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Stereocontrolled Total Synthesis of Amphidinolide X via a Silicon-Tethered Metathesis Reaction

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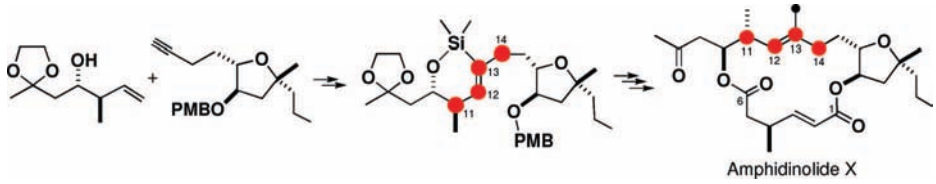
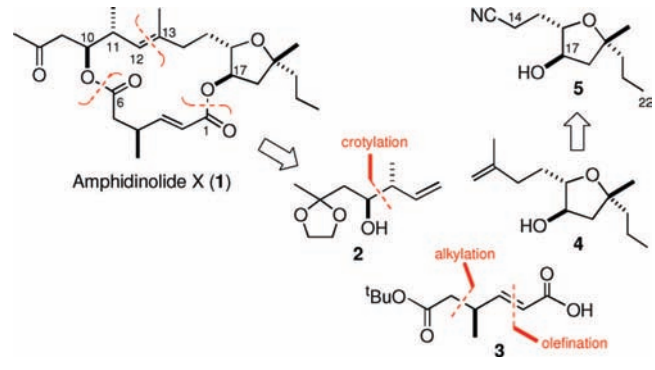
ABSTRACT



Two esterifications and an RCM to create the challenging trisubstituted C12−C13 double bond were required in the total synthesis of amphidinolide X (1) reported here. Assembling the three fragments in this order, no RCM occurred or the process yielded mainly isomer *Z*. However, generating the *E* double bond first, by a new variant of a Si-tethered metathesis (using Schrock's catalyst), and carrying out the esterification and macrolactonization steps later, 1 was obtained exclusively.

Among the long series of cytotoxic macrolides isolated from Amphidinium dinoflagellates,[1] amphidinolide X (**1**) is remarkable for its unusual nonsymmetric diolide structure,[2] which has attracted the attention of synthetic groups[3] since its discovery in 2003. We report a total synthesis of **1**, based on a Si-tethered metathesis reaction and a suitable macrolactonization. Our initial retrosynthetic analysis[4] is shown in Scheme 1. Three fragments (**2**−**4**) resulted from the disconnections of the ester groups and the C12−C13 double bond.

Scheme 1. Retrosynthetic Analysis of **1**



We describe here efficient syntheses of **2** and **3** and the problems encountered during the assembly of **2**−**4**. The challenge was the generation of a trisubstituted *E* alkene by a ring-closing metathesis (RCM) reaction.

Fragment **2** was built from aldehyde **6** (Scheme 2) arising from ethyl acetoacetate in three steps.[5] The reaction of **2** with the crotyltitanium reagent **7**, obtained from TADDOL,[6]

(1) Recent reviews: (a) Kobayashi, J.; Kubota, T. *J. Nat. Prod.* **2007**, *70*, 451. (b) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77.

(2) Tsuda, M.; Izui, N.; Shimbo, K.; Sato, M.; Fukushi, E.; Kawabata, J.; Katsumata, K.; Horiguchi, T.; Kobayashi, J. *J. Org. Chem.* **2003**, *68*, 5339.

(3) First total synthesis of **1**: (a) Fürstner, A.; Kattnig, E.; Lepage, O. *J. Am. Chem. Soc.* **2006**, *128*, 9194. Preliminary communication: (b) Lepage, O.; Kattnig, E.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 15970. For tetrahydrofuran-containing fragments, see: (c) Chen, Y.; Jin, J.; Wu, J.; Dai, W.-M. *Synlett* **2006**, 1177. (d) Rodríguez-Escrich, C.; Olivella, A.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2007**, *9*, 989. (e) Doan, H. D.; Gallon, J.; Piou, A.; Vatèle, J.-M. *Synlett* **2007**, 983. During the preparation of this paper, a different total synthesis of **1** has appeared: (f) Dai, W.-M.; Chen, Y.; Jin, J.; Wu, J.; Lou, J.; He, Q. *Synlett* **2008**, 1737.

(4) As planned in 2004. The strategy had to be modified in 2007: Rodríguez-E., C. Ph.D. Thesis, Universitat de Barcelona, 2008.

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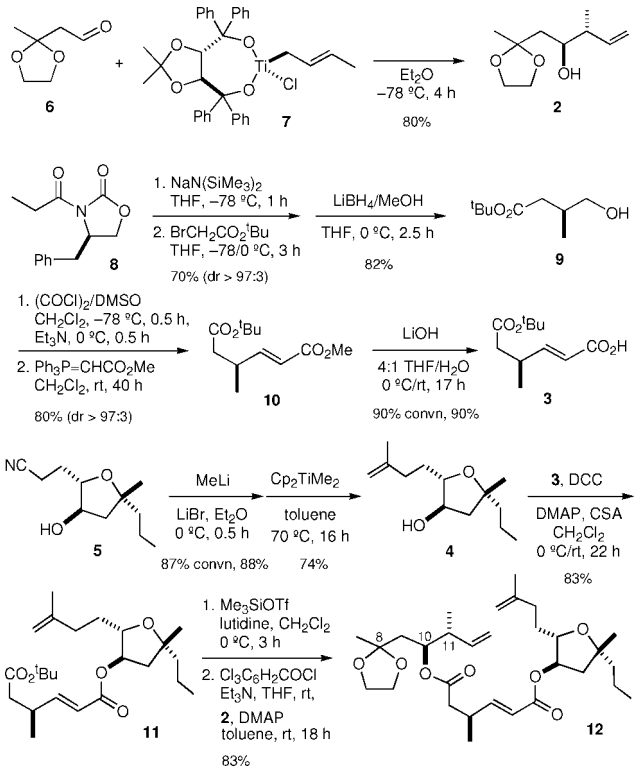
provided the desired homoallylic alcohol **2**. The stereocenter of fragment **3** was created by alkylation of the *N*-propanoyl derivative of the D-Phe-derived chiral auxiliary (**8**) with *tert*-butyl bromoacetate.[7] The removal of the auxiliary with $LiBH_4$/MeOH[8] in THF gave alcohol **9**, which was converted to **10** by a standard two-step procedure. The features of **10** allowed the selective hydrolysis of its methyl ester to furnish carboxylic acid **3**. Assembly of **4** (prepared from **5**)[3d] with **3** and later with **2** was carried out as also indicated in Scheme 2.

Scheme 2. Synthesis and Assembly of Fragments **2**−**4**

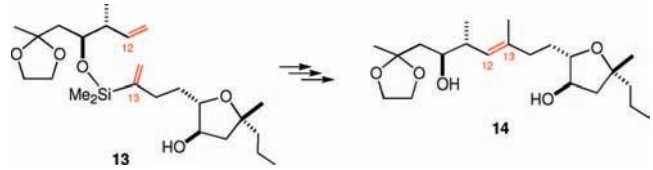


The resulting compound **12** was ready to be subjected to an RCM[9] that could give rise to the trisubstituted double bond of **1**. Provided that the macrocyclization took place, it was not clear whether the desired *trans* (*E*) isomer would predominate over the *cis* (*Z*) isomer, as there are few related cases on which to base predictions[10] and the failures are very common. Actually, simple variations in ring size and/or the number and position of substituents and characteristic groups[9] may lead to success or to a disaster (in the ultimate key step of a total synthesis!).

Unfortunately, none of our attempts to cyclize **12**, its keto derivative (C8-deprotected **12**), and a diastereomer of **12** (with inverted configurations at C10 and C11) using different amounts of the most promising[10] Grubbs II or Hoveyda−Grubbs II reagents were successful (>50% of unreacting starting material was recovered in most cases). In two trials (with the above-mentioned diastereomer), we isolated the *Z* isomers in 30−40% yields, exclusively.

Therefore, an alternative strategy had to be considered (Scheme 3). Fragment **2** was linked first to a fragment derived from **5** to give **13**. The challenging C12−C13 double bond was then created (see **14**), and finally fragment **3** was incorporated.

Scheme 3. Alternative Strategy



The hydroxy group of **5** was protected and then the cyano group was converted into a terminal alkyne by reduction to aldehyde **15** followed by a Corey−Fuchs homologation[11] (Scheme 4) to give **16**. The terminal triple bond was hydrosilylated with dimethylchlorosilane using the Trost catalyst,[12] and the resulting chlorosilane was coupled in situ with alcohol **2** to produce **17** (PMB-protected **13**). The RCM

(5) (a) Oishi, T.; Nagai, M.; Ban, Y. *Tetrahedron Lett.* **1968**, *9*, 491. (b) Uchino, K.; Yamagiwa, Y.; Kamikawa, T.; Kubo, I. *Tetrahedron Lett.* **1985**, *26*, 1319.

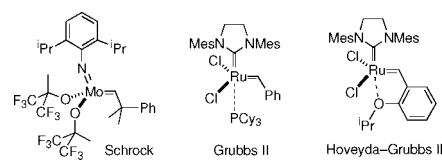
(6) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321.

(7) Evans, D. A.; Wu, L. D.; Wiener, J. J. M.; Johnson, J. S.; Ripin, D. H.; Tedrow, J. S. *J. Org. Chem.* **1999**, *64*, 6411.

(8) (a) Soai, K.; Ookawa, A. *J. Org. Chem.* **1986**, *51*, 4000. (b) Penning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, 307. (c) Evans, D. A.; Gage, J. R. *J. Org. Chem.* **1992**, *57*, 1958.

(9) Very recent reviews on RCM: (a) Coquerel, Y.; Rodriguez, J. *Eur. J. Org. Chem.* **2008**, 1125. (b) Kotha, S.; Lahiri, K. *Synlett* **2007**, 2767. (c) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243. (d) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490. (e) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117.

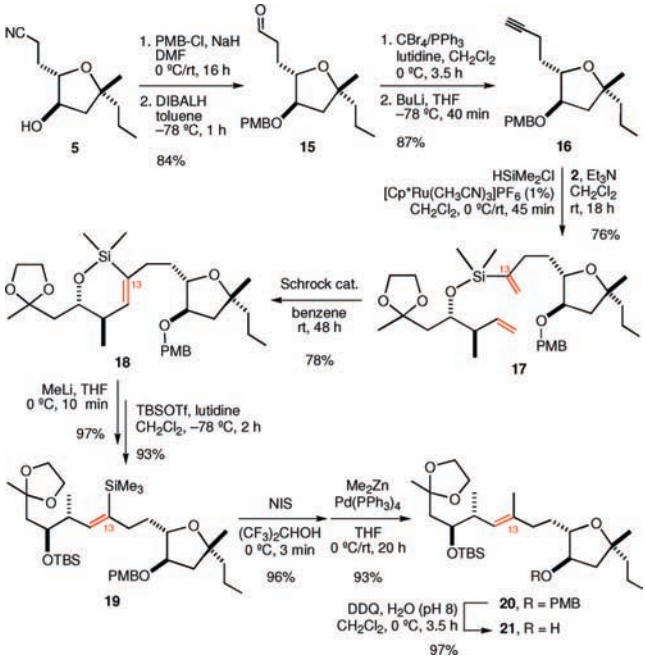
(10) (a) Xu, Z.; Johannes, C. W.; Salman, S. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 10926 ("primer" work on RCM, 14-membered lactam, *Z*, Schrock catalyst). (b) Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302. (c) Fürstner, A.; Thiel, O. R.; Ackermann, L. *Org. Lett.* **2001**, *3*, 449 (14-membered lactone, *E*, Grubbs II-type initiator) and references therein. (d) Park, P. K.; O'Malley, S. J.; Schmidt, D. R.; Leighton, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 2796 (22-membered, low *E*/*Z* ratio, dolabelide, Grubbs II, eventually 31% yield of *E*). (e) Smith, A. B., III; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2006**, *128*, 5292 (kendomycin, only cis, four steps to isomerize the double bond later). (f) Jin, J.; Chen, Y.; Li, Y.; Wu, J.; Dai, W.-M. *Org. Lett.* **2007**, *9*, 2585 (17-membered, amphidinolide Y, *E*, 50 mol % Grubbs II, but not H−G II and Schrock reagents). (g) Tietze, L. F.; Brazel, C. C.; Hölsken, S.; Magull, J.; Ringe, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 5246 (14-membered, terpenoid, *Z*, Grubbs II). (h) Dai et al., see ref 3f (three precursors of amphidinolide X different from ours, viz. C8-OR derivatives, and three catalysts tested; in the best case, 19% of the desired *E* isomer after 6 days in refluxing CH_2Cl_2). For a related case, see the coleophomones of Nicolaou et al. (ref 9d).



(11) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769.

(12) (a) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2001**, *123*, 12726. (b) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2005**, *127*, 17644.

Scheme 4. Synthesis of **21** via Si-Tethered RCM



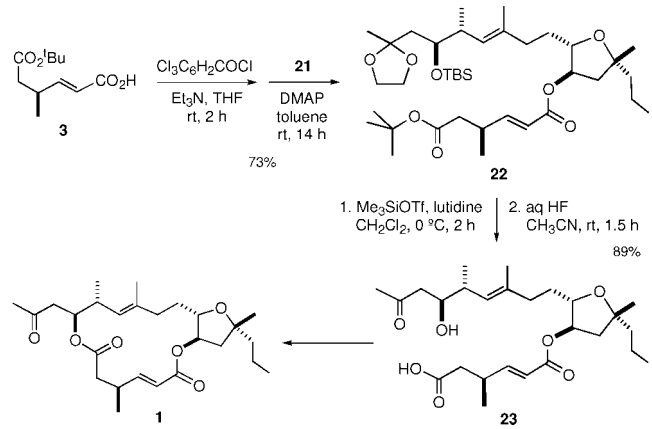
of this silicon-tethered diene in the presence of the Schrock reagent[13] gave the desired siloxane **18** in 78% yield.[14]

We examined different methods of cleaving the tether, that is, to convert the C−Si bond to a C−Me bond, on a model compound (3,6-diethyl-2,2-dimethyl-1-oxa-2-sila-3-cyclohexene). In our case, Hiyama coupling[15] with MeI was unproductive. Generation of the pentacoordinate silicon species by addition of MeLi, followed by trapping with CuBr•Me_2S[16] and MeI, did not furnish the desired compound either.

We had to rely upon a lengthier, novel sequence to add the Me group on C13 (Scheme 4). The tether was cleaved by addition of MeLi to give a hydroxyvinylsilane, which was protected (TBS ether **19**). The $SiMe_3$ group was then converted to a Me group by iododesilylation with *N*-iodosuccinimide in $(CF_3)_2CHOH$[17] and Negishi coupling of the resulting iodoalkene with Me_2Zn.[18] The PMB−O bond of **20** was then cleaved with DDQ. We thus reached the *E* double bond of **21** (a TBS-protected derivative of **14**) in a stereocontrolled manner, which would have been difficult to achieve by olefination of a carbonyl compound.

Reaction of carboxylic acid **3** with alcohol **21** (Scheme 5) was carried out by activation of the carboxyl group as its mixed anhydride, with $(2,4,6\text{-}Cl_3C_6H_2)COCl$ and Et_3N, followed by reaction with the alcohol in the presence of DMAP, according to the method of Yamaguchi et al.[19] Treatment of **22** with Me_3SiOTf/2,6-lutidine cleaved both the *tert*-butyl ester and the acetal moiety. Finally, the TBS group was removed with aqueous HF in CH_3CN to give **23**, a seco-acid ready to be subjected to macrolactonization under high-dilution conditions.

Scheme 5. The Endgame



The macrocyclization of **23** to **1** was examined via the Yamaguchi et al. procedure[19] and via the Shiina et al. method (formation of a mixed anhydride by exchange with 2-methyl-6-nitrobenzoic anhydride, MNBA).[20] The results are shown in Table 1. Entry 3 is the protocol of choice, to date, as it gave **1** in higher yield (42%).

In summary, a new and efficient synthesis of amphidinolide X (**1**) has been achieved that relies upon the assembly of the fragments by means of the Shiina macrolactonization procedure and by using a temporary Si-tether for the key construction of the *E* double bond. Although it has required three additional steps (to cleave the tether with MeLi, to

(13) It has been demonstrated that this kind of compounds cannot be cyclized using Ru initiators: (a) Chang, S.; Grubbs, R. H. *Tetrahedron Lett.* **1997**, *38*, 4757. (b) Barrett, A. G. M.; Beall, J. C.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Salter, M. M. *J. Org. Chem.* **2000**, *65*, 6508.

(14) For related Si-tethered cyclizations, see: (a) Gaich, T.; Mulzer, J. *Org. Lett.* **2005**, *7*, 1311 (disiloxane tether, G II and H−G II, trisubstituted olefin, *Z*/*E* 5:1). For other temporary Si-tethered cyclizations (standard *cis* double bonds), see: (b) Denmark, S. E.; Yang, S.-M. *Tetrahedron* **2004**, *60*, 9695. (c) Evans, P. A.; Cui, J.; Buffone, G. P. *Angew. Chem., Int. Ed.* **2003**, *42*, 1734, and references therein. For reviews on silicon tethers, see: (d) Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthesis* **1997**, 813. (e) Gauthier, D. R.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289.

(15) For a review, see: (a) Denmark, S. E.; Sweis, R. F. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1, p 163. For a similar approach with aryl iodides instead of MeI, see: (b) Denmark, S. E.; Yang, S.-M. *Org. Lett.* **2001**, *3*, 1749.

(16) (a) Taguchi, H.; Tsubouchi, A.; Takeda, T. *Tetrahedron Lett.* **2003**, *44*, 5205, and references therein. (b) Schmidt, D. R.; Park, P. K.; Leighton, J. L. *Org. Lett.* **2003**, *5*, 3535.

(17) The solvent played a crucial role to avoid double-bond isomerization during the iododesilylation: (a) Zakarian, A.; Batch, A.; Holton, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 7822. (b) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Org. Lett.* **2008**, *10*, 1727.

(18) Review: Negishi, E.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichim. Acta* **2005**, *38*, 71.

(19) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. For reviews on its use in macrolactonization reactions, see: (b) Bartra, M.; Urpí, F.; Vilarrasa, J. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ed.; Springer-Verlag: Berlin, 1993; Vol. 2, p 1. (c) Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911.

(20) (a) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822. (b) Shiina, I.; Fukui, H.; Sasaki, A. *Nature Protocols* **2007**, *2*, 2312.

Table 1. Macrolactonization of *seco*-Acid **23** to **1**

entry	reagents and conditions	concn (mM)	yield of **1** (%)
1	2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 1.5 h, then DMAP, toluene, rt, 16 h	1.7	20
2	2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 1.5 h, then DMAP, toluene, 50 °C, 16 h	1.6	26
3	MNBA, Et_3N, DMAP, CH_2Cl_2, 40 °C, slow addition of **23** over 12 h at 40 °C	2.7	42

convert the C−Si to C−I bonds, and to couple the C−I bonds with Me_2Zn/Pd), all of them have been accomplished readily in excellent yields (93−97%). This tactic can be useful in other challenging cases.

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Supporting Information Available: Experimental procedures for all compounds, copies of the ^1H and ^{13}C NMR spectra of the new compounds involved in the second strategy (Schemes 4 and 5), and copies of the NMR spectra of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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