Natural Products

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Expedient Synthesis of (−)-Amphidinolide X**

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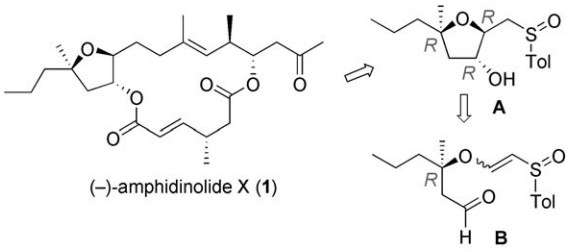
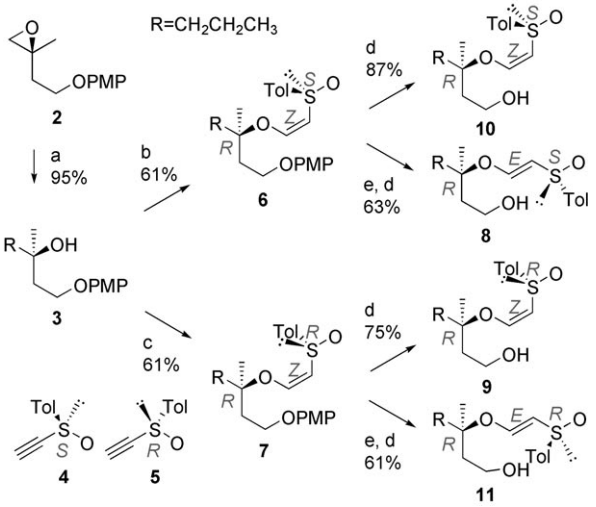
(−)-Amphidinolide X (**1**, Scheme 1) is one of the cytotoxic macrolides isolated by Kobayashi and co-workers from the laboratory-cultured dinoflagellates *Amphidinium* sp., which are symbionts of the Okinawan marine flatworms *Amphisco-*



Scheme 1. Retrosynthetic analysis. Tol: tolyl.

lops sp.[1] Amphidinolide X (**1**) is known to possess cytotoxic activity with IC_{50} values of 0.6 and 7.5 μg mL^{-1} against murine lymphoma L1210 and human epidermoid carcinoma KB cells, respectively, in vitro. It is the only naturally occurring macrodiolide known to date that consists of a diacid and a diol unit, and it has been a popular target for synthetic studies because of its scarcity and unique structure.[2] The most characteristic feature in the structure of **1** is the substituted 3-hydroxyoxolane structure, which is derived from a tertiary alcohol. Construction of this type of motif[3] normally utilizes the nucleophilicity of hydroxy groups, and indeed, hydroxy addition to allenes,[2a,b] epoxides,[2e,g] or olefins[2f] is a key step in the synthesis of **1**. We intended to obtain the key structural element **A** through 5-*exo* cyclization of aldehydo β-alkoxyvinyl sulfoxide **B** (Scheme 1). It is known[4] that 5-*exo* cyclizations of aldehydo β-alkoxyvinyl sulfoxides derived from secondary alcohols proceed under carbinol chirality control, and *cis*-2,5-disubstituted oxolanes are formed regardless of the sulfoxide chirality. For (*E*)- and (*Z*)-β-alkoxyvinyl sulfoxides derived from tertiary alcohols, will the reactions proceed under sulfoxide or carbinol chirality control?

In practice, the known (3*R*)-epoxide *p*-methoxyphenyl (PMP) ether **2**[5] was converted into the (3*R*)-3-methylhexan-1,3-diol PMP ether **3** (Scheme 2). Reaction of **3** with alkynyl



Scheme 2. Synthesis of the β-alkoxyvinyl sulfoxides. a) EtMgBr, CuI, THF; b) **4**, EtMgBr, LiCl, THF; c) **5**, EtMgBr, LiCl, THF; d) CAN, MeCN/H_2O (9:1); e) I_2, CH_2Cl_2. THF: tetrahydrofuran; CAN: ceric ammonium nitrate.

sulfoxides **4** or **5** in the presence of ethylmagnesium bromide and lithium chloride led to (*Z*)-β-alkoxyvinyl sulfoxides **6** or **7**, respectively. The crucial vinyl ether formation did not proceed in the presence of other bases.[6] PMP deprotection of **6** through CAN oxidation provided (*Z*)-β-alkoxyvinyl sulfoxide **10**. When **6** was treated with iodine before the CAN oxidation, (*E*)-β-alkoxyvinyl sulfoxide **8** was obtained. By the same sequence of reactions, (*Z*)- and (*E*)-β-alkoxyvinyl sulfoxides **9** and **11** were prepared from **7**.

Dess–Martin oxidation of (*E*),(*S*)-β-alkoxyvinyl sulfoxide **8** and then reaction with SmI_2 in the presence of methanol yielded a 9.2:1 mixture of the 3-hydroxyoxolane products, with the major product being **12**, which was isolated in 67% yield (Scheme 3). Through the same reaction sequence, a 15.4:1 mixture with **13** as the favored product (62% yield) was obtained from the *Z*,*R* isomer **9**. Likewise, the *Z*,*S* isomer **10** was converted into a 5.7:1 mixture with **14** as the favored product (62% yield). When the *E*,*R* isomer **11** was subjected to the same reaction conditions, a 3.3:1 mixture of products was obtained with **15** as the major product, which was isolated in 73% yield. The minor products were epimeric carbinols.[7] *m*-CPBA oxidation of sulfoxides **12**–**15** produced four different sulfones **16**–**19**.[8]

The SmI_2-mediated 5-*exo* cyclization reactions of aldehydo β-alkoxyvinyl sulfoxides **8**–**11** derived from tertiary

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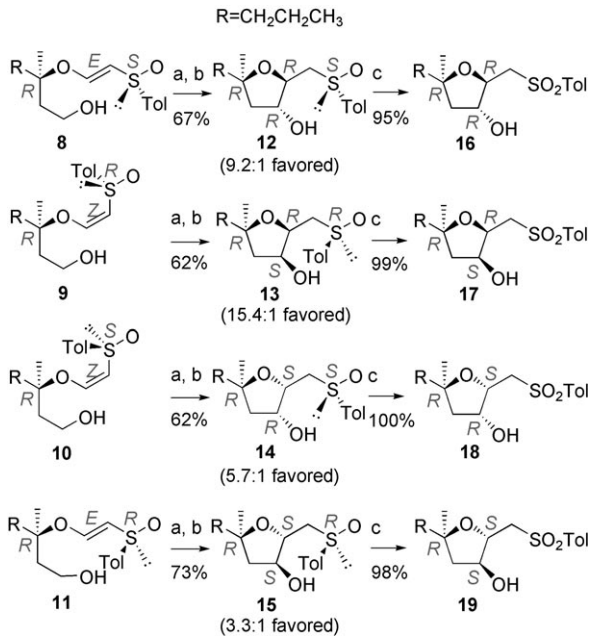
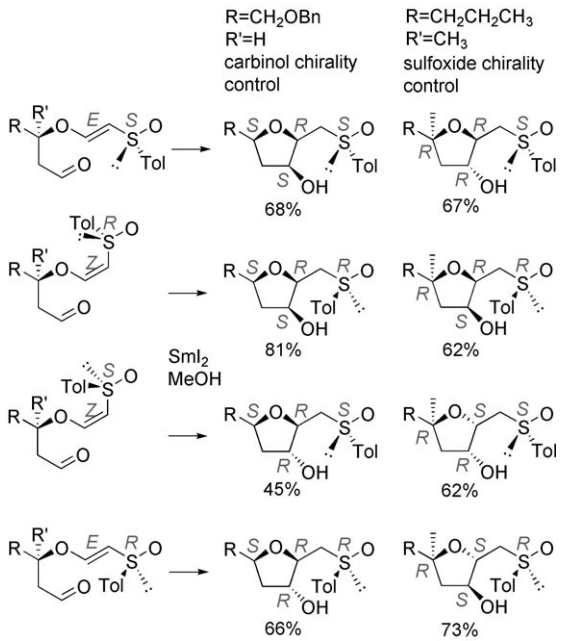


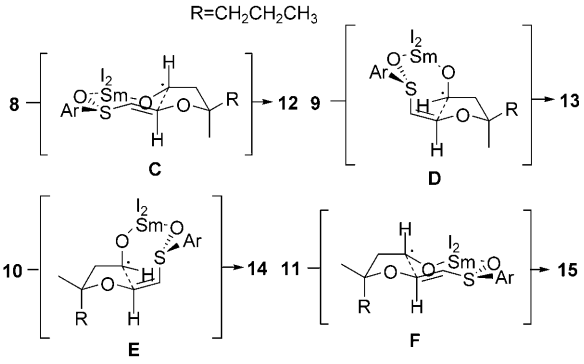
Scheme 3. SmI_2-mediated cyclization of aldehydo β-alkoxyvinyl sulfoxides. a) DMP, CH_2Cl_2, 0 °C; b) SmI_2, MeOH, THF, 0 °C; c) *m*-CPBA, CH_2Cl_2. DMP: Dess–Martin periodinane; *m*-CPBA: *m*-chloroperoxybenzoic acid.



Scheme 4. Comparison of the cyclization products from β-alkoxyvinyl sulfoxides derived from secondary (the previous study)[4] and tertiary alcohols (the present work). Bn: benzyl.

alcohols were stereospecific, and a useful degree of stereoselectivity was achieved. The structures of the major products may be predicted on the basis of the double-bond stereochemistry and the sulfoxide configuration (sulfoxide chirality control). The observed stereospecificity appears to be totally unrelated to the data previously obtained for substrates derived from secondary alcohols.[4] The results of SmI_2-mediated 5-*exo* cyclizations of aldehydo β-alkoxyvinyl sulfoxides prepared from secondary and tertiary alcohols are presented in Scheme 4.

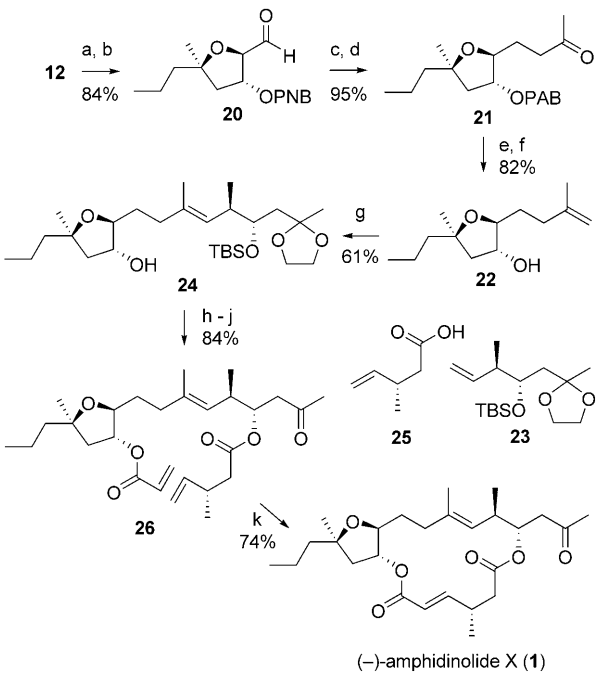
The results may be explained by proposing "eclipsed lone pair" transition states **C**–**F** for the formation of the major product in each case.[9] In these structures, the samarium ketyl group coordinated to the sulfoxide oxygen atom necessarily approaches the double bond opposite from the bulky aryl group (Scheme 5).



Scheme 5. Transition-state structures for the reactions of **8**–**11**.

After *p*-nitrobenzoate protection of the hydroxy group, the Pummerer rearrangement of **12** proceeded smoothly to yield aldehyde **20** (Scheme 6). *p*-Nitrobenzoate protection is advantageous, because the minor product produced along with **12** (and **13**) may also be converted into the same ester by a Mitsunobu reaction. *p*-Aminobenzoate ketone **21** was obtained through Horner–Emmons reaction of **20** and hydrogenation. Wittig homologation of ketone **21** and LAH reduction led to the hydroxy olefin **22**. A cross-olefin metathesis reaction between olefin **22** and TBS ether **23**, prepared from a known alcohol,[2d] proceeded smoothly to produce *E* olefin **24**. The corresponding *Z* olefin was not detected in the product mixture. Reaction of **24** with acryloyl chloride, TBS deprotection, and careful acylation with the acid chloride prepared from the known carboxylic acid **25**[10] produced triene **26**. The key ring-closing olefin metathesis reaction of **26** in the presence of the second-generation Grubbs catalyst was successful and provided (−)-amphidinolide X (**1**) in 74% yield, accompanied by the corresponding *Z* isomer in 11% yield.

In summary, the key 3-hydroxyoxolane fragment of (−)-amphidinolide X was prepared through SmI_2-mediated 5-*exo* cyclization of an aldehydo β-alkoxyvinyl sulfoxide derived from (*R*)-3-hydroxy-3-methylhexanal. Three other possible stereoisomers were also obtained by changing the double-bond stereochemistry and the sulfoxide chirality. In comparison with the results obtained previously,[4] a subtle change in the structure of the substrate (from a hydrogen atom to a methyl group) triggered a dramatic change of stereospecificity. The method described in this communication opens up new and rational ways for the preparation of functionalized oxacycles, particularly those derived from



Scheme 6. Synthesis of **1**. a) PNBA, DCC, DMAP, CH_2Cl_2; b) TFAA, pyridine, MeCN, 0 °C; KOAc, H_2O; c) $MeCOCH_2PO(OMe)_2$, DIPEA, MeCN; d) H_2, Pd/C, MeOH; e) $Ph_3PMe^+Br^-$, *n*BuLi, −20 °C; f) LAH, diethyl ether; g) **23**, 20 mol% $(H_2IMes_2)(Cy_3P)Cl_2RuCHPh$, CH_2Cl_2, reflux; h) $CH_2CHCOCl$, pyridine, CH_2Cl_2, 0 °C; i) AcOH, H_2O, 60 °C; j) $(COCl)_2$, **25**; alcohol, DMAP, CH_2Cl_2; k) 7 mol% $(H_2IMes_2)(Cy_3P)Cl_2RuCHPh$, CH_2Cl_2, reflux. TBS: *tert*-butyldimethylsilyl; PNB: *p*-nitrobenzoyl; PAB: *p*-aminobenzoyl; PNBA: *p*-nitrobenzoic acid; DCC: *N*,*N*′-dicyclohexylcarbodiimide; DMAP: 4-dimethylaminopyridine; TFAA: trifluoroacetic anhydride; DIPEA: diisopropylethylamine; LAH: lithium aluminum hydride; Mes: mesyl; Cy: cyclohexyl.

tertiary alcohols. Future studies will focus on these bioactive oxacyclic natural products.

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[6] The reaction did not proceed in the presence of *N*-methylmorpholine, lithium hexamethyldisilazide, lithium diisopropylamide, calcium hydride, or cesium carbonate.

[7] For example, the minor product accompanying **12** was converted into sulfone **17** upon *m*-CPBA oxidation.

[8] NOESY correlations were used in the structural assignment of **16**–**19**.

[9] In the cyclization studies of β-alkoxyvinyl sulfoxides derived from secondary alcohols, transition states were proposed with the R group "equatorial" at the flap of the envelope, which resemble the stable conformation of methylcyclopentane. For discussions on conformations of methylcyclopentanes, see: E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, pp. 758 – 759. In the case of transition states **C**–**F**, it may be proposed that the tertiary carbinol center avoids the flap side of the envelope due to steric reasons.

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