h	95/5	83%
P=Bn	LDA, (2eq) + LiCl (3eq)	45 min	95/5	87%
4(*R*), 6(*S*)-**3a**-(***E***)	LDA, (2eq) + LiCl, (3eq)	45 min	95/5	70%

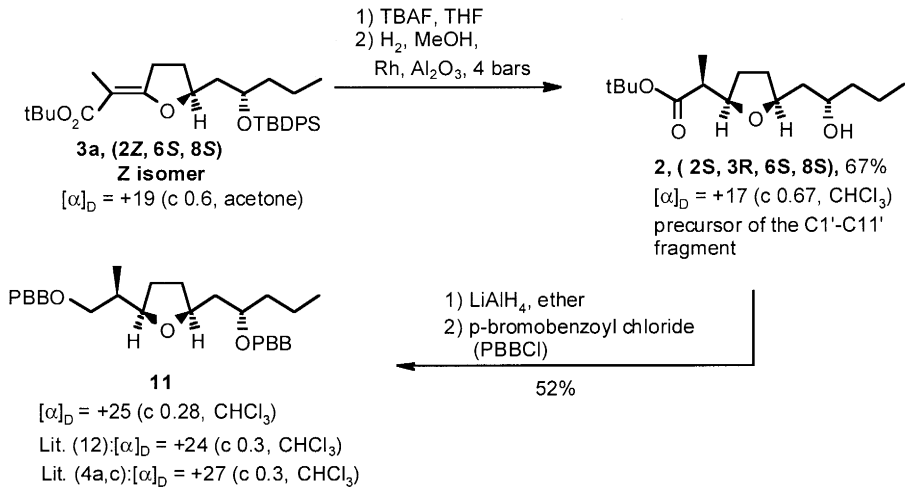
[a] determined by 200 MHz ^{1}H NMR. [b] after chromatography

In the case of the silylated ether **10a** the addition of LiCl was necessary to get a complete conversion. Finally, when these last conditions were applied to the enantiomerically pure **3a**-(*E*), the *Z*-isomer was obtained in 70% yield.

Then (Scheme 5) the pure *Z*-isomer[8] of **3a** 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.[9] The target molecule **2** was obtained in 73% yield.[10] Direct hydrogenation of silylated **3a** led only to starting material even under more drastic conditions. In the case of the benzyl ether of **3**, we observed competitive hydrogenation of the aromatic ring giving a cyclohexylmethyl ether.[11]

The absolute configuration of **2** was confirmed by correlation to the known product **11** by ester reduction with $LiAlH_4$ and acylation with *p*-bromobenzoyl chloride. All the characteristics of **11** are in agreement with those described by Marumo et al.[12]

In conclusion, it has been demonstrated that the two important intermediates **1** and **2** for the total synthesis of pamamycin 607 can be obtained in high ees in 14 and 15 steps and in 17 and 11% overall yield, respectively, from a common intermediate readily made from ethyl butyryl acetate and with only (−)-(*S*)-methyl-*p*-tolylsulfoxide as chiral auxiliary.



Scheme 5.

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8. (a) (2*E*,6*S*,8*S*)-**3a**: $[\alpha]_D$=+17 (*c* 0.6, acetone); ^{1}H NMR (200 MHz, $CDCl_3$): 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 (50 MHz, $CDCl_3$): 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; (b) (2*Z*,6*S*,8*S*)-**3a**: $[\alpha]_D$=+19 (*c* 0.6 acetone); ^{1}H NMR ($CDCl_3$, 200 MHz): δ=0.74 (t, *J*=7.0 Hz, 3H), 1.06 (s, 9H), 1.22–1.44 (m, 4H), 1.45 (s, 9H), 1.70 (s, 3H), 1.61–1.76 (m, 2H), 1.78–1.84 (m, 2H), 2.38–2.64 (m, 2H), 3.95–4.04 (m, 1H), 4.32–4.47 (m, 1H), 7.32–7.48 (m, 6H), 7.67–7.73 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=167.1, 165.6, 136.0, 134.7, 134.5, 129.6, 127.6, 96.3, 82.5, 79.0, 71.1, 42.6, 39.6, 31.1, 29.2, 28.5, 27.2, 19.6, 17.8, 14.7, 14.2; (c) (2*S*,3*R*,6*S*,8*S*)-**2**: $[\alpha]_D$=+17 (*c* 0.67 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ=0.93 (t, *J*=7.0 Hz, 3H), 1.20 (d, *J*=7 Hz 3H), 1.45 (s, 9H), 1.32–1.81 (m, 8H), 1.89–2.08 (m, 2H), 2.48–2.34 (m, 1H), 2.82 (broad s, 1H), 3.78–3.98 (m, 2H), 4.06–4.19 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=173.9, 80.9, 80.5, 77.3, 69.0, 46.3, 41.1, 39.5, 30.9, 29.2, 28.1, 19.1, 14.4, 14.2.
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10. Hydrogenation of the double bond resulted in an 85:15 distereomeric ratio of the expected product and a mixture ot three diastereoisomers. See Ref. 9a.
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