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# Total Synthesis of 10-Deoxymethynolide and Narbonolide

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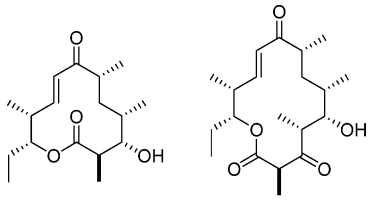


10-Deoxymethynolide (**1**) Narbonolide (**2**)

A flexible and convenient approach was developed for the synthesis of 10-deoxymethynolide (**1**) and narbonolide (**2**), which are aglycones of the methymycin and the pikromycin families of macrolide antibiotics. These lactones are produced by pikromycin polyketide synthase from *Streptomyces venezuelae*. Polyketide lactones, 10-deoxymethynolide and narbonolide, which contain 12- and 14-membered rings, respectively, were synthesized efficiently. These target lactones were retrosynthetically divided into three parts and assembled by using an asymmetric aldol reaction, the Yamaguchi esterification, and ring-closing metathesis. The ring-closing metathesis reaction catalyzed by the second-generation Grubbs catalyst is particularly efficient in preparing these macrocyclic polyketide lactones.

## Introduction

Pikromycin polyketide synthase (Pik PKS) is a enormous enzyme with the activity to produce macrolide antibiotics. Pik PKS from *Streptomyces venezuelae* produces 12- and 14-membered polyketide macrolides. Polyketide biosynthesis is achieved through the activity of PKSs, which have modular structures.[1] We became interested in developing a general synthetic route for synthesizing all the possible 12- and 14-membered polyketide lactones from the pikromycin biosynthetic pathway (Figure 1) because we realized the importance of acquiring the ability to handle and analyze polyketide lactones, which are essential for investigating the biosynthetic mechanisms aimed at combinatorial biosynthesis. In addition, these macrolide antibiotics belong to a synthetically attractive class of natural products that possess a stereochemically interesting array of stereogenic centers[2] and a potential to exhibit biological activities. Recently, neopikromycin and novapikromycin were isolated and characterized.[3] Therefore, there are possibly eight types of macrolactones (aglycones) related to the pikromycin biosynthetic pathway depending on the ring size (12- or 14-membered rings) and the oxidation pattern (locations and number of hydroxyl groups) (Figure 1).

A literature survey shows that all 12-membered lactones have been targets for synthetic efforts. The TBS-protected 10-deoxymethynolide was synthesized by Ireland using a relatively long sequence of transformations starting from a material derived from D-glucose.[4] A recent total synthesis of 10-deoxymethynolide was reported by Pilli.[5] They employed the intramolecular Nozaki−Hiyama−Kishi (NHK) reaction[6] for the key macrocyclization. Among the aglycones of the methymycin family of compounds, a great deal of synthetic effort has been focused on methynolide (**3**).[7,8] Yamaguchi examined the aglycone of neomethymycin, neomethynolide (**5**), as a target for total synthesis.[9]

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(1) Hopwood, D. A. *Chem. Rev.* **1997**, *94*, 2465.

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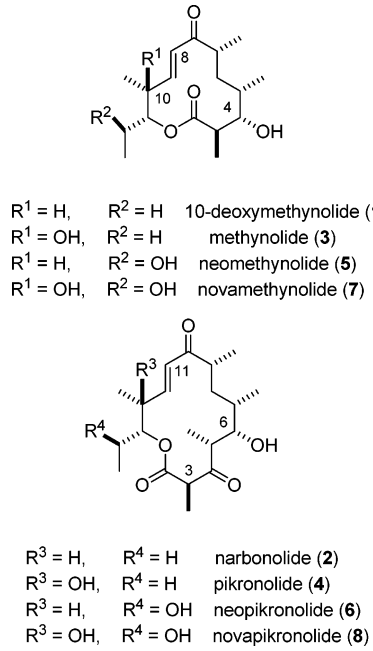
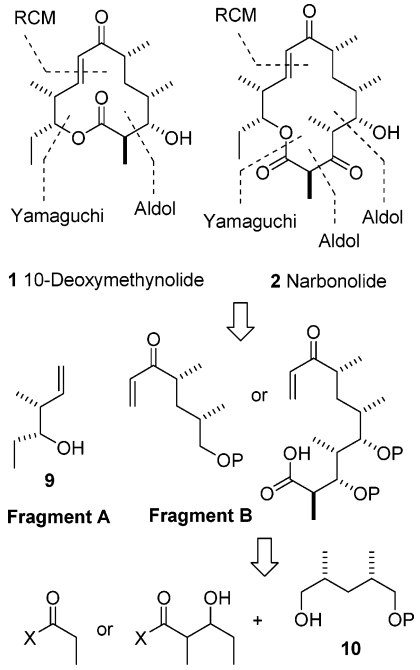



**FIGURE 1.** Polyketide macrolactones from the pikromycin biosynethic pathway.

Only a few chemical syntheses of the 14-membered lactones have been reported. Masamune reported the total synthesis of narbonolide (**2**).[10] Fecik recently reported the total synthesis of narbonolide using an intramolecular Nozaki−Hiyama−Kishi (NHK) reaction, which was previously used to synthesize 10-deoxymethynolide,[5] as a key reaction for cyclization.[11] The total synthesis of pikronolide (**4**) has been reported by Yonemitsu, who used the Horner−Wadsworth−Emmons (HWE) reaction[12] for macrocyclization.[13]

**SCHEME 1. Retrosynthetic Analysis of 10-Deoxymethynolide and Narbonolide**




10-Deoxymethynolide (**1**) and narbonolide (**2**) are the key substances from which all the other polyketide macrolactones are derived biosynthetically and possess the basic structural features for all other 12- and 14-membered lactones. Therefore, it is natural to choose these compounds as representative synthetic targets for all macrolide lactones in the pikromycin biosynthetic pathway. Herein we report the total synthesis of 10-deoxymethynolide (**1**) and narbonolide (**2**).

## Results and Discussion

For the purpose of developing a general and efficient synthetic route for all the aglycones of macrolide produced through the pikromycin biosynthetic pathways (Figure 1), a retrosynthesis of the macrolactones was performed to generate the common intermediates that could eventually be used to synthesize all the polyketide lactones.

The synthesis of 10-deoxymethynolide (**1**) [and narbonolide (**2**)] was based on the retrosynthetic analysis shown in Scheme 1. Fragment **A**, the structure of which varies according to the polyketide lactones, needs to be synthesized by a stereoselective synthesis. Fragment **B** can be further simplified to the protected diol **10** and the third fragment, which is simply chiral esters. The appropriate selection of the key cyclization method is critical for the synthesis of these lactones. For example, the Horner−Wadsworth−Emmons (HWE) reaction and Nozaki−Hiyama−Kishi (NHK) reaction were used as the most prominent

(6) Nozaki−Hiyama−Kishi reaction: (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179. (b) Okude, Y.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1977**, 3829. (c) Hiyama, T.; Okude, Y.; Kimura, Nozaki, K. H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561. (d) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281. (e) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (f) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.

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(8) Synthesis of the protected form of the methynolide seco-acid; Grieco, P. A.; Ohfune, Y.; Yokoyama, Y.; Owens, W. *J. Am. Chem. Soc.* **1979**, *101*, 4749.

(9) Total synthesis of neomethynolide: (a) Inanaga, J.; Kawamani, Y.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1521. (b) Inanaga, J.; Kawamani, Y.; Yamaguchi, M. *Chem. Lett.* **1981**, 1415.

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(11) (a) Venkatraman, L.; Aldrich, C. C.; Sherman, D. H.; Fecik, R. A. *J. Org. Chem.* **2005**, *70*, 7267. (b) Venkatraman, L.; Salomon, C. E.; Sherman, D. H.; Fecik, R. A. *J. Org. Chem.* **2006**, *71*, 9853.

(12) Horner−Wadsworth−Emmons (HWE) reaction: (a) Horner, L.; Hoffmann, H.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61. (b) Horner, L.; Hoffman, H.; Wippel. H. G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499. (c) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733. (d) Wadsworth, D. H.; Schupp, I. O. E.; Sous, E. J.; Ford, J. J. A. *J. Org. Chem.* **1965**, *30*, 680. (e) Marayanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(13) (a) Nakajima, N.; Hamada, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *J. Am. Chem. Soc.* **1986**, *108*, 4645. (b) Nakajima, N.; Tanaka, T.; Hamada, T.; Oikawa, Y.; Yonemitsu, O. *Chem. Pharm. Bull.* **1987**, *35*, 2228. (c) Nakajima, N.; Ubukata, M.; Yonemitsu, O. *Heterocycles* **1997**, *46*, 105.

methods for synthesizing lactones not to mention the esterification reaction.

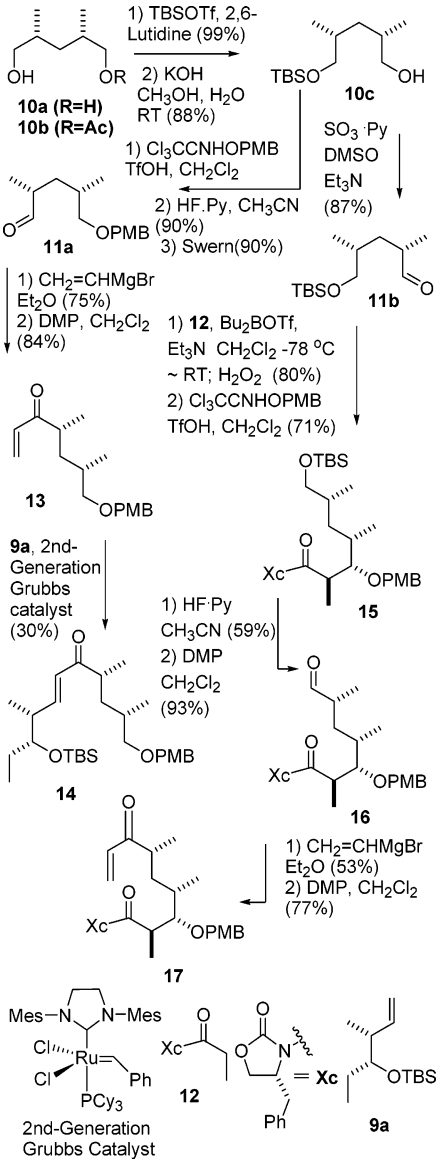
Searching for a more efficient cyclization method, it was decided to adopt the ring-closing metathesis to introduce the required trans double bond in the target polyketide lactones. The ring-closing metathesis (RCM) reaction, particularly with Grubbs catalysts, is a reliable method for synthesizing many cyclic compounds including a wide variety of natural products.[14] Although RCM reaction-based approaches to natural product synthesis have been successful, for macrocycles with more than 10-membered rings, this method sometimes suffers from a lack of control of the configuration of the double bond or from a slow reaction rate.[15] There are no reports on the synthesis of aglycones from the methymycin and pikromycin families of macrolides based on the RCM reactions.

One of the aims of this study is to develop a general and efficient synthetic route for all the aglycones of macrolides produced by the pikromycin biosynthetic pathways (Figure 1). Therefore, it was decided to break the macrolactones in a way that retrosynthesis generates the common intermediates that can be used to synthesize all polyketide lactones. The three parts generated by the retrosynthesis could be reassembled to the targets by aldol, the Yamguchi, and cross metathesis or ring-closing metathesis (RCM) reactions.

The synthesis of aglycones of the methymycin family of macrolides was first considered for the development of efficient synthetic routes for the target polyketide lactones. The total synthesis of 10-deoxymethynolide (**1**) was first examined because it is the simplest polyketide macrolactone among the aglycones of the methymycin family of macrolides. Obviously, a successful synthetic route developed for 12-membered macrolactones would be easily extended to the synthesis of the remaining 12-membered lactones as well as the 14-membered aglycones of the pikromycin family of macrolides.

Scheme 2 shows the first attempt to develop a general synthetic pathway, in which a cross-metathesis reaction was used to establish the double bond configuration at the C-8 position in 10-deoxymethynolide. The corresponding fragment **A** was prepared by a simple Wittig reaction of the previously reported aldehyde.[16] For fragment **B**, the known *syn*-1,3-dimethylated alcohol **10b** (R = Ac) was prepared from the *meso*-alcohol **10a** (R = H) by enzymatic desymmetrization with PPL.[17] Alcohol **10b** was converted to a TBS-protected alcohol **10c** by silylation followed by hydrolysis. The free hydroxy group was protected

**SCHEME 2. Attempts To Prepare the Desired Intermediates**




with a PMB group and the TBS-protected hydroxy group was deprotected. Oxidation of the resulting alcohol produced aldehyde **11a**. The vinyl ketone **13** was prepared by vinylation followed by oxidation to perform a cross-metathesis reaction. The cross-metathesis reaction with the second-generation Grubbs catalyst provided the desired $\alpha,\beta$-unsaturated ketone **14** but in only 30% yield. The low yield in the cross-metathesis step led to a search for another route. It is believed that the inefficiency in the metathesis step could be circumvented by incorporating the intramolecular metathesis reaction, i.e., a ring-closing metathesis (RCM) reaction. An attempt was made to prepare the precursor for the RCM reaction, which is also shown in Scheme 2. The aldol reaction[18] of aldehyde **11b**, which had been prepared by the oxidation of **10c**, provided the desired aldol

(14) For recent reviews on the application of the RCM reaction to the total synthesis of macrocyclic natural products, see: (a) Gradillas, A.; Perez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490. (c) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (d) Mulzer, J.; Ohler, E.; Gaich, T. Ring-closing Olefin Metathesis for Organic Synthesis. In *Comprehensive Organometallic Chemistry III*; Crabtree, R. H., Mingos, D. M. P., Eds.; Elsevier: Amsterdam, The Netherlands, 2007; Vol. 11, p 207.

(15) For a recent example for the formation of an electron-deficient double bond by RCM, see: Matsuya, Y.; Kawaguchi, T.; Nemoto, H. *Org. Lett.* **2003**, *5*, 2939.

(16) (a) Kim, S.-J.; Kang, H.-Y.; Sherman, D. H. *Synthesis* **2001**, 1790. (b) Yang, H.-H.; Kim, E.-S.; Yoon, Y. J.; Kang, H.-Y. *Bull. Korean Chem. Soc.* **2006**, *27*, 473. (c) Oh, H.-S.; Yun, J.-S.; Nah, K.-H.; Kang, H.-Y.; Sherman, D. H. *Eur. J. Org. Chem.* **2007**, 3369.

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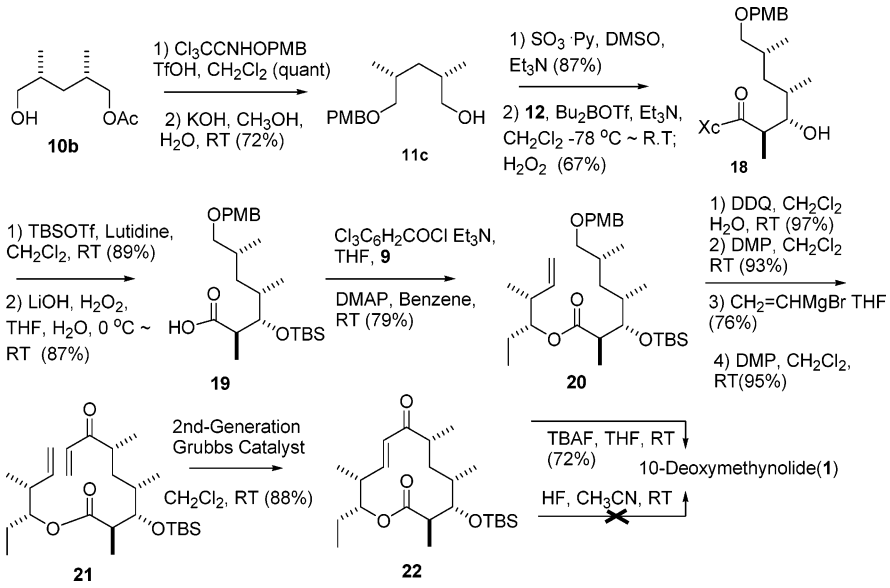
(18) Evans aldol reaction: (a) Evans, D. A; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, *53*, 1109. (c) Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*: Elsevier Academic: Amsterdam, The Netherlands, 2005; p 162 and references therein.

**SCHEME 3. Total Synthesis of 10-Deoxymethynolide (1)**




adduct that was converted to the fully protected diol **15**. After the primary TBS-protected hydroxy group was freed by HF, Dess−Martin oxidation[19] provided aldehyde **16**. Vinylation followed by oxidation offered vinyl ketone **17**. To continue the synthesis, the Evans' chiral auxiliary (Xc) should be removed. However, the standard reaction condition to eliminate the auxiliary by hydrolysis (LiOH, $H_2O_2$, THF, $H_2O$) failed to provide the desired carboxylic acid. Therefore, a change in strategy was needed. A successful synthetic route for the total synthesis of 10-deoxymethynolide (**1**) was finally developed, which is shown in Scheme 3.

The total synthesis of 10-deoxymethynolide was achieved by combining all the fragments prepared. Since the ring-closing metathesis reaction, particularly with the Grubb's catalyst, was selected as the key macrolactonization method, it is important to prepare first the key precursor for the RCM reaction. PMB-protected alcohol **11c** was prepared from **10b** by protecting the hydroxyl group (PMB) followed by hydrolysis. Oxidation ($SO_3$-pyridine, DMSO)[20] of the alcohol **11c** provided an aldehyde, which was subjected to an aldol reaction with compound **12**. An aldol reaction based on the Evans' methodology offered the product **18**. The hydroxy group was silylated (TBSOTf, lutidine) and the auxiliary was removed (LiOH, $H_2O_2$) to provide carboxylic acid **19**. The esterification of carboxylic acid **19** with alcohol **9** (as fragment **A**) was achieved to give ester **20** under the Yamaguchi conditions.[21] The PMB protecting group was removed (DDQ) and the Dess−Martin oxidation of the resulting alcohol provided the corresponding aldehyde. The Grignard reaction followed by oxidation furnished vinyl ketone **21**, which has the desired structure for the cyclization reaction. It should be noted that the vinyl Grignard reagent only added to the aldehyde with the ester group remaining intact. The critical ring-closing metathesis cyclization was successfully achieved by using the second-generation Grubbs catalyst to give the 12-membered lactone **22** in good yield (88%). As expected, only a single (trans-)stereoisomer was formed. The synthesis of 10-deoxymethynolide (**1**) was finally achieved by desilylation (TBAF, THF). HF-acetonitrile was not suitable for the desilylation of lactone **22**. Interestingly, it was reported that deprotection of lactone **22** could not be accomplished under a variety of conditions including the identical condition used successfully for desilylation (TBAF, THF).[7b] Thus, the 10-deoxymethynolide obtained showed identical spectral properties with those reported in the literature.[5]

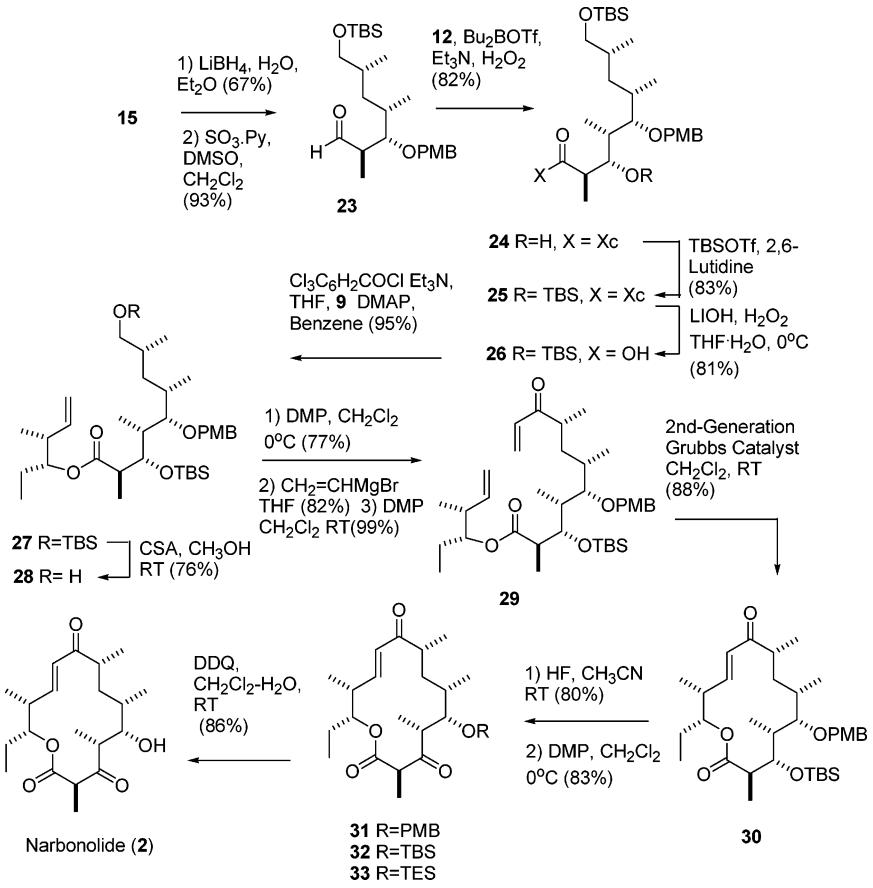
Having successfully synthesized 10-deoxymethynolide, we decided to examine the generality of this synthetic strategy to determine if it could be extended to the synthesis of 14-membered polyketide lactones. Therefore, the narbonolide (**2**) was chosen as the next synthetic target to test this strategy because it is the simplest 14-membered polyketide lactone among the aglycones from the pikromycin family of macrolides.

Scheme 2 shows the retrosynthetic analysis for narbonolide, which is similar to that shown for 10-deoxymethynolide. It was believed that another aldol reaction was required to prepare the corresponding fragment **B** and eventually for synthesizing a 14-membered ring. Total synthesis of narbonolide is shown in Scheme 4.

Aldehyde **23** for another aldol reaction was prepared from compound **15** by removing the chiral auxiliary ($LiBH_4$) followed by Parikh−Doering oxidation ($SO_3$-pyridine, DMSO). Another asymmetric aldol reaction produced aldol adduct **24**. The hydroxy group was protected by silylation, and the chiral auxiliary was removed by hydrolysis. Yamaguchi esterification with alcohol **9** provided ester **27**. The TBS group was then removed and the resulting hydroxy group was oxidized to an aldehyde with Dess−Martin periodinane. A Grignard reaction followed by oxidation provided the vinyl ketone **29**, which set the stage for the key metathesis reaction. Ring-closing metathesis (RCM) with the second-generation Grubbs catalyst generated the desired cyclized lactone **30** as a single (trans-)stereoisomer in good yield. Deprotection of the silyl group gave the secondary alcohol, which was oxidized to lactone **31**. Fortunately, the stereochemistry of the carbon bearing a methyl group at the 3-position was completely controlled and no epimerization at the 3-position was observed. Finally, the PMB group was removed to complete the total synthesis of narbonolide. The

(19) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(20) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
(21) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

**SCHEME 4. Total Synthesis of Narbonolide (2)**




spectroscopic data were matched precisely to those reported[11] and to the authentic sample.

During the synthesis, it was realized that selection of the protecting groups for the hydroxy functionality is crucial for achieving successful synthesis. This highlights the difference in reactivity between the 12- and the 14-membered ring polyketide lactones. TBS-protected narbonolide **32** was first synthesized through a similar synthetic sequence shown in Scheme 4. However, the final deprotection of the TBS group was problematic, which was unexpected and in contrast to the facile deprotection of the TBS group in the synthesis of 10-deoxymethynolide. Many typical methods (TBAF, HCOOH, TBAF/HCOOH, or $CH_3COOH$/PPTS) for desilylation failed to produce the desired product. Although HF was found to be most successful to produce narbonolide among all the conditions attempted (HF/$CH_3CN$, HF•pyridine/THF, HF•pyridine/$CH_3CN$, or HCl/$CH_3OH$), we were only able to obtain the desired narbonolide (**2**) contaminated with unidentifiable impurities that were difficult to separate. The pure nabonolide could be prepared by the reaction of the impure crude product **2** with $Et_3SiOTf$ to produce the TES-protected narbonolide **33** first, which was then easily deprotected without causing contamination to the product. The inefficiency in the final deprotection step led to the use of a better protecting group for the hydroxy group, the PMB group, as shown in Scheme 4.

In conclusion, synthetic routes were successfully developed for the total synthesis of the aglycones of the methymycin and pikromycin families of macrolide antibiotics. The synthesis of 10-deoxymethynolide (**1**) and narbonolide (**2**) was achieved in 13 and 19 steps (longest linear sequences) with 11% and 3% overall yields, respectively, from the readily available alcohol **10b**. These routes involve an asymmetric aldol reaction, the Yamaguchi cyclization, and ring-closing metathesis for the key cyclization. The efficiency of the developed synthetic routes was demonstrated by completing the total synthesis of 10-deoxymethynolide and narbonolide. The synthetic routes developed in this study were quite efficient and could be scaled up to prepare sufficient amounts of materials for further studies. Research on the synthesis of other aglycones of the methymycin and pikromycin families of macrolide antibiotics is currently underway.

## Experimental Section

**(*E*)-(3*R*,4*S*,5*S*,7*R*,11*R*,12*R*)-4-(*tert*-Butyldimethylsilanyloxy)-12-ethyl-3,5,7,11-tetramethyloxacyclododec-9-ene-2,8-dione (22).** A flame-dried round-bottomed flask was charged with a solution of vinyl ketone **21** (8.5 mg, 19 $\mu$mol) in $CH_2Cl_2$ (4 mL). Grubbs catalyst (second generation) (0.8 mg, 0.95 $\mu$mol) was subsequently added as a solid, producing a light brown solution that was stirred for 12 h at room temperature. The mixture was then concentrated to give a dark brown oil. Purification of this residue by flash chromatography (hexane:EtOAc = 7:1) afforded the lactone **22** (7.0 mg, 88%) as a colorless oil: $[\alpha]^{25.0}_D$ +87.7 (*c* 1.20, $CHCl_3$); IR (film) $\nu_{max}$ 2926, 2885, 1727, 1693, 1627, 1461, 1376, 1322, 1257, 1168, 1137, 1091, 978, 837, 775, 686 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$,) $\delta$ 0.06 (s, 3H), 0.07 (s, 3H), 0.90 (t, $J$ = 7.3 Hz, 3H), 0.90 (s, 9H), 0.93 (d, $J$ = 6.6 Hz, 3H), 1.10 (d, $J$ = 6.8 Hz, 3H), 1.21 (d, $J$ = 6.8 Hz, 6H), 1.20−1.40 (m, 1H), 1.45−1.80 (m, 4H), 2.40−2.57 (m, 1H), 2.57−2.70 (m, 2H), 3.61 (d, $J$ = 10.0 Hz, 1H), 4.96 (ddd, $J$ = 8.1, 5.5, 2.2 Hz, 1H), 6.42 (dd, $J$ = 15.7, 0.7 Hz, 1H), 6.74 (dd, $J$ = 15.7, 5.4 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$

205.1, 175.3, 146.9, 125.8, 79.3, 73.4, 45.0, 44.2, 37.8, 34.2, 33.6, 26.8, 26.2, 25.1, 18.5, 18.4, 17.8, 17.2, 10.3, 9.5, −3.1, −3.3; HRMS calcd for $C_{23}H_{42}O_4Si$ 410.2852, found 410.2863.

**10-Deoxymethynolide (1).** To a stirred solution of lactone **22** (11.0 mg, 0.0268 mmol) in dry THF (1 mL) at room temperature was added TBAF (1.0 M in THF) (268 $\mu$L, 0.268 mmol) via a syringe. After 2.5 h, the reaction mixture was concentrated. Purification by flash chromatography on a silica gel column (hexane:EtOAc = 2:1) afforded 10-deoxymethynolide (**1**) (5.7 mg, 72%) as a colorless oil: $[\alpha]^{26.9}_D$ +94.1 (*c* 0.42, $CHCl_3$); IR (film) $\nu_{max}$ 3479, 2966, 1724, 1627, 1457, 1376, 1326, 1276, 1172, 1083, 987, 894, 809, 736 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.91 (t, $J$ = 7.4 Hz, 3H), 1.0 (d, $J$ = 7.2 Hz, 3H), 1.12 (d, $J$ = 6.8 Hz, 3H), 1.22 (d, $J$ = 7.0 Hz, 3H), 1.30 (d, $J$ = 6.8 Hz, 3H), 1.2−1.37 (m, 2H), 1.47−1.78 (m, 4H), 2.46−2.66 (m, 3H), 3.56 (dd, $J$ = 10.4 Hz, 1H), 5.00 (ddd, $J$ = 8.5, 5.5, 2.3 Hz, 1H), 6.42 (dd, $J$ = 15.7, 1.1 Hz, 1H), 6.75 (dd, $J$ = 15.8, 5.4 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 204.9, 174.7, 147.1, 125.6, 78.2, 73.7, 45.1, 43.3, 38.0, 33.2, 25.1, 17.7, 17.4, 16.4, 10.3, 9.5; HRMS calcd for $C_{17}H_{28}O_4$ 296.1988, found 296.1989.

**(*E*)-(3*R*,4*S*,5*R*,6*S*,7*S*,9*R*,13*R*,14*R*)-4-(*tert*-Butyldimethylsilanyloxy)-14-ethyl-6-(4-methoxybenzyloxy)-3,5,7,9,13-pentamethyloxacyclotetradec-11-ene-2,10-dione (30).** A flame-dried round-bottomed flask was charged with vinyl ketone **29** (128 mg, 0.207 mmol) and $CH_2Cl_2$ (20 mL). Grubbs catalyst (second-generation) (35.2 mg, 0.0414 mmol) was subsequently added as a solid, producing a light brown solution that was stirred for 12 h at room temperature. The mixture was then concentrated. Purification of this residue by flash chromatography (hexane:EtOAc = 5:1) afforded the lactone **30** (108 mg, 88%) as a yellow liquid: $[\alpha]^{26.0}_D$ +28.9 (*c* 1.11, $CHCl_3$); IR (film) $\nu_{max}$ 2931, 1932, 1731, 1693, 1623, 1511, 1461, 1380, 1249, 1172, 1060, 833, 775 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.11 (d, $J$ = 17.7 Hz, 6H), 0.90 (m, 3H), 0.94 (s, 9H), 1.03 (d, $J$ = 7.0 Hz, 3H), 1.06 (d, $J$ = 7.0 Hz, 3H), 1.12 (m, 6H), 1.15(d, $J$ = 2.8 Hz, 3H), 1.33(m, 3H), 1.54 (m, 2H), 1.76 (m, 2H), 2.58 (m, 3H), 3.19 (d, $J$ = 9.3 Hz, 1H), 3.79 (m, 1H), 3.80 (s, 3H), 4.46 (ddd, $J$ = 10.5, 10.5, 10.5 Hz, 2H), 5.01 (ddd, $J$ = 7.2, 5.2, 1.9 Hz, 1H), 6.22 (dd, $J$ = 15.7, 1.8 Hz, 1H), 6.87 (d, $J$ = 8.6 Hz, 2H), 7.08 (dd, $J$ = 17.8, 4.6 Hz, 1H), 7.26 (d, $J$ = 8.5 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 202.8, 176.4, 159.0, 150.0, 131.1, 129.0, 122.6, 113.7, 84.7, 76.1, 75.3, 72.2, 55.3, 45.1, 45.0, 44.9, 38.8, 34.7, 34.5, 26.3, 25.0, 19.0, 18.6, 17.7, 14.8, 10.5, 10.3, 9.1, −3.1, −3.8; HRMS calcd for $C_{34}H_{56}O_6Si$ $[M + Na]^+$ 611.3744, found 611.3741.

**(*E*)-(3*R*,5*R*,6*S*,7*S*,9*R*,13*R*,14*R*)-14-Ethyl-6-(4-methoxybenzyloxy)-3,5,7,9,13-pentamethyloxacyclotetradec-11-ene-2,4,10-trione (31).** To a solution of lactone **30** (25.0 mg, 0.0424 mmol) and $CH_3CN$ (1 mL) at room temperature was added a solution of [HF:$H_2O$:$CH_3CN$ (v/v/v) = 1:0.5:8.5] (4 mL). After the mixture was stirred for 17 h, it was neutralized with saturated $NaHCO_3$ (10 mL) and extracted with ether (3 × 10 mL). The combined organic solution was washed with aqueous saturated NaCl (10 mL) then dried ($MgSO_4$) and concentrated. Purification by flash chromatography (hexane:EtOAc = 5:1) afforded the desired alcohol (16.0 mg, 80%) as a colorless oil: $[\alpha]^{19.1}_D$ +28.1 (*c* 1.00, $CHCl_3$); IR (film) $\nu_{max}$ 3494, 2966, 1724, 1619, 1511, 1457, 1376, 1249, 1172, 1049, 983, 825 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.91 (t, $J$ = 7.4 Hz, 3H), 1.01 (m, 6H), 1.09 (m, 6H), 1.27 (d, $J$ = 6.6 Hz, 3H), 1.77−1.40 (m, 3H), 1.98 (m, 2H), 2.35 (m, 1H), 2.66(m, 4H), 3.55 (t, $J$ = 4.1 Hz, 1H), 3.76 (d, $J$ = 9.8 Hz, 1H), 3.81 (s, 3H), 4.47 (ddd, $J$ = 10.8, 10.8, 10.8 Hz, 2H), 5.14 (ddd, $J$ = 4.8, 3.2, 1.7 Hz, 1H), 6.07 (d, $J$ = 16.4 Hz, 1H), 6.81 (dd, $J$ = 16.3, 6.1 Hz, 1H), 6.89 (d, $J$ = 8.5 Hz, 2H), 7.20 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 204.3, 176.2, 159.3, 149.4, 130.1, 129.5, 126.9, 114.0, 84.1, 75.9, 71.7, 55.3, 43.8, 40.8, 39.3, 38.9, 37.3, 32.5, 29.7, 25.3, 17.0, 15.2, 15.0, 11.8, 10.4, 8.1; HRMS calcd for $C_{28}H_{42}O_6$ $[M + Na]^+$ 497.2879, found 497.2874.

The alcohol (16.0 mg, 0.0337 mmol) prepared as described in the previous procedure was dissolved in $CH_2Cl_2$ (3 mL). To this solution was added Dess−Martin periodinane (DMP) (28.6 mg, 0.0674 mmol). The resulting solution was stirred for 30 min at room temperature. After the reaction was completed, aqueous saturated $NaHCO_3$ (5 mL) was added and the mixture was extracted with $CH_2Cl_2$ (3 × 5 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane:EtOAc = 7:1) offered the desired ketone **31** (13.2 mg, 83%) as a colorless oil: $[\alpha]^{25.5}_D$ +83.1 (*c* 0.38, $CH_2Cl_2$); IR (film) $\nu_{max}$ 2966.0, 1739.5, 1700.9, 1623.8, 1511.9, 1457.9, 1373.1, 1303.6, 1249.7, 1184.1, 1068.4, 987.4, 821.5, 736.7 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.90 (t, $J$ = 7.3 Hz, 3H), 1.01 (d, $J$ = 6.6 Hz, 3H), 1.09 (t, $J$ = 7.4 Hz, 6H), 1.23 (m, 1H), 1.28 (d, $J$ = 7.5 Hz, 3H), 1.36 (d, $J$ = 7.0 Hz, 3H), 1.64−1.51 (m, 4H), 2.63 (m, 1H), 2.70 (m, 1H), 2.84 (dddd, $J$ = 7.3, 7.3, 7.3, 7.3 Hz, 1H), 3.80 (s, 3H), 3.82 (m, 1H), 3.90 (d, $J$ = 5.8 Hz, 1H) 4.49 (s, 2H), 4.94 (ddd, $J$ = 7.5, 7.5, 2.9 Hz, 1H), 6.30 (dd, $J$ = 15.8, 1.2 Hz, 1H), 6.74 (dd, $J$ = 15.8, 6.1 Hz, 1H), 6.88 (d, $J$ = 8.6 Hz, 2H), 7.28 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 208.2, 203.1, 169.5, 159.2, 147.6, 130.7, 129.3, 126.9, 113.7, 79.5, 78.4, 73.7, 55.3, 50.7, 49.2, 43.0, 38.4, 35.8, 29.7, 23.2, 17.8, 16.0, 14.4, 13.8, 12.1, 10.5; HRMS calcd for $C_{28}H_{40}O_6$ 472.2825, found 472.2823.

**Narbonolide (2).** To a solution of ketone **31** (7.7 mg, 0.016 mmol) in $CH_2Cl_2$:$H_2O$ [10:1 (v/v), 3 mL] was added dichlorodicynoquinone (DDQ) (5.4 mg, 0.024 mmol) at 0 °C. The solution was stirred for 2 h. After the reaction was completed, the solution was filtered through a pad of Celite. The Celite pad was washed with $CH_2Cl_2$ (3 × 10 mL). After the combined filtrate was concentrated, purification by flash chromatography (hexane/EtOAc = 2:1) provided the desired narbonolide (**2**) as a white solid (4.9 mg, 86%): mp 124.6−125.5 °C; $[\alpha]^{27.4}_D$ +68.7 (*c* 0.08, $CH_2Cl_2$); IR (film) $\nu_{max}$ 3475, 2927, 1735, 1627, 1457, 1376, 1257, 1187, 1099, 1022, 806 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.93 (t, $J$ = 7.3 Hz, 3H), 0.93 (d, $J$ = 7.3 Hz, 3H), 1.09 (d, $J$ = 6.8 Hz, 3H), 1.13 (d, $J$ = 7.0 Hz, 3H), 1.14 (d, $J$ = 6.9 Hz, 3H), 1.36 (d, $J$ = 7.0 Hz, 3H), 3.04 (m, 1H), 3.71 (q, $J$= 7.1 Hz, 1H), 3.86 (q, $J$ = 4.8 Hz, 1H), 5.15 (m, 1H), 6.10 (dd, $J$ = 16.3, 1.8 Hz, 1H), 6.91 (dd, $J$ = 16.3, 4.8 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 207.6, 205.1, 171.1, 148.5, 128.9, 78.0, 72.6, 50.2, 39.5, 38.8, 36.4, 34.9, 24.2, 18.6, 18.3, 14.3, 10.8, 10.6, 10.4; HRMS calcd for $C_{20}H_{32}O_5$ 352.2250, found 352.2248.

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**Supporting Information Available:** Experimental procedures and characterization of compounds **10c**, **11b**−**c**, **15**, **18**−**21**, and **23**−**29**, and $^1H$ NMR and $^{13}C$ NMR spectra of compounds **1**, **2**, **10c**, **11b**−**c**, **15**, **18**−**22**, and **23**−**31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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