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Synthesis of the C9–C21 fragment of debromoaplysiatoxin and oscillatoxins A and D

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Abstract—A highly stereoselective synthesis of the C9–C21 fragment of debromoaplysiatoxin and oscillatoxins A and D has been devised. This new approach relies on the cross coupling of titanium enolates from *N*-acyl-1,3-thiazolidine-2-thiones and dialkyl acetals and the selective hydrogenolysis of *O*-benzyl protecting groups.

Debromoaplysiatoxin (**1**) is a bicyclic diolide isolated from the sea hare *Stylocheilus longicauda*[1] as well as the blue-green algae belonging to *Oscillatoriaceae* class along with several structurally related bioactive metabolites as oscillatoxin A (**2**), oscillatoxin D (**3**), and 30-methyloscillatoxin D (**4**) shown in Scheme 1.[2–4] Debromoaplysiatoxin is a highly inflammatory agent responsible for severe contact dermatitis that sometimes affects sea swimmers (*swimmers itch*),[2–4] but interest on it and oscillatoxin A mainly stems from their remarkable character as tumor promoters that operate on protein kinase C, which has been used to better understand carcinogenic processes.[4,5] Conversely, oscillatoxin D and 30-methyloscillatoxin D are nontoxic metabolites with antileukemic activity.[3b]

Synthetic efforts on this family of metabolites have culminated in several total syntheses[6–8] and a plethora of reports on advanced intermediates.[9] Most of these approaches depend on the construction of an acyclic precursor, whose careful manipulation should eventually trigger the formation of the spiro or the macrocyclic systems. Success of such strategy depends to a great extent on the proper choice of C20-phenol protecting group, since it must be removed in a late step of the synthesis under very mild conditions. Not surprisingly, total syntheses reported so far have made use of benzyl like protecting groups that can be cleaved by hydrogenolysis.

In this context, we disclose herein our studies toward the synthesis of the benzyl-protected C9–C21 fragment of the debromoaplysiatoxin (**1**) and oscillatoxin A (**2**) based on the cross-coupling reactions between titanium enolates from *N*-acyl-l,3-thiazolidine-2-thiones **5** and **6** (see Scheme 2) and dialkyl acetals previously developed in our group,[10–12] and the selective cleavage of benzyl ethers.[13] Furthermore, the configuration of the new stereocenters has been confirmed by correlation to an advanced intermediate for the synthesis of oscillatoxin D, taking advantage that C9–C21 fragment is common to all of these metabolites.[14]

According to these ideas, we envisaged the retrosynthetic analysis for the benzyl-protected C9–C21 fragment summarized in Scheme 2, which relies on two crucial steps: (i) the stereoselective C10–C11 bond formation by means of the addition of the titanium enolate from *N*-propanoyl auxiliary **5** to dibenzyl acetal **7**; and (ii) the stereoselective formation of C15 methyl ether through addition of the titanium enolate from *N*-acetyl auxiliary **6** to dimethyl acetal **8**.

The synthesis began with the preparation of dimethyl acetal **8** in multigram scale (>5 g, 80% yield) from commercially available 3-hydroxybenzaldehyde following standard procedures.[15] With acetal **8** in hand, we faced the stereoselective construction of methyl ether at C15. As expected,[10b] cross coupling reaction between titanium enolate from *N*-acetyl-4-isopropyl-1,3-thiazolidine-2-thione (**6**) and dimethyl acetal **8** in 10 mmol scale afforded a mixture (dr 87:13 by HPLC) that was purified by column chromatography. Eventually, the diastereomerically pure adduct **9** was isolated in 82% yield (see Scheme 3).

Keywords: Debromoaplysiatoxin; Oscillatoxin; Stereoselective synthesis.
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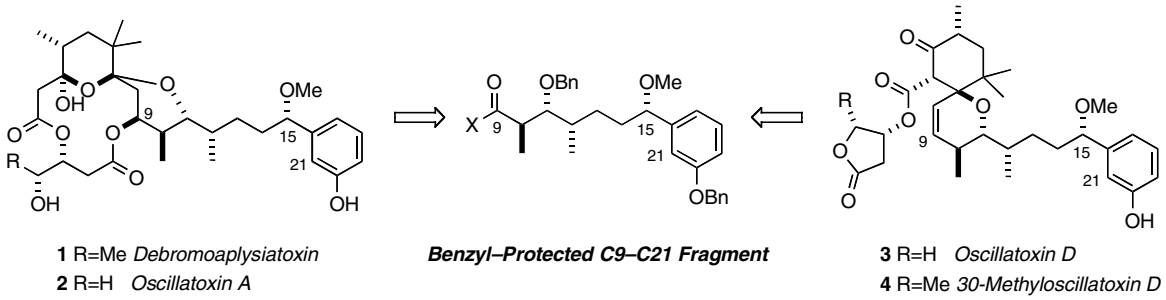
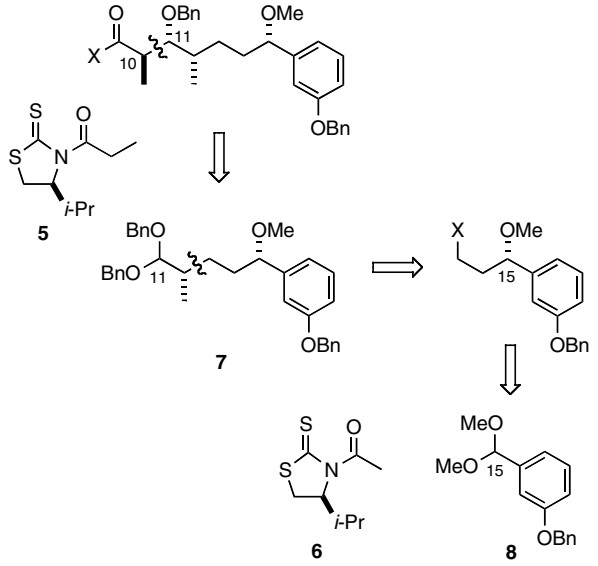


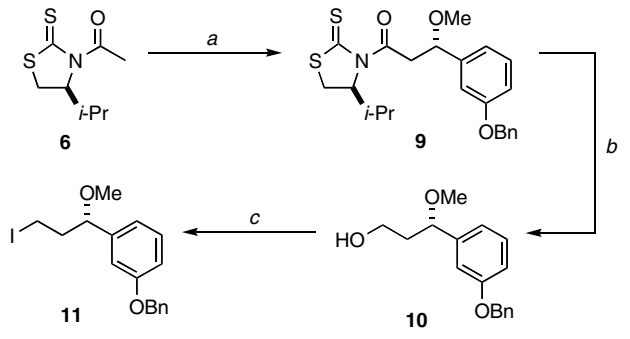
Scheme 1.



Scheme 2.

Removal of the chiral auxiliary was achieved under very mild conditions and the resulting alcohol **10** was converted into iodide **11** in excellent yield.

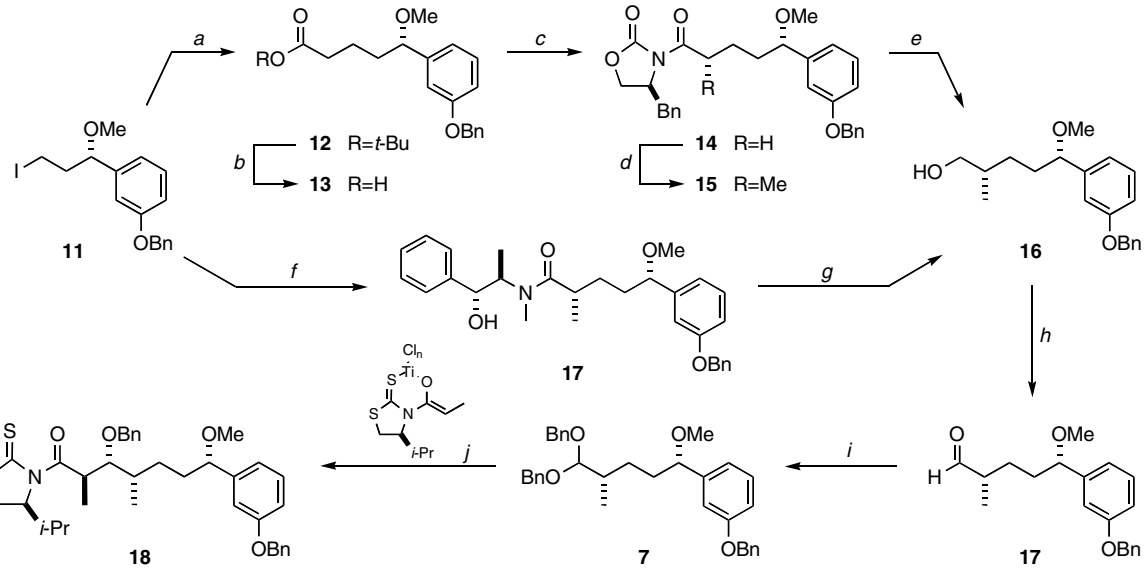
Once the C15 methyl ether was installed, we focused our attention on the construction of C12 stereocenter (see Scheme 4). Looking for crystalline products, we initially envisioned that it could arise from a stereoselective alkylation of a more elaborated intermediate using Evans methodology.[16] Thus, treatment of lithium enolate from *tert*-butyl acetate with iodide **11** provided quantitatively ester **12**, which was easily transformed into the corresponding carboxylic acid **13**. The acylation of (*S*)-4-benzyl-1,3-oxazolidinone with **13** and the subsequent stereoselective alkylation with methyl iodide were carried out according to the reported procedures. Analysis of the reaction mixture revealed the presence of a single diastereomer **15** (dr >97:3 by ^{1}H NMR), which was isolated in 78% yield after purification by column chromatography. Finally, removal of the chiral auxiliary afforded alcohol **16** in 91% yield. Unfortunately, neither **15** nor alcohol derivative **16** were crystalline solids and we decided to explore a more expeditious route based on Myers methodology.[17] In this case, alkylation of lithium enolate from (*R*,*R*)-*N*-propanoylpseudoephedrine with iodide **11** provided quantitatively amide **17** that was easily reduced to alcohol **16**, identical to that obtained along the former route. Therefore, enantiomerically pure alcohol **16** had been obtained from acetal **8** in 60% yield after a five-step sequence.



Scheme 3. Reagents and conditions: (a) i. $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 2 h; ii. $BF_3{\cdot}OEt_2$, **8**, 2 h; 82%. (b) $NaBH_4$, THF, rt, 4 h; 87%. (c) I_2, Ph_3P, imidazole, CH_2Cl_2, rt, 1.5 h; 97%.

Next, we confronted the synthesis of dibenzyl acetal **7** required for the last cross-coupling reaction (see Scheme 4). After careful optimization, it was established that such acetal could be easily obtained through Swern oxidation of alcohol **16** followed by treatment of the crude reaction mixture with BnOTMS under Noyori's conditions.[18] Thus, the stage was now set for a double stereodifferentiation reaction involving *N*-propanoyl auxiliary **5** and acetal **7**. We were pleased to confirm[10a] that the Lewis acid mediated addition of the titanium enolate from **5** to **7** proceeded in a highly stereoselective manner (dr >98:2 by ^{1}H NMR and HPLC), being able to isolate diastereomerically pure adduct **18** in 74% yield. At this point, it is worth mentioning that adduct **18** *should* be viewed as a benzyl protected derivative of the corresponding *anti* aldol intermediate, whose stereochemical array is still reluctant to most of the standard methodologies.

Such exceptional stereocontrol can be understood considering that it is a matched case of a double asymmetric process. Indeed, the reaction takes place through an open transition state **A** that involves the addition of the chelated titanium enolate to a putative oxonium intermediate **I** (Scheme 5). Hence, the configuration of C10 is controlled by the auxiliary (the *Re* face of the enolate is blocked by the isopropyl group), whereas that of C11 arises from the stereoelectronically favored

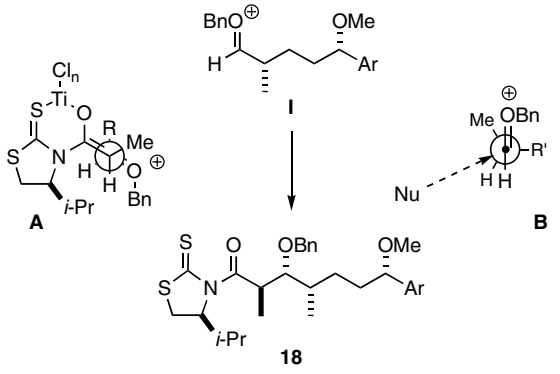


Scheme 4. Reagents and conditions: (a) *t*-BuOAc, LDA, THF–DMPU, −78 °C, 2 h; 100%. (b) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h; 91%. (c) i. *t*-BuOCOCl, Et_3N, THF, 0 °C, 2 h; ii. (*S*)-Benzyl-1,3-oxazolidin-2-one, BuLi, THF, −78 °C, 30 min; 93%. (d) i. NaHMDS, THF, −78 °C, 2 h; ii. MeI, −78 °C, 3 h; 78%. (e) $LiBH_4$, MeOH, THF, −20 °C, 17 h; 91%. (f) (*R*,*R*)-*N*-Propanoylpseudoephedrine, LDA, LiCl, THF, 0 °C, 5 h. (g) $LiH_2N{\cdot}BH_3$, THF, rt, 2 h; 80% over two steps. (h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; 96%. i. BnOTMS, TMSOTf cat., CH_2Cl_2, −50 °C; 78%. (j) $SnCl_4$, CH_2Cl_2, −20 °C, 2 h; 74%.

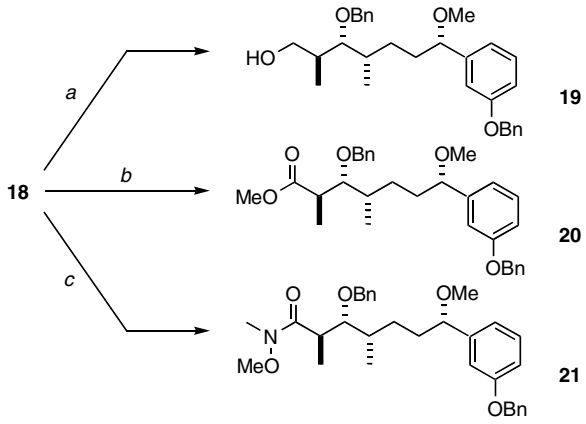
antiperiplanar approach of the enolate to conformation **B** preferred by the Felkin model.[19–21]

Finally, removal of the chiral auxiliary was carried out under very mild conditions to afford enantiomerically pure alcohol **19**, ester **20**, and Weinreb amide **21** (see Scheme 6) as potential representatives of the C9–C21 fragment in high yields.

Although the configuration of adduct **18** was rooted on well-established asymmetric methodologies[16,17] and the chemistry developed in our own group,[10] it was obviously desirable to prove it unambiguously. Additionally, we were interested in challenging the synthetic potentiality of our approach and go ahead in the synthesis of the metabolites described in Scheme 1. For these reasons, we decided to transform amide **21** into a more elaborated intermediate **22** (see Scheme 7) in route to oscillatoxin D already reported in the literature.[3b] Keeping in mind both goals, we adjusted the protecting group strategy. Selective hydrogenolysis conditions disclosed in the



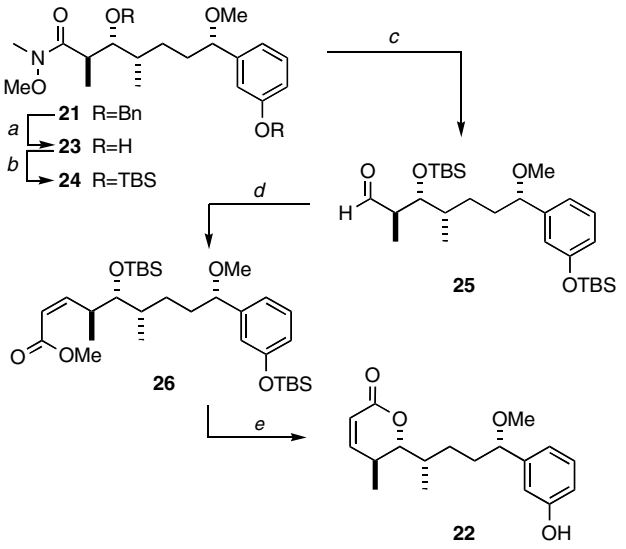
Scheme 5.



Scheme 6. Reagents and conditions: (a) $NaBH_4$, THF, rt, 5 h; 65%. (b) MeOH, DMAP cat., rt, 24 h; 95%. (c) MeNH(OMe)·HCl, Et_3N, DMAP cat., CH_2Cl_2, rt, 16 h; 90%.

preceding communication yielded dihydroxyamide **23** without affecting the integrity of C15 methyl ether. Then, it was subsequently treated with TBSOTf/2,6-lutidine and the ensuing silicon protected Weinreb amide **24** was smoothly reduced with DIBALH. Submission of the resulting aldehyde **25** to Still–Gennari olefination conditions[22] afforded the α,β-unsaturated ester **26** (91% yield, *Z*/*E* ratio >95:5), which was finally converted into the desired lactone **22** in 58% yield. Eventually, analysis of the ^1H NMR of lactone **22**[23] supported the configuration of the C9–C21 fragment.

In summary, we have disclosed a highly stereoselective synthesis of the C9–C21 fragment of debromoaplysiatoxin and oscillatoxins A and D based on cross-coupling reactions of chiral titanium enolates and acetals. Furthermore, the preparation of a more advanced



Scheme 7. Reagents and conditions: (a) i. H_2, 10% Pd/C, toluene, rt, 3 h; ii. H_2, 5% Rh/Al_2O_3, MeOH, rt, 1 h; 95%. (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 13 h; 61%. (c) DIBALH, THF, −78 °C, 3 h; 88%. (d) $(CF_3CH_2O)_2POCH_2CO_2Me$, K_2CO_3, 18-crown-6, toluene, 0 °C, 4 h; 91%. (e) HCl, MeOH, rt, 24 h; 58%.

intermediate toward oscillatoxin D proves the potentiality of our approach to tackle the synthesis of the abovementioned metabolites.

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23. Selected spectroscopic data for **22**: $[\alpha]_D$ +8.8 (*c* 0.25, $CHCl_3$); IR (film): 3338, 1702 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.21 (1H, t, $J = 7.7$ Hz, Ar*H*), 6.85–6.80 (2H, m, Ar*H*), 6.79–6.75 (1H, m, Ar*H*), 6.64 (1H, dd, $J = 9.7$,

2.1 Hz, H9), 5.94 (1H, dd, $J = 9.7$, 2.6 Hz, H8), 5.25 (1H, br s, OH), 4.05–4.00 (1H, m, H15), 4.02 (1H, dd, $J = 10.7$, 2.7 Hz, H11), 3.21 (3H, s, OCH_3), 2.65–2.58 (1H, m, H10), 1.84–1.72 (1H, m, H12), 1.70–1.58 (2H, m, H14), 1.50–1.48 (2H, m, H13), 1.06 (3H, d, $J = 7.3$ Hz, Me10), 0.95 (3H, d, $J = 6.7$ Hz, Me12); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 164.9, 156.0, 152.6, 143.7, 129.6, 120.0, 119.5, 114.8, 113.3, 85.5, 83.7, 56.6, 35.2, 33.7, 30.8, 29.5, 15.8, 13.4.