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Stereoselective Synthesis of Pamamycin-607

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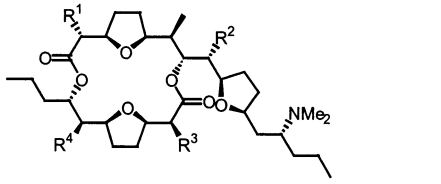
Abstract: A macrodiolide antibiotic pamamycin-607 was synthesized by joining two hydroxy acid components. Three *cis*-2, 5-disubstituted tetrahydrofuran rings in the molecule were stereoselectively prepared by radical cyclization reactions of β-alkoxyvinyl ketone intermediates and a β-alkoxymethacrylate substrate. The key step of the synthesis is characterized by the predominant threo product formation in the radical cyclization reaction of a β-alkoxymethacrylate intermediate.

Pamamycins were first isolated by McCann and Pogell[1] in 1979 from *Streptomyces alboniger* ATCC 12461 for their aerial mycelium-inducing acitivity, and classified as new family type antibiotics active against Gram-positive bacteria, *Mycobacteria*, and *Neurospora*. Isolation of pamamycin-607 (**1**) was reported by Marumo and co-workers[2] in 1987 from *S. alboniger* IFO 12738, and they were also successful in structure determination studies on the basis of spectroscopic analysis. Subsequent studies by Marumo[3] and other groups[4] on pamamycins led to discovery of their anionophoric activity and identification of further members of the family (**2**, **3**, **4**, **5**, and others) as well as evaluation of structure−activity relationship (Figure 1). Pamamycin-607 (**1**) is especially interesting for its potent activity[5] against gram-positive bacteria including multiple antibiotic-resistant strains of *Mycobacterium tuberculosis* as well as against phytopathogenic fungi.

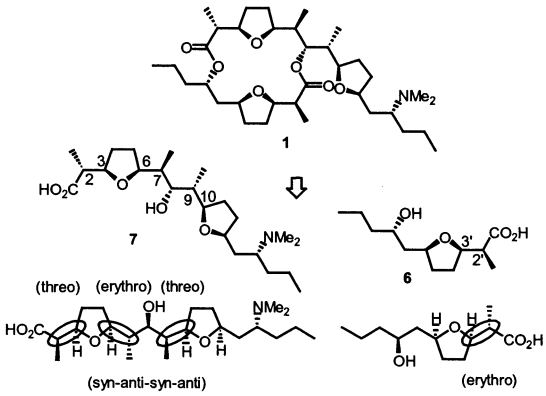
Pamamycins are sixteen-membered macrodiolides incorporating two of the three *cis*-2, 5-disubstituted tetrahydrofuran rings within the macrocycle framework. The prototype pamamycin-607 (**1**) consists of the two hydroxy acids **6** and **7**. The most characteristic structural features in **6** and **7** are *cis*-2, 5-disubstituted tetrahydrofuran rings adjacent to methyl-substituted stereogenic centers (Scheme 1). The hydroxy acid **6** is an erythro (C2′−C3′) isomer, and the acid **7** features a threo (C2−C3)-erythro (C6−C7)-threo (C9−C10) arrangement. Efficient and stereoselective construction of these structural units is not trivial,



R^1	R^2	R^3	R^4	
CH_3	CH_3	CH_3	H	**1** Pamamycin-607
CH_3	CH_2CH_3	CH_3	CH_3	**2** Pamamycin-635A
CH_3	CH_3	CH_2CH_3	CH_3	**3** Pamamycin-635B
CH_2CH_3	CH_2CH_3	CH_2CH_3	H	**4** Pamamycin-649A
CH_2CH_3	CH_2CH_3	CH_3	CH_3	**5** Pamamycin-649B

Figure 1. Representative pamamycins.

Scheme 1. Pamamycin-607



and the difficulty therein is manifested by the absence of reports on the total synthesis[6] of pamamycins in the literature at the outset of this research, despite intense synthetic efforts by a number of research groups.[7−14]

(1) McCann, P. A.; Pogell, B. M. *J. Antibiot*. **1979**, *32*, 673−678.
(2) Kondo, S.; Yasui, K.; Katayama, M.; Marumo, S.; Kondo, T.; Hattori, H. *Tetrahedron Lett.* **1987**, *28*, 5861−5864.
(3) (a) Kondo, S.; Yasui, K.; Natsume, M.; Katayama, M.; Marumo, S. *J. Antibiot*. **1988**, *41*, 1196−1204. (b) Natsume, M.; Kondo, S.; Marumo, S. *J. Chem. Soc. Chem. Comm*. **1989**, 1911−1913. (c) Natsume, M.; Yasui, K.; Kondo, S.; Marumo, S. *Tetrahedron Lett.* **1991**, *32*, 3087−3090. (d) Natsume, M.; Tazawa, J.; Yagi, K.; Abe, H.; Kondo, S.; Marumo, S. *J. Antibiot*. **1995**, *48*, 1159−1164. (e) Natsume, M.; Honda, A.; Oshima, Y.; Abe, H.; Kondo, S.; Tanaka, F.; Marumo, S. *Biosci. Biotech. Biochem*. **1995**, *59*, 1766−1768.
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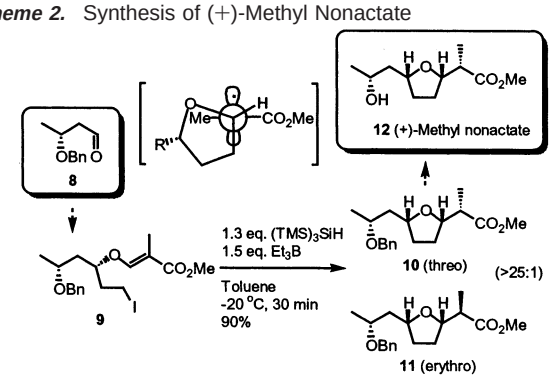
(6) A total synthesis of pamamycin-607 was communicated by Professor Sung Ho Kang (Korea Advanced Institute of Science and Technology) at the CMDS Symposium 2000, Nov. 9, 2000, Daejon, Korea. A preliminary report on the total synthesis was communicated by us: (a) Lee, E.; Jeong, E. J.; Kang, E. J.; Sung, L. T.; Hong, S. K. *J. Am. Chem. Soc*. **2001**, *123*, 10 131−10 132. One paper appeared in the literature before publication of our communication and a second one appeared after publication of ours: (b) Germay, O.; Kumar, N.; Thomas, E. J. *Tetrahedron Lett*. **2001**, *42*, 4969−4974 (c) Wang, Y.; Bernsmann, H.; Gruner, M.; Metz, P. *Tetrahedron Lett*. **2001**, *42*, 7801−7804.

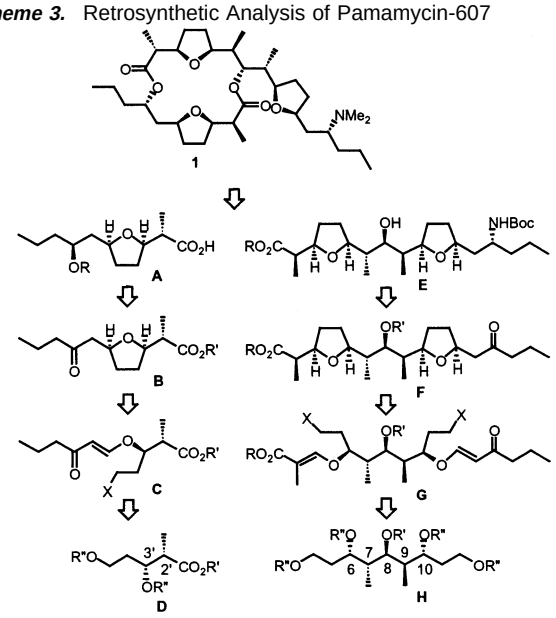
Radical cyclization of β-alkoxyacrylates is a highly useful method for stereoselective preparation of *cis*-2, 5-disubstituted tetrahydrofurans and *cis*-2, 6-disubstituted tetrahydropyrans.[15,16] Radical cyclization reactions of different β-alkoxyacrylates were employed as key steps in the total syntheses of dactomelynes,[17] kumausyne,[18] and kumausallene,[19] demonstrating the generality of these reactions. Further development concerning these types of reactions would be the control of the stereoselectivity outside of the oxacycle when α-substituted β-alkoxyacrylates are employed in the radical cyclization. In this context, reported work by Guindon and co-workers on radical-mediated reduction of α-halo carboxylates was highly pertinent; it was reported that radical-mediated reduction of α-substituted β-alkoxy-α-halo carboxylates resulted in high threo selectivity.[20] Theoretical studies indicated that the stereoselectivity originated primarily from the preference for "outside alkoxy" conformation of the intermediate radical species. In this model, both allylic 1, 3-strain and electrostatic repulsions were minimized, and an early transition state for hydrogen abstraction in which attack occurs from the least hindered face of the radical is apparently operative. The "cis-2, 5" selectivity encountered in the β-alkoxyacrylate radical cyclization reactions in forming tetrahydrofuranyl ring systems and the "threo" selectivity at the exocyclic α sites were simultaneously demonstrated in an expedient synthesis of (+)-methyl nonactate (**12**).[21] In the synthesis, the threo ester **10** was obtained stereoselectively from the β-alkoxymethacrylate **9** (Scheme 2).

In the retrosynthetic analysis of **1** (Scheme 3), it was decided to form the more hindered ester bond first, which called for preparation of the carboxylic acid **A** and the alcohol **E** (Scheme 3). The ester bond formation between **A** and **E** would set the stage for the final macrodiolide cyclization required in the preparation of **1**. The acid **A** may be obtained from the ester **D** employing the key radical cyclization reaction converting the β-alkoxyvinyl ketone **C** into the tetrahydrofuranyl ester **B**. The

Scheme 2. Synthesis of (+)-Methyl Nonactate



Scheme 3. Retrosynthetic Analysis of Pamamycin-607



two tetrahydrofuran rings in **E** and **F** were also envisaged to arise from radical cyclization reactions of the intermediates such as **G**. In practice, two separate radical cyclization reactions were deemed necessary: the first one was reminiscent of the key reaction employed in the synthesis of **12**, and the second radical cyclization reaction was analogous to the conversion of **C** to **B**. The substrates for radical cyclization were then to be synthesized from the protected dimethylpentahydroxynonane derivative **H**. Intermediates **H** and **D** were to be prepared employing Evans asymmetric aldol reactions.[22]

Synthesis of the carboxylic acid **A** started with the reaction of the PMB-protected 3-hydroxypropanal (**14**) and the (*Z*)-boron enolate prepared from the chiral imide **13**. The aldol imide **15** was converted into the corresponding methyl ester **16** using samarium triflate[23] in methanol-THF, and the diol ester **17** was obtained from **16** via PMB-deprotection. Regioselective tosylation of **17** provided the primary tosylate **18**. The reaction of **18** with 1, 1-dimethoxyhexan-3-one (**19**) under acidic conditions afforded the β-alkoxyvinyl ketone **20**.[24] Subsequent iodide substitution of **20** afforded the corresponding iodide **21**. Radical cyclization of **21** in the presence of tributylstannane and AIBN

(7) (a) Walkup, R. D.; Park, G. *Tetrahedron Lett.* **1988**, *29*, 5505−5508. (b) Walkup, R. D.; Kim, S. W.; Wagy, S. D. *J. Org. Chem.* **1993**, *58*, 6486−6490. (c) Walkup, R. D.; Kim, S. W. *J. Org. Chem.* **1994**, *59*, 3433−3441. (d) Walkup, R. D.; Kim, Y. S. *Tetrahedron Lett.* **1995**, *36*, 3091−3094.
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(14) Kang, S. H.; Jeong, J. W. *Tetrahedron Lett.* **2002**, *43*, 3613−1616.
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(16) Lee, E. In *Radicals in Organic Synthesis, Vol. 2: Applications*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; pp 303−333.
(17) Lee, E.; Park, C. M.; Yun, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 8017−8018.
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(21) Lee, E.; Choi, S. J. *Org. Lett.* **1999**, *1*, 1127−1128.
(22) For an example of asymmetric aldol reactions, see: Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001−7031.
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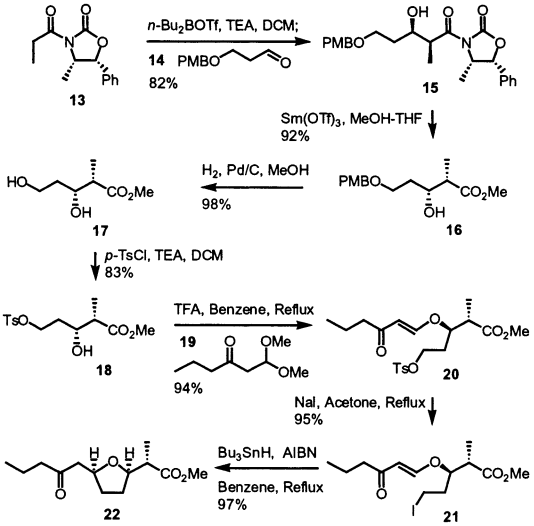
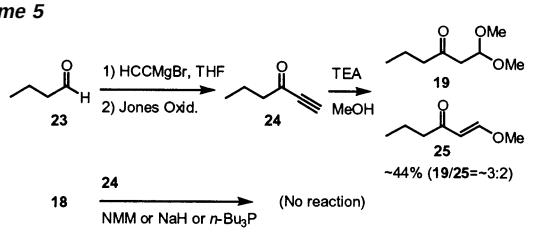
(24) For an example of radical cyclizations of β-aminovinyl ketones, see: Lee, E.; Kang, T. S.; Chung, C. K. *Bull. Kor. Chem. Soc.* **1996**, *17*, 212−214.

Scheme 4



Scheme 5



under the standard high-dilution conditions proceeded efficiently to give the tetrahydrofuranyl ketone product **22** in high yield (Scheme 4). The acetal ketone **19** and the β-methoxyvinyl ketone **25** were synthesized from butanal (**23**) via 1-hexyn-3-one (**24**). Column chromatographic separation of **19** and **25** was tedious, and the mixture of **19** and **25** could be used in place of pure **19** in the synthesis of the β-alkoxyvinyl ketone **20** with equal efficiency. Direct preparation of **20** from the reaction of **18** with **24** did not proceed in the presence of *N*-methylmorpholine, sodium hydride, or tri-*n*-butylphosphine (Scheme 5).

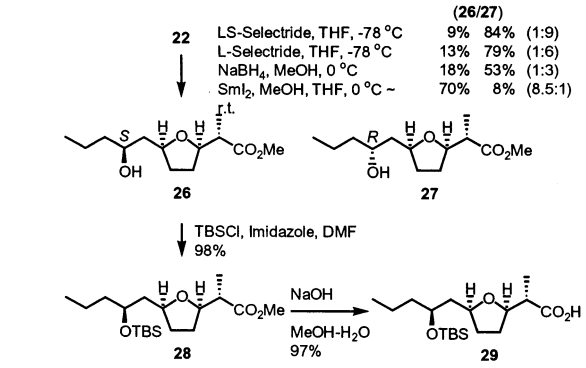
The next problem was the introduction of the stereogenic center at C8′. A number of reducing agents were tested for the stereoselective reduction of **22**. LS-Selectride and L-Selectride reduction[25] of **22** in THF at low-temperature resulted in the predominant formation of the wrong epimer **27** (9:1∼6:1). Sodium borohydride reduction afforded a 3:1 mixture of **27** and **26**.[7a] Eventually, it was found that an acceptable stereoselectivity (**26**:**27** = 8.5:1) was obtained when samarium(II) iodide[26] was used as the reducing agent in the presence of methanol (Scheme 6). TBS-protection of the hydroxy group provided the TBS ether **28**, which was converted into the carboxylic acid **29** via basic hydrolysis of the methyl ester moiety.

Synthesis of the alcohol **E** commenced with the reaction of the aldehyde **14** with the (*Z*)-boron enolate of the imide **30** (Scheme 7). The Weinreb amide **32** was obtained from the aldol imide **31** via transamination, and it was transformed into the BOM-protected derivative **33**, which was converted into the aldehyde **34** via DIBAL reduction.

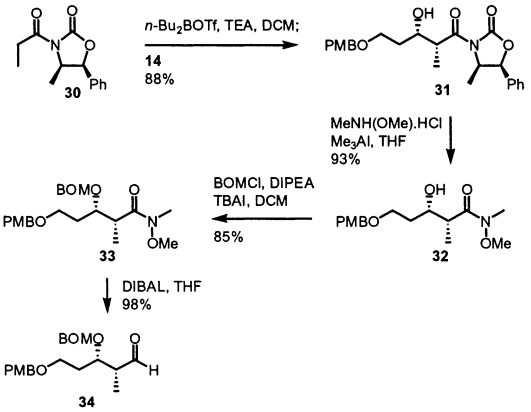
(25) Arco, M. J.; Trammell, M. H.; White, J. D. *J. Org. Chem.* **1976**, *41*, 2075−2083.

(26) (a) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693−2698. (b) Keck, G. E.; Wager, C. A. *Org. Lett.* **2000**, *2*, 2307−2309. (c) Keck, G. E.; Wager, C. A.; Sell, T.; Wager, T. T. *J. Org. Chem.* **1999**, *64*, 2172−2173.

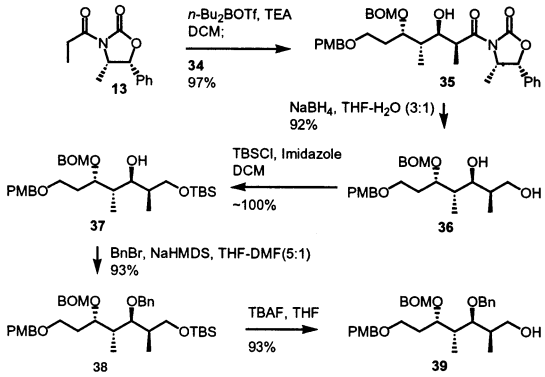
Scheme 6



Scheme 7



Scheme 8

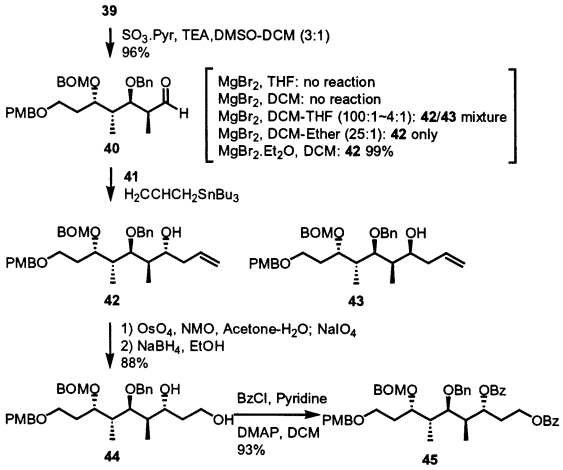


The aldol imide **35** was obtained from the reaction of **34** with the (*Z*)-boron enolate of the imide **13** in high yield. The aldol imide **35** was converted into the diol **36** via $NaBH_4$ reduction, and protection of the primary hydroxy group with TBSCl led to the formation of the secondary alcohol **37**. Benzylation of the secondary hydroxy group provided the protected tetrahydroxy intermediate **38**. The primary alcohol **39** was obtained after TBS-deprotection of **38** (Scheme 8). Generation of the four stereogenic centers in **H** was thus accomplished in a straightforward manner employing two consecutive Evans aldol reactions.

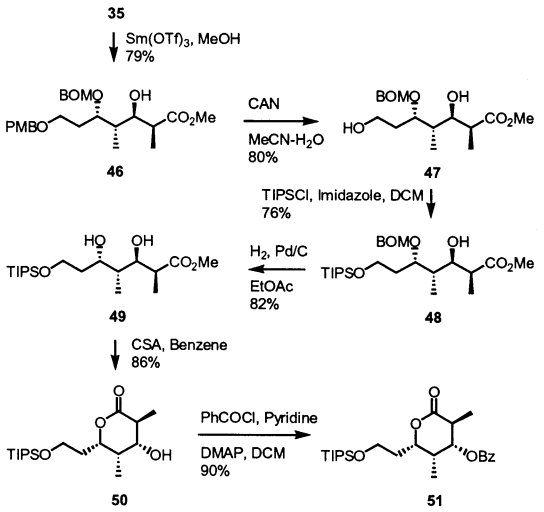
Considerable experimentation was necessary for the generation of the stereogenic center at C10, and eventually, Lewis acid-catalyzed allylation of an aldehyde intermediate was examined.[27] Oxidation of **39** with sulfur trioxide-pyridine complex led to the aldehyde **40**. Conditions for stereoselective allylation of the aldehyde **40** were examined in detail. Reaction

(27) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883−1886.

Scheme 9



Scheme 10



of **40** with allyltributylstannane (**41**) did not proceed in the presence of magnesium bromide in THF or dichloromethane. The reaction in dichloromethane-THF mixture (100:1∼4:1) in the presence of magnesium bromide yielded a mixture of the homoallylic alcohols **42** and **43**. The allylation reaction proceeded stereoselectively when **40** and **41** were allowed to react in dichloromethane-diethyl ether mixture (25:1) in the presence of magnesium bromide. Highly efficient stereoselective allylation of **40** was also achieved upon addition of allyltributylstannane (**41**) in dichloromethane in the presence of magnesium bromide-diethyl ether complex (Scheme 9). The homoallylic alcohol **42** thus obtained was converted into the diol **44** via oxidative cleavage of the double bond and sodium borohydride reduction, and subsequent benzoylation led to the dibenzoate-protected pentahydroxy intermediate **45**.

At this point, confirmation of the stereochemical assignments C6∼10 was deemed necessary. The aldol imide **35** was converted into the corresponding methyl ester **46**, which was converted into the primary alcohol **47** via PMB-deprotection. BOM-deprotection of the corresponding TIPS ether **48** led to the formation of the diol **49**. Formation of the lactone **50** from **49** was accomplished efficiently under acidic conditions, and subsequent benzoylation led to the benzoate lactone **51** (Scheme 10). NOE analysis of **51** (Figure 2) confirmed the relative stereochemical assignments at C6∼9.

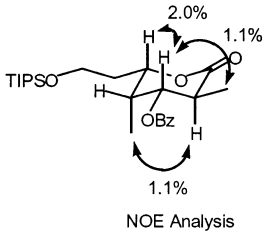
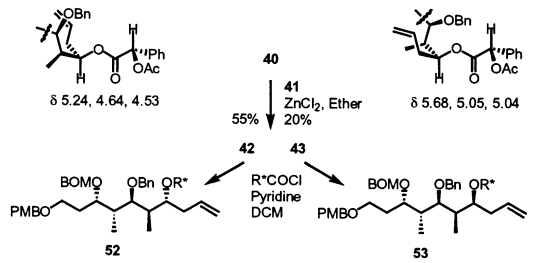
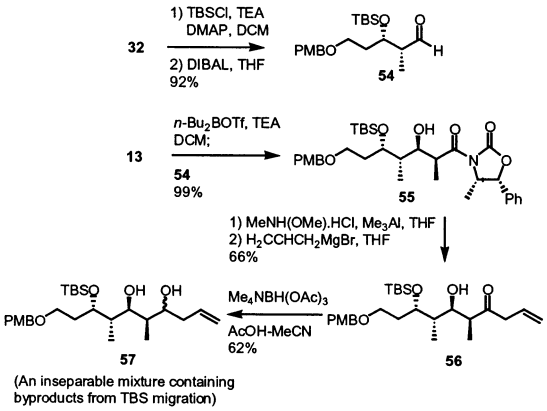


Figure 2. NOE Analysis of the Lactone **51**.

Scheme 11



Scheme 12



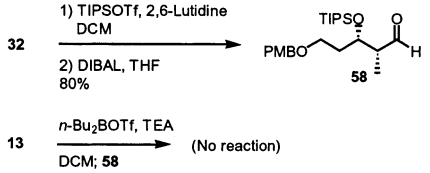
For confirmation of the stereochemistry at C10, the aldehyde **40** was allowed to react with allyltributylstannane (**41**) in ether in the presence of zinc chloride. From this reaction, the major product **42** was obtained in 55% yield, and the epimeric homoallylic alcohol **43** was obtained in 20% yield. Both were derivatized to form the *O*-acetyl (*S*)-mandelate esters[28] **52** and **53**. From inspection of NMR spectra of **52** and **53**, it was clear that the vinylic protons in **52** gave rise to signals more upfield compared to those in **53**, confirming (10*R*) configuration for **52** and (10*S*) for **53** (Scheme 11).

Unsuccessful attempts on the alternative preparation of the intermediates such as **45** may deserve some comments. The Weinreb amide **32** was converted into the corresponding TBS ether and DIBAL reduction afforded the aldehyde **54**. Reaction of the (*Z*)-boron enolate obtained from **13** and **54** proceeded in high yield to produce the aldol imide **55**. The C−C bond forming reaction between the Weinreb amide obtained from **55** and allylmagnesium bromide proceeded uneventfully to yield the hydroxy ketone **56**. Tetrabutylammonium triacetoxyborohydride reduction produced the anti/syn diol mixture **57**, but the sample was contaminated with the byproducts from TBS migration (Scheme 12).

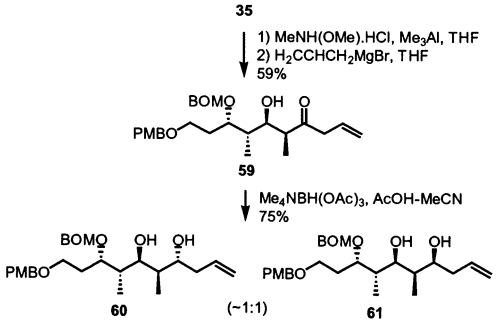
More stable protecting groups were examined. The TIPS-protected aldehyde **58** was obtained from **32** via the corre-

(28) For examples of determination of absolute stereochemistry via *O*-acetyl (*S*)-mandelate esters, see: Lee, E.; Lee, Y. R.; Moon, B.; Kwon, O.; Shim, M. S.; Yun, J. S. *J. Org. Chem.* **1994**, *59*, 1444−1456.

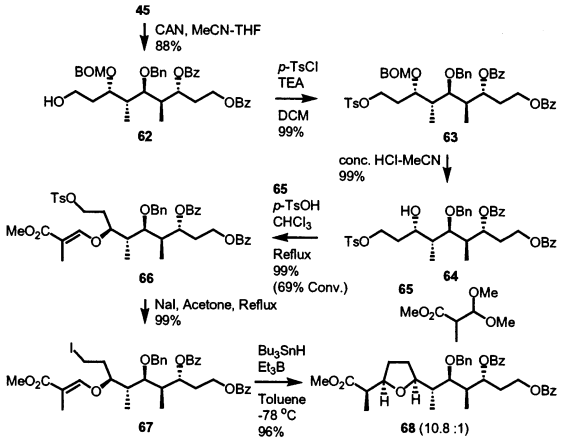
Scheme 13



Scheme 14



Scheme 15



sponding Weinreb amide, but the aldol reaction of **58** with the boron enolate generated from **13** did not proceed (Scheme 13).

Transamination of **35** and allyl Grignard reaction on the Weinreb amide led to the ketone **59**, but the subsequent reduction of **59** with tetrabutylammonium triacetoxyborohydride proceeded to give a random mixture of the anti diol **60** and the syn diol **61** (Scheme 14).

As the stereochemical integrity of **45** was ascertained, tetrahydrofuran annulation was at hand in the next stage. The alcohol **62** was obtained from **45** via PMB-deprotection with ceric ammonium nitrate. Tosylation of the primary hydroxy group in **62** led to the intermediate **63**, and the secondary alcohol **64** was prepared via BOM-deprotection under acidic conditions. Reaction of **64** with a mixture (3:2) of methyl 3,3-dimethoxy-2-methylpropanoate (**65**) and methyl β-methoxymethacrylate in the presence of an acid catalyst in chloroform provided the desired β-alkoxymethacrylate derivative **66**, which was converted into the iodide **67** via iodide substitution. Low-temperature radical cyclization reaction of **67** in toluene in the presence of tributylstannane and triethylborane proceeded efficiently producing a mixture of the tetrahydrofuranyl products favoring (10.8:1) the correct threo isomer **68** (Scheme 15).

For generation of the second tetrahydrofuran ring, the benzoate moieties in **68** were hydrolyzed to give the diol **69**, and tosylation of the primary hydroxyl group provided the

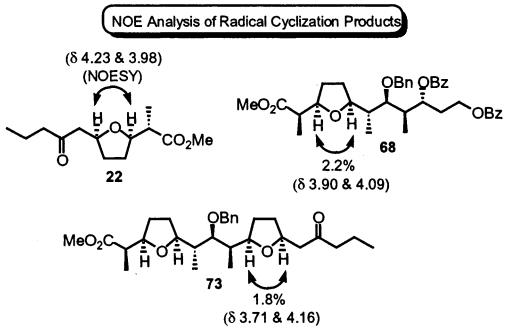
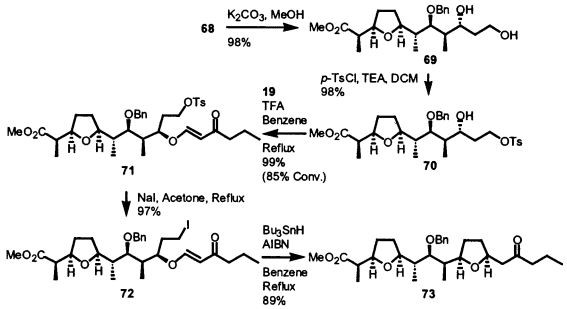


Figure 3. NOE Analysis of **22**, **68**, and **73**.

Scheme 16



alcohol **70**. The reaction of **70** with 1, 1-dimethoxyhexan-3-one (**19**) proceeded uneventfully, and the β-alkoxyvinyl ketone **71** obtained was converted into the iodide **72** via iodide substitution. Radical cyclization reaction of **72** under the standard high-dilution conditions in benzene in the presence of tributylstannane and AIBN afforded the ketone **73** in high yield as expected (Scheme 16). At this stage, it was possible to obtain pure samples of the ketone **73** by column chromatographic removal of the erythro (C2−C3) contaminant originating from the minor product in the radical cyclization step leading to **68**. Stereoselectivity in the conversion of **72** to **73** was difficult to determine, as the formation of the minor product epimeric at C13 was insignificant.

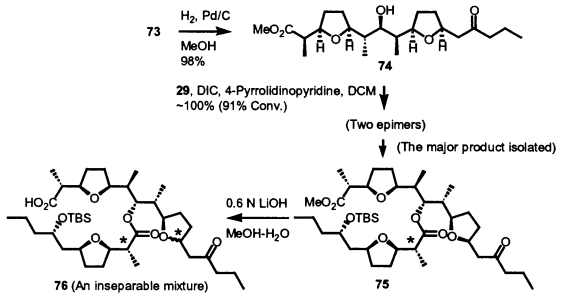
The stereochemical outcome of radical cyclization reactions in forming three tetrahydrofuran rings in **22**, **68**, and **73** was confirmed by NOE (or NOESY) analysis (Figure 3).

Debenzylation of **73** via hydrogenolysis provided the alcohol **74**. Having synthesized the carboxylic acid **29** and the alcohol **74** (**A** and **E** in Scheme 3) successfully, attention was next turned to finding conditions for the efficient esterification reaction. Use of 1, 3-diisopropylcarbodiimide and 4-pyrrolidinopyridine[29] in dichloromethane led to efficient esterification reaction between **74** and **29**, but two epimeric products were obtained. The major isomer **75** was hydrolyzed to the carboxylic acid **76** with lithium hydroxide in aqueous methanol, but it was clear that an epimeric mixture again was obtained (Scheme 17).

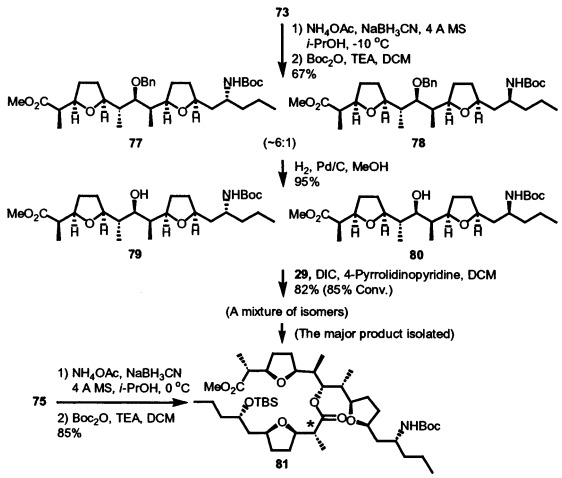
The site most vulnerable to epimerization in the hydrolysis step was thought to be C13, and an early introduction of the 15-amino group was considered to prevent epimerization at C13 via retro-Michael/Michael reaction. Reductive amination[30] on **73** and Boc-protection led to a mixture (~6:1) of the (15*R*)-amino derivative **77** and the (15*S*)-epimer **78**, which was

(29) Somers, P. K.; Wandless, T. J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 8045−8056.
(30) (a) Narasaka, K.; Ukaji, Y.; Yamazaki, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 525−533. (b) Haddad, M.; Dorbais, J.; Larchevêque, M. *Tetrahedron Lett.* **1997**, *38*, 5981−5984.

Scheme 17



Scheme 18

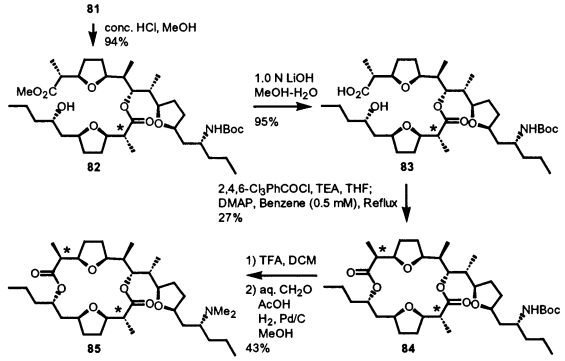


converted into the mixture of the alcohols **79**/**80** via hydrogenolysis. Reaction of the **79**/**80** mixture with the carboxylic acid **29** in the presence of 1,3-diisopropylcarbodiimide and 4-pyrrolidinopyridine yielded a mixture of isomers, and the major product **81** was obtained from column chromatographic separation. Importantly, reductive amination on **75** was highly stereoselective, and the same product **81** was obtained after Boc-protection (Scheme 18).

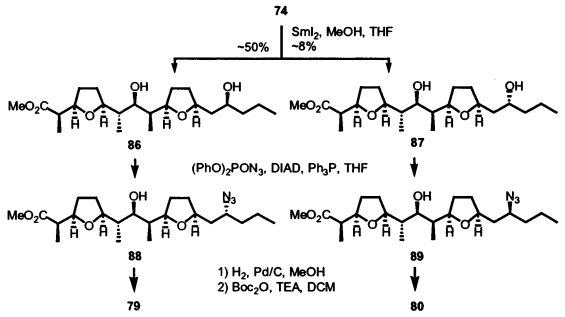
The ester **81** was converted into the alcohol **82** after TBS-deprotection under acidic conditions, and hydrolysis of **82** by lithium hydroxide in aqueous methanol proceeded without epimerization to yield the hydroxy carboxylic acid **83**. After considerable experimentation, a mixture of products was obtained from **83** under Yamaguchi esterification conditions[31] in benzene under reflux, from which a macrodiolide **84** was separated in low yield. Boc-deprotection of **84** and reductive amination in the presence of excess formaldehyde[32] led to a dimethylamino macrodiolide **85**, but it was clearly different from **1** (Scheme 19).

The product **85** was thought to be a stereoisomer of **1**, and it was decided first to confirm the stereochemical assignment at C15. Accordingly, the hydroxy ketone **74** was converted into the major diol **86** and the minor diol **87** via samarium iodide reduction. The stereochemical outcome in this conversion was assumed to follow the pattern encountered in the conversion of **22** to **26** and **27** (Scheme 20). The major diol **86** was converted into the azide intermediate **88** upon Mitsunobu-type azide substitution using diphenylphosporyl azide[33] and diisopropyl

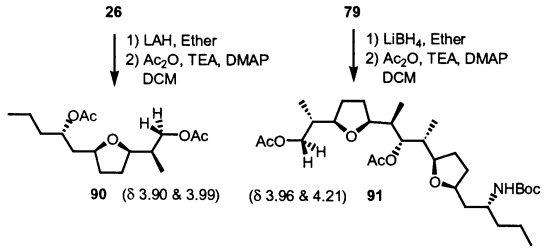
Scheme 19



Scheme 20



Scheme 21

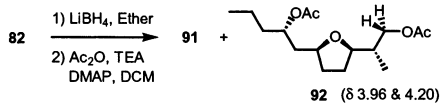


azodicarboxylate in the presence of triphenylphosphine. Hydrogenation of the azide **86** and Boc-protection led to the alcohol **79**, confirming the original assignment on C15. The minor diol **87** was converted into the epimer **80** via the corresponding azide **89**.

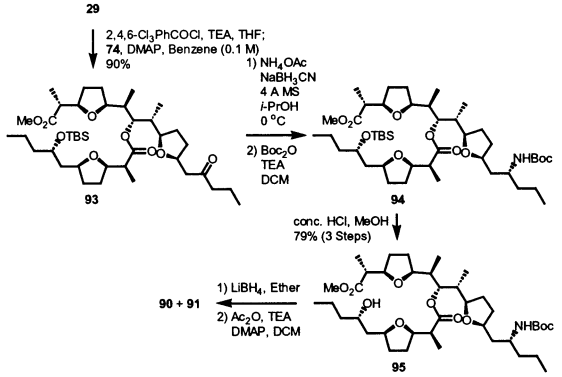
It was evident that problems arose during the esterification reactions, but pinpointing the site(s) of epimerization within the complex esters and macrodiolides proved to be quite difficult. The more viable alternative would be reductive cleavage of these intermediates and comparison of partial structures. For this purpose, the hydroxy ester **26** was reacted with lithium aluminum hydride, and the resulting diol was converted into the diacetate **90**. Similarly, the hydroxy ester **79** was reduced with lithium borohydride and the diacetate **91** was obtained after acetylation (Scheme 21). Fortunately, examination of the NMR spectra of **90** and **91** revealed a clear difference: the AB signals of the ABX system arising from the methylene protons at C1′ of **90** were centered at δ 3.90 and 3.99, and the corresponding signals from the analogous protons at C1 of **91** were more widely separated at δ 3.96 and 4.21. In other words, the erythro C2′−C3′ and the threo C2−C3 arrangements could be distinguished easily by comparing the C1′ or C1 methylene proton signals of the appropriate diacetate derivatives.

(31) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.
(32) Brouillette, W. J.; Saeed, A.; Abuelyaman, A.; Hutchison, T. L.; Wolkowicz, P. E.; McMillin, J. B. *J. Org. Chem.* **1994**, *59*, 4297−4303.
(33) Takano, S.; Sugihara, T.; Satoh, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1988**, *110*, 6467−6471.

Scheme 22



Scheme 23



The stereochemical integrity of the intermediate **81** was immediately tested. Lithium borohydride reduction of **82** and exhaustive acetylation of the resultant diols yielded the diacetate **91** and a new diacetate **92**, which exhibited signals centered at δ 3.96 and 4.20 (Scheme 22). It was now clear that formation of the major product **81** from **79**/**80** and **29** (and the major product **75** from **74** and **29**) in the presence of 1, 3-diisopropylcarbodiimide and 4-pyrrolidinopyridine had been accompanied by the epimerization at C2′.

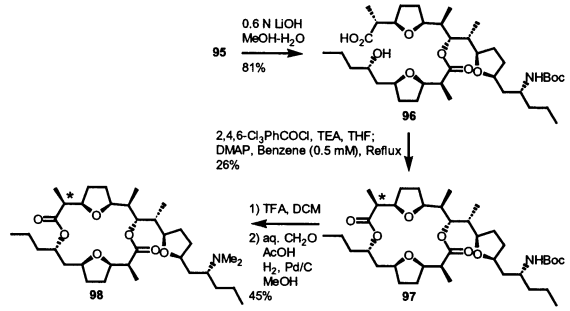
Attention was now turned to finding esterification conditions free from epimerization problems. Gratifyingly, the ester **93** was obtained in high yield from **29** and **74** following the room-temperature Yamaguchi protocol.[34] Reductive amination on **93** proceeded in high stereoselectivity as anticipated, and subsequent Boc-protection led to the ester **94**. The presence of the epimeric (at C15) product was not noticed. TBS-deprotection of **94** then led to the hydroxy ester **95** (Scheme 23). Lithium borohydride reduction of **95** and acetylation of the diols obtained produced **90** and **91** confirming the stereochemical integrity.

The seco acid **96** was obtained from lithium hydroxide hydrolysis of **95**. For macrodiolide synthesis, the seco acid **96** was subjected to the Yamaguchi esterification conditions in benzene under reflux (previously employed for conversion of **83** to **84**), and the macrodiolide **97** was obtained as the major product in low yield. Boc-deprotection of **97** and reductive amination in the presence of excess formaldehyde resulted in the formation of the dimethylamino derivative **98**, which was again clearly different from **1** (Scheme 24).

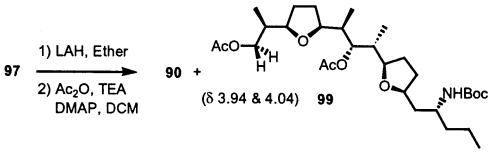
The stereochemical integrity of **97** was then checked by reduction-acetylation protocol: the macrodiolide **97** was converted into the known diacetate **90** and a new diacetate **99**, which exhibited ABX signals centered at δ 3.94 and 4.04 (Scheme 25). It was now clear that the high-temperature Yamaguchi esterification had caused epimerization at C2 in the major product **97** from **96** (and the major product **84** from **83**).

The seco acid **96** was converted back to the hydroxy ester **95** via diazomethane treatment confirming that the hydrolysis step was not the source of the problem. For the safe and efficient macrodiolide formation, a number of esterification protocols

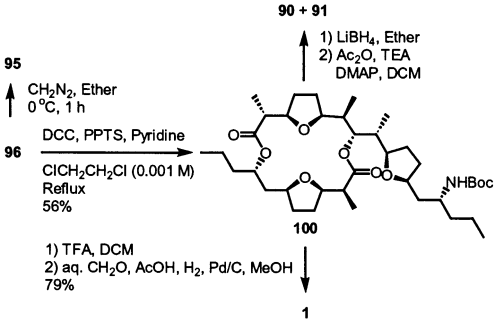
Scheme 24



Scheme 25



Scheme 26



were examined. For example, use of 2, 2′-dipyridyl disulfide and triphenylphosphine (with and without silver perchlorate) in benzene under reflux did not yield any macrodiolide product. Use of 1-methyl-2-chloropyridinium iodide and triethylamine in acetonitrile under reflux gave an intractable product mixture. Room-temperature Yamaguchi esterification did not proceed. Finally, the macrodiolide **100** was obtained in an acceptable yield by slow addition of **96** to the hot 1, 2-dichloroethane solution of 1, 3-dicyclohexylcarbodiimide, pyridine, and pyridinium tosylate[35] (Scheme 26). Lithium borohydride reduction of **100** and acetylation produced the diacetates **90** and **91** confirming the stereochemical integrity. Finally, pamamycin-607 (**1**) was prepared by Boc-deprotection of **100** under acidic conditions and reductive amination in the presence of excess formaldehyde.

In the present synthesis, the three *cis*-2, 5-disubstituted tetrahydrofuran rings in **1** were stereoselectively introduced via radical cyclization reactions of β-alkoxyvinyl ketone intermediates and a β-alkoxymethacrylate substrate. In particular, the difficulty in introducing stereogenic centers at C2, 3, 6, 7, 8, 9, 10, 13, and 15 was solved by first building stereogenic centers at C6∼10 in a systematic manner and then using two outward tetrahydrofurn-forming radical cyclization reactions. This synthesis provides another efficacious example of radical-mediated reactions for construction of complex natural products.

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Supporting Information Available: Full experimental procedures and spectral data for intermediates and **1** (46 pages, print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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