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Synthesis of a C1-C14 Subunit of the Macrodiolide Antibiotics Pamamycin-607 and Pamamycin-635B

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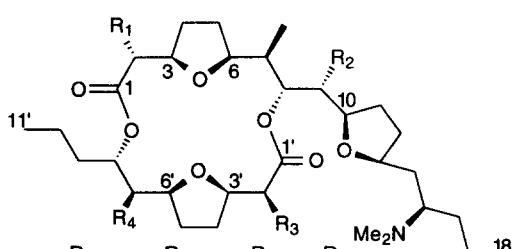
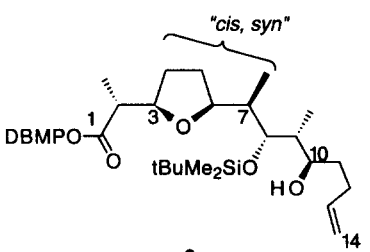
Abstract: *A nonracemic C_1-C_{14} portion of the antibiotics pamamycin-607 and -635B was prepared using a route which features two stereoselective aldol reactions (including an apparent kinetic resolution via the Evans aldol reaction), a stereospecific intramolecular oxymercuration of a γ-silyloxyallene, a stereospecific conjugate reduction of a β-alkoxy-α-methylene carboxylate ester, and use of the 2,6-di-tert-butyl-4-methoxyphenyl ester group to "protect" a carboxylate function from reactions which normally occur at ester groups.*

The pamamycins (**1**-**5**) are a unique class of antibiotics and autoregulatory agents produced by Streptomyces.[1] Using methodology developed in our laboratory for the synthesis of the "cis,syn" 2,5-disubstituted tetrahydrofuran structural pattern which exists around two of the three tetrahydrofuran rings in the pamamycins,[2] we have prepared the $C_{1'}$ - $C_{11'}$ "lower" portions of each of the pamamycins.[1d] In this Letter, we report the application of this methodology to the synthesis of a C_1-C_{14} intermediate (**6**) of pamamycin-607 and pamamycin-635B having 7 out of the 9 stereogenic centers found in the C_1-C_{18} "upper" portion of the pamamycins and functionalized for further manipulation to the complete upper portion.[3]

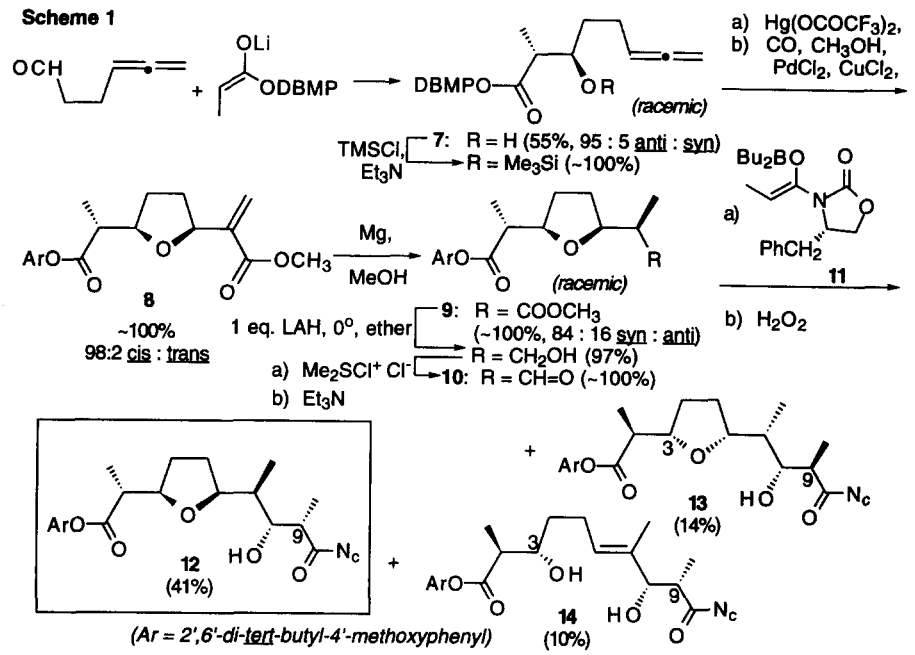


	R1	R2	R3	R4	
1:	CH_3	CH_3	CH_3	H	(Pamamycin-607)
2:	CH_3	CH_2CH_3	CH_3	CH_3	(Pamamycin-635A)
3:	CH_3	CH_3	CH_2CH_3	CH_3	(Pamamycin-635B)
4:	CH_2CH_3	CH_2CH_3	CH_2CH_3	H	(Pamamycin-649A)
5:	CH_2CH_3	CH_2CH_3	CH_3	CH_3	(Pamamycin-649B)



6
(DBMP = 2,6-di-tert-butyl-4-methoxyphenyl)

Reaction of 4,5-hexadienal[2] with the (E) lithium enolate derived from DBMP propanoate gave **7** with high anti diastereoselectivity (Scheme 1).[4,5] The TMS ether derivative of this ester underwent stereoselective oxymercuration-transmetallation-methoxycarbonylation[2] to yield the cis diester **8**. Chelation-controlled conjugate reduction using magnesium in methanol then yielded **9** with good syn selectivity.[2] Chemoselective reduction, then oxidation, produced the aldehyde **10**, which reacted with 3 equivalents of the chiral boron enolate **11**[6] to yield the aldol **12**, a single stereoisomer, along with the byproducts **13** and **14**. An excess of the enolate was necessary for the reaction to proceed: when 1 or 2 equivalents of the enolate were employed, less than 10% of **12** was obtained.[7] Byproduct **13** apparently arose from an anti selective aldol addition of the enolate to a Lewis acid-base complex between the aldehyde and excess boron enolate,[8] and the acyclic aldol product **14** arose from a Lewis acid-mediated ring opening.[9] Thus the Evans aldol reaction between **10** and **11**



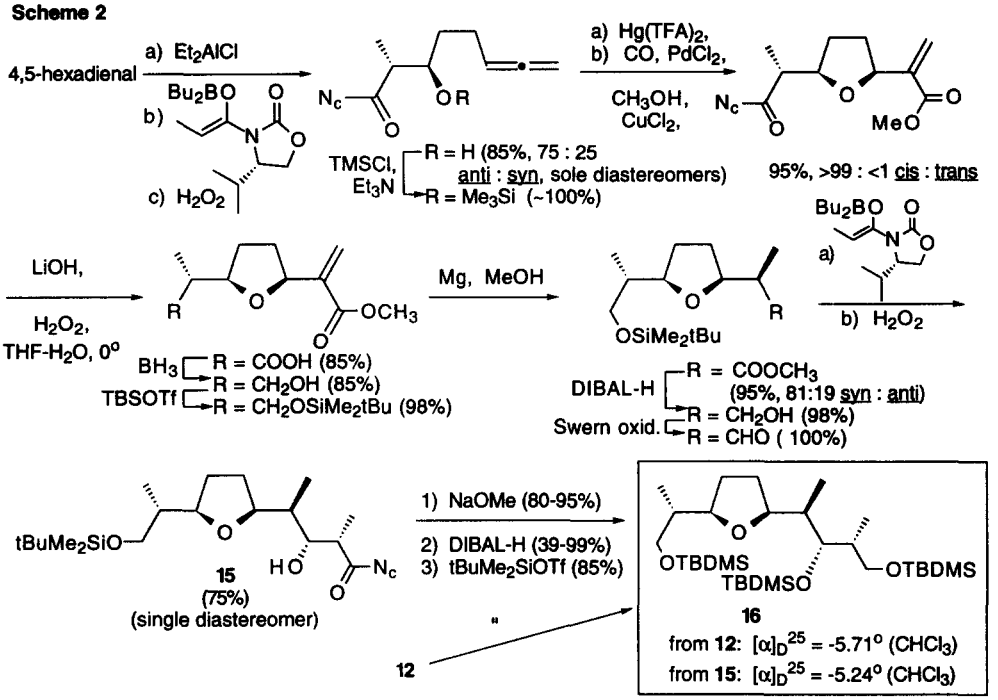
apparently proceeded with kinetic resolution: the 2R,3R,6S,7R enantiomer of **10** reacted with the enolate more rapidly than the 2S,3S,6R,7S enantiomer. The absolute configurations of the C_2, C_3, C_6, and C_7 centers of the anti byproduct **13**, and of the C_2 and C_3 centers of **14** are still tentative. However, if the 2S,3S,6R,7S enantiomer of **10** undergoes aldol addition slowly, then it would persist in the reaction mixture long enough for Lewis acid-mediated reactions to occur to yield the anti aldol or ring opened products derived from that slow-reacting enantiomer. Further investigations of this kinetic resolution will test these predictions and discern its generality for other α-(tetrahydrofuran-2-yl)propanals.

To confirm the absolute configuration assigned to **12**, the "C_1-reduced" pamamycin subunit **15** was prepared using the precedented and unambiguous asymmetric and diastereoselective methodology indicated in Scheme 2. When **12** and **15** were esterified, reduced (using excess reducing agent for **12**), and silylated, the tris(tert-butyldimethylsilyl) ether **16** was produced in each case. The ^{1}H- and ^{13}C-NMR spectra and the optical activities of **16** were identical for the product obtained from each route, thus verifying the stereochemical assignment given to **12**, the kinetically resolved aldol product.

As indicated in Scheme 3, **12** was esterified to **17**, whose hydroxyl group was then silylated. Chemoselective ester reduction yielded **18**, which was then oxidized to the aldehyde **19** and treated with 3-buten-1-ylmagnesium bromide to yield a 30:70 mixture of the alcohols **6** and **20**. The configurations assigned to **6** and **20** were based on their conversions to the corresponding acetonides [1) Bu4NF, 79%; 2) $Me_2C(OMe)_2$, TsOH, 72%]. The acetonide derived from **6** was assigned the "1,3-anti-diol" (10R) configuration, and the acetonide from **20** was assigned the "syn" (10S) configuration on the basis of their relative ^{13}C-NMR chemical shift values for the geminal methyl groups.[10]

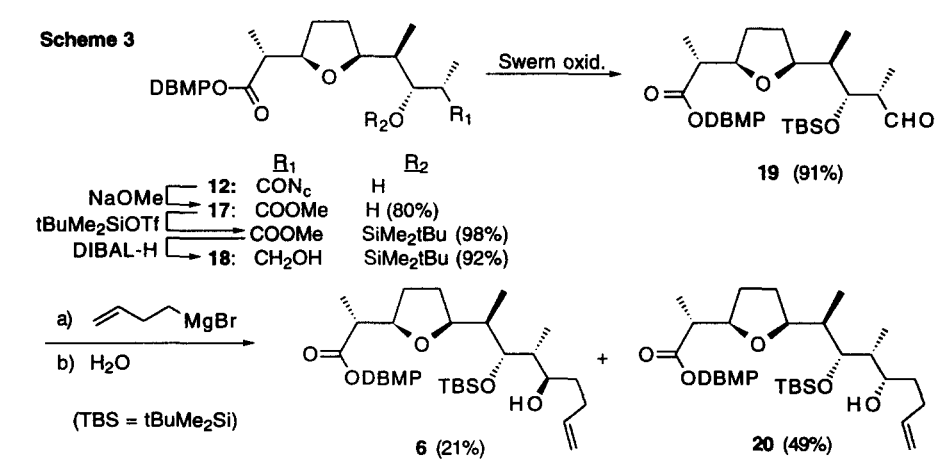
Thus a C_1-C_{14} subunit of pamamycin-607 and -635B, **6**, is accessible as a single stereoisomer in 12 steps and 2% overall yield from 4,5-hexadienal using a synthetic route which features two stereoselective aldol

Scheme 2



reactions (including an apparent kinetic resolution via the Evans aldol reaction), a stereospecific intramolecular oxymercuration of a γ-silyloxyallene, and a chelation-controlled conjugate reduction of a β-alkoxy-α-methylene carboxylate ester. The addition of the C_{11}-C_{14} moiety via the addition of 3-buten-1-ylmagnesium bromide to a C_{10} aldehyde was demonstrated, albeit with Cram's rule stereoselectivity in favor of the undesired epimer (**19**), but a change of the 8-hydroxyl protecting group from a trialkylsilyl group to an alkyl ether group may allow this Grignard reaction to proceed with chelation control to favor the desired 10R epimer.[11] The synthesis of **6** is also notable for its use of the DBMP ester group as a means of "protecting" the pamamycin C_1 carboxylate

Scheme 3



group; this ester group did not undergo side reactions when exposed to such reagents as LAH (when not in excess), DIBAH (when not in excess), boron enolates, methanolic magnesium, sodium methoxide, oxidizing agents, Lewis acids, and a Grignard reagent. The DBMP ester can be cleaved to the acid using CAN oxidation,[5] a reaction which we have found to proceed (50%) with the polyfunctional intermediate **12**. Future efforts are aimed at optimizing this deprotection step, exploring in more detail the kinetic resolution of α-tetrahydrofuranylpropanals by the Evans aldol reaction, improving the stereoselectivity of the Grignard addition to the C_{10} aldehyde, and completing the syntheses of pamamycin-607 and -635B.[12]

References and Notes

1. a) First report: McCann, P. A.; Pogell, B. M. J. Antibiotics **1979**, *32*, 673-678. b) First structure elucidation: Kondo, S.; Yasui, K.; Katayama, M.; Marumo, S.; Kondo, T.; Hattori, H. Tetrahedron Lett. **1987**, *28*, 5861-5864. c) First details on biological activity: Kondo, S.; Yasui, K.; Natsume, M.; Katayama, M.; Marumo, S. J. Antibiotics **1988**, *41*, 1196-1204. d) Up-to-date overview of subsequent structural elucidations, characterizations, and synthetic efforts: Walkup, R.D.; Kim, S.W. J. Org. Chem. **1994**, *59*, 3433-3441.

2. a) Walkup, R. D.; Park, G. Tetrahedron Lett. **1987**, *28*, 1023-1026; b) Walkup, R. D.; Park, G. J. Am. Chem. Soc. **1990**, *112*, 1597-1603 (Correction: J. Am. Chem. Soc. **1990**, *112*, 5388).

3. An iodoetherification reaction between the protected 10-hydroxyl and Δ^{13} alkene groups of **6** would stereoselectively produce the second tetrahydrofuran ring of the upper portion of the pamamycins (Bartlett, P.A. Asymmetric Synth. **1984**, *3*, 411-454).

4. Heathcock, C.H.; Pirrung, M.C.; Montgomery, S.H.; Lampe, J. Tetrahedron **1981**, *37*, 4087-4095.

5. All new compounds were fully characterized by spectrometric means, and their compositions were affirmed by elemental analyses and/or high resolution mass spectrometric analysis. The stereochemical assignments were made on the basis of precedented NMR methods or as discussed in the text.

6. Evans, D.A.; Bartroli, J.; Shih, T.L. J. Am. Chem. Soc. **1981**, *103*, 2127-2129.

7. One explanation for this observation is the formation of stable complexes between the oxygen rich substrate **10** and the boron enolate. Indeed, when **10** was exposed to less than 3 eq. of **11**, a product which, according to ^{1}H-NMR analysis, possessed the enolate structure and no aldehyde proton, implying a complex between the aldehyde and the enolate, was isolated. Upon attempted chromatography on silica gel, this complex decomposed to the aldehyde **10** and the N-propionyloxazolidinone precursor to **11**.

8. a) Danda, H.; Hansen, M.M.; Heathcock, C.H. J. Org. Chem. **1990**, *55*, 173-181; b) Walker, M.A.; Heathcock, C.H. J. Org. Chem. **1991**, *56*, 5747-5750.

9. Eliminative ring opening of α-tetrahydropyranylpropanoates by R_2BX to form α,β-unsaturated esters: Abel, S.; Linker, T.; Giese, B. Synlett **1991**, 171-172. Nucleophilic ring-opening of tetrahydrofurans by R_2BX: Guindon, Y.; Anderson, P.C.; Yoakim, C.; Girard, Y.; Berthiaume, S.; Morton, H. Pure Appl. Chem. **1988**, *60*, 1705.

10. a) Rychnovsky, S.D.; Skalitzky, D.J. Tetrahedron Lett. **1990**, *31*, 945-948; b) Evans, D.A.; Rieger, D.L.; Gage, J.R. Tetrahedron Lett. **1990**, *31*, 7099-7100.

11. a) Reetz, M.T. Angew. Chem. Int. Ed. Engl. **1984**, *23*, 556-569; b) Oishi, T.; Nakata, T. Synthesis **1990**, 635-645.

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