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Toward a Total Synthesis of Amphidinolide X and Y. The Tetrahydrofuran-Containing Fragment C12–C21

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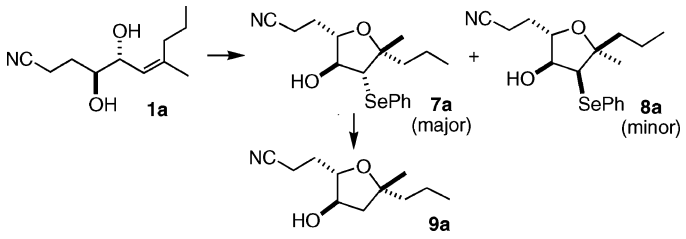
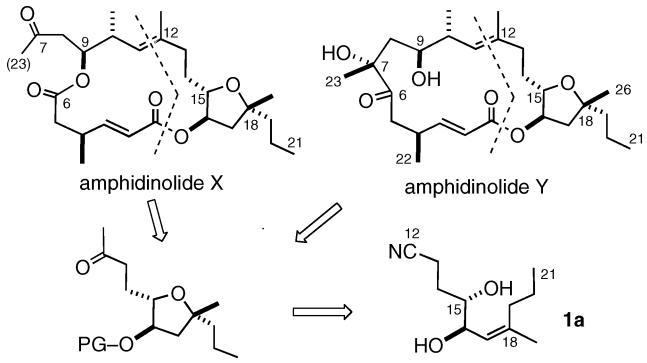
ABSTRACT



The key THF derivative (9a) for an enantioselective synthesis of amphidinolide X/Y was obtained from 1a via a selenoetherification reaction. In fact, among the cyclization methods investigated, the highest yield and stereocontrol were achieved at −78 °C with PhSeCl/Et^{i}Pr$_2$N from diols 1a (*anti-Z*) and 1b (*anti-E*) and with PhSeCl/ZnBr$_2$ from diols 1c (*syn-Z*) and 1d (*syn-E*). Also, surprisingly, use of protecting groups (on the allylic OH) was detrimental in the cases studied. The diverse THF-tetrasubstituted stereoisomers will provide a series of amphidinolide X/Y analogues.

Amphidinolide X and its supposed biogenetic precursor amphidinolide Y were isolated by Kobayashi et al.[1] from a marine dinoflagellate of the genus *Amphidinium* sp. Among the members of the amphidinolide family,[2] many of which exhibit a strong cytotoxic activity against several cancer cell lines,[2] amphidinolide X drew our attention both by its unusual nondimeric macrodiolide structure and by the synthetic challenge posed by the quaternary stereocenter of the tetrahydrofuran ring. As shown in Scheme 1, where the numbering of amphidinolide X was adapted to that of amphidinolide Y for the sake of simplification, our synthetic strategy was based on two disconnections that led to tetrasubstituted oxolane derivatives.

Scheme 1



(1) (a) Tsuda, M.; Izui, N.; Shimbo, K.; Sato, M.; Fukushi, E.; Kawabata, J.; Katsumata, K.; Horiguchi, T.; Kobayashi, J. *J. Org. Chem.* **2003**, *68*, 5339. (b) Tsuda, M.; Izui, N.; Shimbo, K.; Sato, M.; Fukushi, E.; Kawabata, J.; Katsumata, K.; Horiguchi, T.; Kobayashi, J. *J. Org. Chem.* **2003**, *68*, 9109.

(2) Reviews: (a) Chakraborty, T. K.; Das, S. *Curr. Med. Chem.: Anti-Cancer Agents* **2001**, *1*, 131. (b) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 778. For a review on oxacyclic macrodiolides, see: (c) Kang, E. J.; Lee, E. *Chem. Rev.* **2005**, *105*, 4348.

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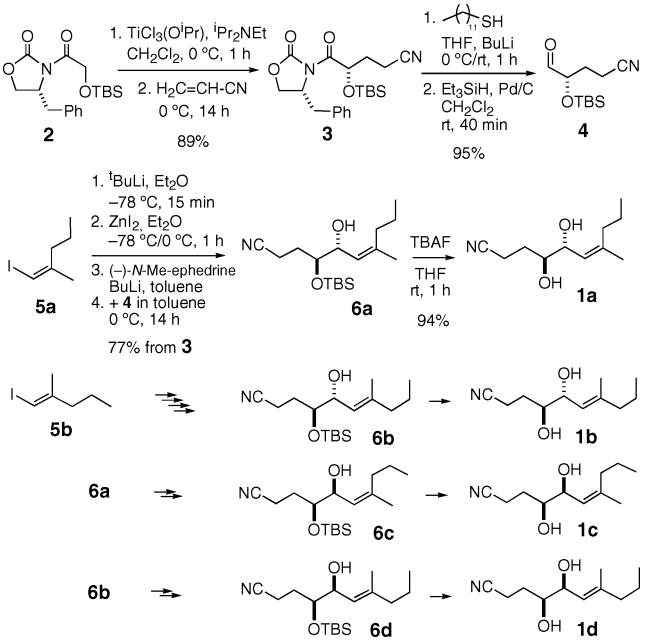
Thus, we envisaged the formation of the five-membered ring by an electrophile-mediated cyclization of **1a**. An alternative approach to the key five-membered ring has been reported by Fürstner et al. in their outstanding total syntheses of amphidinolide X and Y;[3] construction of the THF derivative relied upon the conversion of a chiral epoxy−alkyne to a hydroxy−allene, which was cyclized with $AgNO_3$ to afford an 8:1 mixture of *cis*/*trans*-dihydrofurans, separated after a subsequent bromoesterification. Dai et al. have reported another interesting approach to this THF ring, through an acid-catalyzed 5-*endo* cyclization of a vinyl epoxide.[4]

We have synthesized **1a** as indicated in Scheme 2. Nonnatural Evans' chiral auxiliary was converted to the *tert*-butyldimethylsilyloxy derivative **2**, the titanium enolate of which was treated with acrylonitrile,[5] to give enantiopure **3** in 89% overall yield.[6] By the method of Fukuyama et al.,[7] **3** was reduced to aldehyde **4**. Reaction of **4**[8] with the appropriate alkenylzincate (from **5a**)[9] led to **6a** as a 92:8 *anti*/*syn* mixture, which was purified by chromatography. Cleavage of the TBS ether under standard conditions ($Bu_4N^+F^-\cdot 3H_2O$, THF) afforded the desired enantiopure 4,5-dihydroxy-7-methyl-6-decenenitrile **1a**.

Scheme 2



Analogously, but starting from the *E*-iodoalkene (**5b**)[10] shown in Scheme 2, we obtained the decenenitrile **6b**, again as an *anti*/*syn* mixture (93:7), which was deprotected and purified to give **1b**. The Swern oxidation of **6a**, followed by reduction with L-Selectride (lithium tri-*sec*-butylborohydride) in THF at −78 °C, afforded in ca. 60% overall yield the *syn*-diol **6c**, which was deprotected to **1c**. Similarly, a sample of the *anti-E* derivative **6b** was transformed to the *syn-E* **6d** and **1d**. In this way, four different series of enediols (**a** = *anti-Z*, **b** = *anti-E*, **c** = *syn-Z*, and **d** = *syn-E*) were finally in our hands. In principle, it was expected that the cyclization of some of these derivatives would afford a THF-containing fragment with the absolute configuration of amphidinolides X/Y, whereas the other series would give rise eventually to diverse stereoisomers (analogues), whose cytotoxicities would deserve to be evaluated as well.

Cycloetherification of homoallylic alcohols (formation of tetrahydrofurans by 5-*endo* processes) and cyclization between more distant hydroxy groups and olefinic carbon atoms (5-*exo* vs 6-*endo*, etc.) have been extensively investigated,[11] but competition studies involving di-OH or tri-OH olefins are scarce.[12] In our case ("α,β-di-OH trisubstituted olefins"), as regioselective electrophilic attacks giving rise to intermediates with some tertiary carbenic ion character were plausible, it was thought that the oxolane would predominate over the two possible oxetanes and over the oxirane. Therefore, the unprotected diols **1a** and **1b** were subjected to various electrophile-mediated cyclization reactions.[13]

(3) (a) Lepage, O.; Kattnig, E.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 15970. (b) Fürstner, A.; Kattnig, E.; Lepage, O. *J. Am. Chem. Soc.* **2006**, *128*, 9194.

(4) Chen, Y.; Jin, J.; Wu, J.; Dai, W.-M. *Synlett* **2006**, 1177.

(5) (a) Evans, D. A.; Bilodeau, M. T.; Somers, T. C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, *56*, 5750. (b) Mas, G.; González, L.; Vilarrasa, J. *Tetrahedron Lett.* **2003**, *44*, 8805.

(6) Reactions with alternative Michael acceptors and drawbacks with the enolate of the *O*-Bn derivative will be described later. The absolute configuration of **3** and **4** was confirmed by reduction to the alcohol, removal of the TBS group, and formation of the isopropylidene acetal, a known compound ($[\alpha]_D$ −27.3, *c* 1.1, $CHCl_3$, cf. Buchanan, J. G.; Craven, D. A.; Wightman, R. H.; Harnden, M. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 195).

(7) (a) Miyazaki, T.; Han-ya, Y.; Tokuyama, H.; Fukuyama, T. *Synlett* **2004**, 477. (b) For a review: Fukuyama, T.; Tokuyama, H. *Aldrichimica Acta* **2004**, *37*, 87.

(8) Compound **4** was used after a simple filtration on Celite. Further purification of this racemization-prone aldehyde, to remove the coproduct $C_{12}H_{25}SSiEt_3$, proved to be unnecessary.

(9) (*Z*)-1-Iodo-2-methyl-1-pentene (**5a**) was prepared from propyne, propylmagnesium chloride, and CuBr, followed by iodination, according to: (a) Hoffmann, R. W.; Schlapbach, A. *Liebigs Ann. Chem.* **1990**, 1243. For the preparation of the zincate and its addition to aldehyde **4**, see: (b) Marshall, J. A.; Eidam, P. *Org. Lett.* **2004**, *6*, 445 and references therein.

(10) (*E*)-1-Iodo-2-methyl-1-pentene (**5b**) was prepared from 1-pentyne (with $AlMe_3$ and Cp_2ZrCl_2), followed by iodination. See: Negishi, E.; Horn, D. E. V.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639.

(11) For recent reviews, see: (a) Gruttadauria, M.; Meo, P. L.; Noto, R. *Targets Heterocycl. Syst.* **2001**, *5*, 31. (b) Silva, F. M.; Jones, J.; Mattos, M. C. S. *Curr. Org. Synth.* **2005**, *2*, 393. For relevant papers, see: (c) Lipshutz, B. H.; Gross, T. *J. Org. Chem.* **1995**, *60*, 3572 and references therein. (d) Bravo, F.; Kassou, M.; Castillón, S. *Tetrahedron Lett.* **1999**, *40*, 1187. (e) Bew, S. P.; Barks, J.; Knight, D. W.; Middleton, R. J. *Tetrahedron Lett.* **2000**, *41*, 4447. (f) Senda, Y.; Takayanagi, S.; Sudo, T.; Itoh, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 270. (g) Kang, S. H.; Kang, S. Y.; Park, C. M.; Kwon, H. Y.; Kim, M. *Pure Appl. Chem.* **2005**, *77*, 1269. (h) Alonso, F.; Meléndez, J.; Soler, T.; Yus, M. *Tetrahedron* **2006**, *62*, 2264 and references therein.

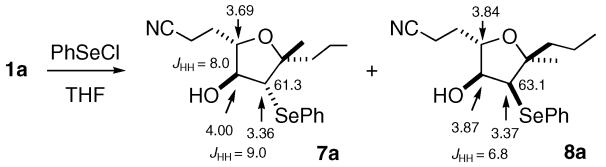
(12) Recent examples: (a) Bravo, F.; Castillón, S. *Eur. J. Org. Chem.* **2001**, 507 (β,γ-di-OH). (b) Gruttadaria, M.; Aprile, C.; Riela, S.; Noto, R. *Tetrahedron Lett.* **2001**, *42*, 2213 (β,δ-di-OH). (c) Weghe, P. V.; Bourg, S.; Eustache, J. *Tetrahedron* **2003**, *59*, 7365 (α,β′-di-OH, *Z* olefin). (d) Fettes, A.; Carreira, E. M. *J. Org. Chem.* **2003**, *68*, 9274 (α,δ′-di-OH) and references therein. (e) Li, D.-R.; Zhang, D.-H.; Sun, C.-Y.; Zhang, J.-W.; Yang, L.; Chen, J.; Liu, B.; Su, C.; Zhou, W.-S.; Lin, G.-Q. *Chem.−Eur. J.* **2006**, *12*, 1185 (β,γ-di-OH). (f) Nicolaou, K. C.; Pihko, P. M.; Bernal, F.; Frederick, M. O.; Qian, W.; Uesaka, N.; Diedrichs, N.; Hinrichs, J.; Koftis, T. V.; Loizidou, E.; Petrovic, G.; Rodríquez, M.; Sarlah, D.; Zou, N. *J. Am. Chem. Soc.* **2006**, *128*, 2244 (α,γ,δ-tri-OH).

(13) Reviews: (a) Tiecco, M. *Top. Curr. Chem.* **2000**, *208*, 7. (b) Wirth, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 3742. (c) Petragnani, N.; Stefani, H. A.; Valduga, C. J. *Tetrahedron* **2001**, *57*, 1411. Also see: (d) Khokhar, S. S.; Wirth, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 631 and references therein.

In practice, iodoetherification (with $I_2/NaHCO_3$ in CH_3CN) as well as treatment with $Hg(OAc)_2$ gave complex final mixtures. Cyclization by small amounts of TfOH was unsuccessful (decomposition products). Also, Me_3SiOTf was inefficient. Heating with AgOTf as reported[14] gave dehydrated products (probably due to the instability of the allylic system to Lewis acids or when Brönsted acids are generated in the medium), whereas at room temperature other reactions were noted.[15] $Cu_2(OTf)_2$ behaved as AgOTf.[15] Only the PhSeCl-induced cyclizations gave clean results.

As shown in Table 1 for the reaction of **1a** with PhSeCl under quite standard conditions,[16] a compound largely

Table 1. Reaction of **1a** with PhSeCl



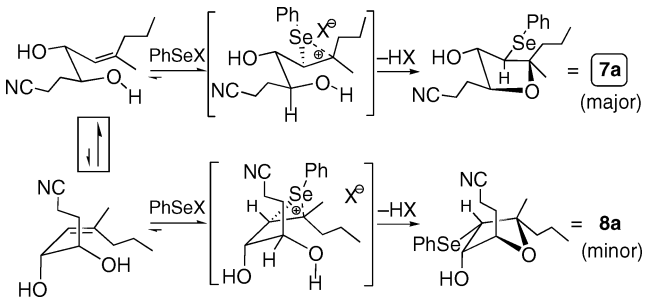
entry	conditions[a]	yield of **7a** (%)	yield of **8a** (%)
1	$ZnBr_2$, rt, 15 min	60	18
2	K_2CO_3, rt, 30 min	75	10
3	$ZnBr_2$, −78 °C, 30 min	85	8
4	K_2CO_3, −78 °C, 6 h	92	3
5	Et^{i}Pr$_2$N, −78 °C, 8 h	92	3

[a] To 1.0 mmol of **1a** in 10 mL of THF at the indicated temperature were added 1.5 mmol of PhSeCl and 1.0 mmol of $ZnBr_2$ in 4 mL of THF via canula, and stirring was maintained for several minutes or hours. In entries 2, 4, and 5, the PhSeCl solution was added to the suspension or solution of **1a** with the base (1.0 mmol).

predominated (see **7a**) but another isomer (see **8a**) of higher R_f (with 95:5 CH_2Cl_2/EtOAc as the eluent) was also isolated. Apart from the relevant ^1H and ^{13}C chemical shifts and $^3J_{HH}$ values, which agree with those reported for related oxolanes,[17] NOESY confirmed the configurations of these products. The maximum stereocontrol in favor of the desired compound **7a** (see entries 4 and 5) was obtained at −78 °C and when no Lewis acid was used to activate PhSeCl, but a base was introduced to remove HCl as soon as generated. Thus, under the conditions of entries 4 and 5, 92% of **7a** could be obtained after column chromatography.

Sound explanations for the stereocontrolled PhSeX-induced cyclizations (*anti* stereospecific additions to double bonds) have been given[11−13] so that the main arguments will not be repeated. We are dealing, however, with the special case of a trisubstituted alkene with allylic and homoallylic hydroxy groups. The major compound of the PhSe$^{\delta+}$-promoted cyclization of *anti-Z* diol **1a** may be accounted for by a predominant envelope or chairlike conformation of the complex and intermediates leading to **7a** (see the upper part of Scheme 3, where X means Cl, $ZnBr_2Cl$, or any

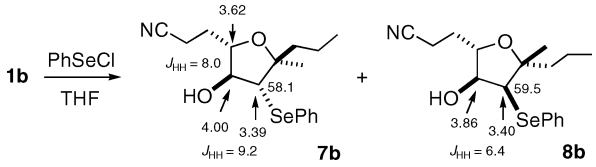
Scheme 3



counterion of PhSe$^+$), in which both the allylic OH group and the CH_2CH_2CN chain are in an equatorial-like arrangement. In the lower part of Scheme 3, the less favorable conformation leading to **8a** is depicted. For more details, see the Supporting Information.

The results obtained by the PhSeCl-promoted cyclization of **1b** are summarized in Table 2. A THF derivative largely

Table 2. Reaction of **1b** with PhSeCl



entry	conditions[a]	yield of **7b** (%)	yield of **8b** (%)
1	$ZnBr_2$, rt, 15 min	73	6
2	$ZnBr_2$, −78 °C, 30 min	76	6
3	K_2CO_3, rt, 30 min	80	5
4	K_2CO_3, −78 °C, 4 h	90	4
5	Et^{i}Pr$_2$N[b] −78 °C, 6 h	90	4

[a] See footnote *a* in Table 1. In THF, CH_2Cl_2, and toluene, at −78 °C for 30 min, without any additive, the product ratios were similar, with isolation of **7b** in ca. 80% yields. [b] With lutidine and 2,6-di-*tert*-butylpyridine, the reactions were slower, but the product ratios were similar.

predominated, to which structure **7b** could be attributed on the basis of its NMR spectra (especially the high $^3J_{HH}$ values between the ring protons, which indicate that they are in a *trans*−*trans* relationship, and NOE experiments).

From **6b**, we prepared its *O*-MEM derivative (protection of the allylic OH) and removed the *O*-TBS protecting group (deprotection of the homoallylic OH) by standard procedures, to obtain the so-called MEM-**1b**. With PhSeCl at room

(14) Yang, C.-G.; Reich, N. W.; Shi, Z.; He, C. *Org. Lett.* **2005**, *7*, 4553.

(15) Such as the addition of the homoallylic OH group to the CN group, to afford five-membered lactones after the workup. For example, **1b** stirred in CH_2Cl_2 with AgOTf for 4 days at room temperature gave 35% of a butyrolactone. When MEM-**1b** (the 5-*O*-MEM derivative of **1b**, see the main text) was treated in CH_2Cl_2 with 0.5 equiv of AgOTf overnight, 21% of the corresponding *O*-MEM butyrolactone was isolated (together with 43% of recovered starting material). When MEM-**1b** was stirred with $Cu_2(OTf)_2$ for 1 day, ca. 70% of the same butyrolactone was isolated.

(16) Kang, S. H.; Hwang, T. S.; Kim, W. J.; Lim, J. K. *Tetrahedron Lett.* **1990**, *31*, 5917. Because stereoselectivities obtained with commercially available PhSeCl were encouraging in the first trials, more sterically hindered reagents such as Lipshutz's 2,4,6-triisopropylphenylselenyl bromide (see refs 11c and 12d) were not investigated.

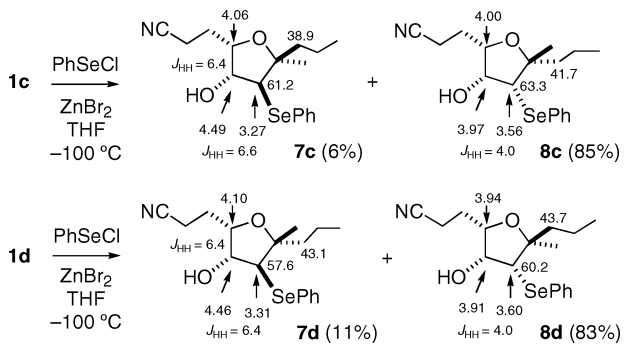
(17) (a) Tiecco, M.; Testaferri, L.; Santi, C. *Eur. J. Org. Chem.* **1999**, *4*, 797. (b) Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E.; Liotta, D.; Monahan, R. *J. Org. Chem.* **1987**, *52*, 4191.

temperature, without any additive, MEM-**1b** gave a mixture of two oxolanes in a 75:25 ratio. Cyclization of MEM-**1b** with PhSeCl/Et^{i}Pr$_2$N at −78 °C gave a similar crude product, with the two oxolanes in an 80:20 ratio. The major isomer was in all cases MEM-**7b**, as expected, and could be obtained in ca. 70% yield after column chromatography. The second isomer, isolated in ca. 15% yield, correlated with MEM-**8b**. The relevant fact is that the stereocontrol was much lower from MEM-**1b** than from **1b**. In other words, with this substrate it is better to discard the use of protecting groups,[18] not only to save steps but also to improve the selectivity.

We explain this fact by a destabilizing gauchelike interaction between the OMEM and CH_2CH_2CN chains of MEM-**1b**, which may change the relative percentages of the conformers (see Supporting Information).

When *syn*-*Z* diol **1c** and *syn*-*E* diol **1d** were subjected to diverse selenoetherification conditions such as those shown in Tables 1 and 2, almost equimolar mixtures of oxolanes **7c** and **8c** and, on the other hand, **7d** and **8d** were obtained at room temperature. However, the main products at low temperatures (see Scheme 4) were **8c** and **8d**, respectively;

Scheme 4

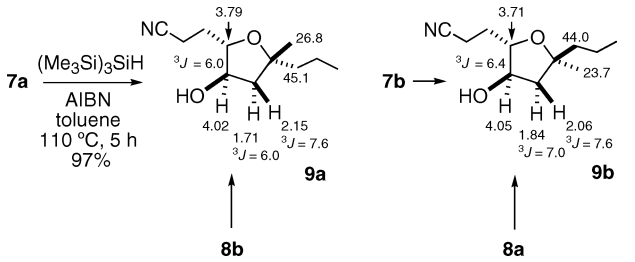


i.e., they had the OH and SePh groups in a *cis* relationship, in contrast to that observed in series **a** and **b**. The configurations were assigned by NMR and were confirmed by the X-ray structure of **8c** (see Supporting Information). By contrast again to **1a** and **1b**, under basic conditions at −78 °C, **1c** gave a **7c**/**8c** ratio of only 25:75 and **1d** afforded only a 40:60 **7d**/**8d** ratio. To our surprise, the highest ratios were reached in the presence of 1 equiv of $ZnBr_2$ at −78 °C or, even slightly better, at −100 °C (see in Scheme 4 the highest isolated yields of **8c** and **8d**).

(18) The benzyl (Bn) and *p*-methoxybenzyl (PMB) groups were not convenient as protecting groups because we obtained many byproducts when various cyclizations were attempted with them instead of MEM.

Removal of the SePh group of oxolanes **7a**, **7b**, **8a**, and **8b** was carried out with $(Me_3Si)_3SiH$/AIBN[19] in yields >95%, as summarized in Scheme 5. Deselenylation of **7a**

Scheme 5



gave **9a**, the same product as that of **8b**, and deselenylation of **7b** afforded **9b**, the same compound as that of **8a**, confirming the structural assignments we had previously carried out.

In summary, compound **9a**, the key fragment in our total synthesis of amphidinolide X/Y, was achieved in excellent yields by a cyclization of an *anti* dihydroxy (allylic and homoallylic), unprecedented trisubstituted-alkene substrate (**1a**), followed by deselenylation. Other isomers of **9a**, such as **9b** (and those arising from **7c** and **8d** and from **8c** and **7d**, to be reported in a future full work), will be used for the syntheses and SAR studies of amphidinolide X/Y analogues. As we obtained the C1−C6 synthon some time ago, our present efforts are focused on the elaboration of the C23/C7−C11 segment and the assembly of the three fragments.

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Supporting Information Available: Experimental data for compounds **1a**−**d**, **7a**, **7b**, **8c**, **8d**, **9a**, and **9b**, their NMR spectra, the X-ray structure of **8c**, and mechanistic interpretations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Classical review: (a) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188. Also see: (b) Parsons, A. *Chem. Br.* **2002**, *38*, 42. (c) Perchyonok, V. T. *Tetrahedron Lett.* **2006**, *47*, 5163 and references therein.