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Asymmetric synthesis of a C1–C19 fragment of ulapualide A

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Abstract—The stereocontrolled synthesis of a C1–C19 fragment of ulapualide A has been accomplished. The C3 hydroxyl-bearing stereocenter was established by Jacobsen's hydrolytic kinetic resolution (HKR) of a terminal epoxide, while the C9 methyl stereocenter was introduced through an asymmetric crotylation using chiral organosilane (*S*)-**7**. Union of the C1–C6 and the C7–C19 fragments by a Kishi–Nozaki coupling, followed by oxidation and conjugate addition of hydride completed the preparation of the fragment.

Ulapualide A (**1**), first isolated from the red eggmasses of the nudibranch *Hexabranchus sanguineus*, belongs to a unique family of tris-oxazole containing marine metabolites (Fig. 1).[1] Other members of this family include mycalolides,[2] kabiramides,[3] halichondramides,[4] jaspisamides,[5] and halishigamides.[6] The ulapualides exhibit inhibitory activity against L1210 leukemia cell proliferation and also display ichthyotoxic and antifungal properties. Complex natural products constitute interesting targets for asymmetric synthesis, particularly when new or improved methods are developed and used to assign the relative and absolute stereochemistry. In that context, the stereochemistry of the C20–C35 subunit has been assigned through extensive degradation, synthetic, and spectroscopic studies and was shown to be identical to the mycalolides.[7,8] The absolute stereochemistry of the C3-hydroxyl bearing stereocenter[9] and the C9-methyl bearing stereocenter[10] of the ulapualides has not been unambiguously assigned through experimental methods. Herein, we report the synthesis of an advanced intermediate **2** of ulapualide A,[11] which constitutes the tris-oxazole linked to the C1–C9 tether.

In considering a retrosynthesis of ulapualide A **1**, the initial bond disconnection lead to a C1–C19 tris-oxazole subunit **2** and a C20–C35 polypropionate derived subunit **3** (Fig. 1).[12] Further bond disconnection at C6–C7 provided two subunits, each containing one stereocenter. The C3 stereocenter was established by Jacobsen's hydrolytic kinetic resolution (HKR) of a terminal epoxide[13] and the C9 stereocenter was intro-

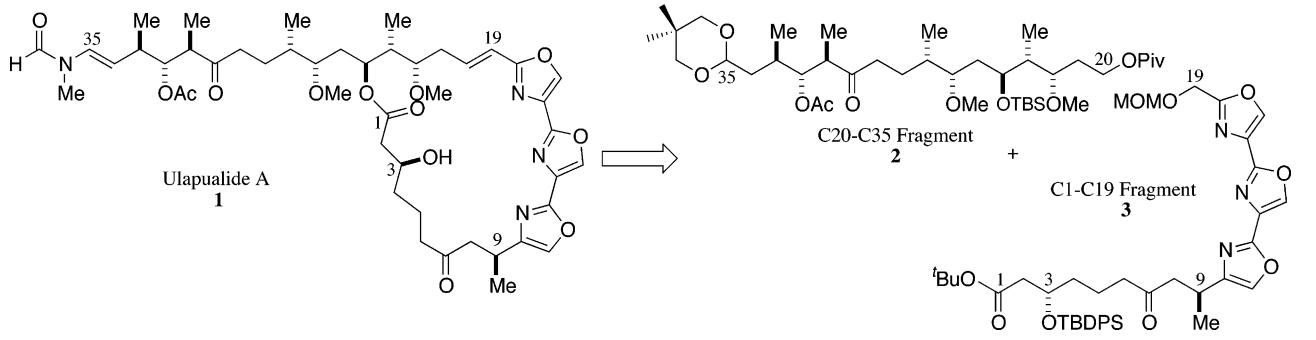

Figure 1. Retrosynthetic analysis of ulapualide A.

Keywords: marine metabolites; tris-oxazole; ulapualide A.

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duced through an asymmetric crotylation using a chiral organosilane reagent.[14] To accomplish the selective deprotection of the fragment in late stages of the synthesis, the C3-hydroxyl group was protected as its *tert*-butyldiphenylsilyl ether and the C19 primary hydroxyl was protected as a methoxymethyl ether.

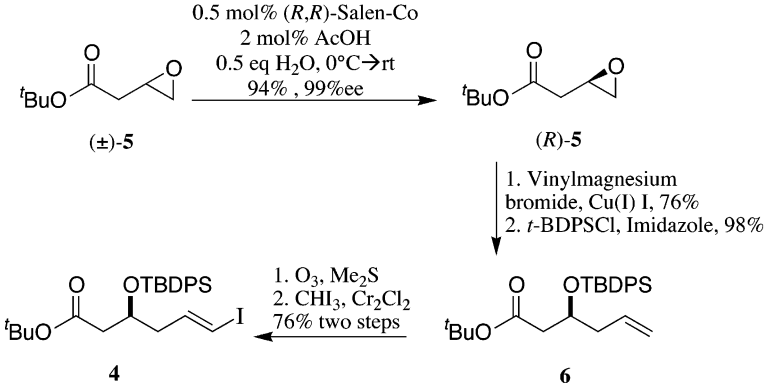
Synthesis of the C1–C6 subunit **4** was initiated by HKR of the readily available racemic epoxide **5**[15] with (*R*,*R*)-Salen–Co complex to provide the (*R*)-epoxide **5** in 94% yield and 99% ee (Scheme 1).[16] Addition of vinylmagnesium bromide in the presence of catalytic copper(I) iodide lead to epoxide ring opening and provided the secondary alcohol in 76% yield. The resultant C3-hydroxyl was then protected as its *tert*-butyldimethylsilyl ether **6** in 98% yield. Oxidative cleavage of the terminal olefin with ozone followed by Takai iodo-olefination provided the C1–C6 fragment **4** as a 5:1 mixture of isomers in 76% yield (two steps.)[17] This subunit is obtained in four steps and 57% overall yield from the chiral epoxide (*R*)-**5**.

The C9 methyl-bearing stereocenter and the nitrogen of the third oxazole ring were introduced through a $BF_3{\cdot}OEt_2$ promoted addition of (*S*)-silane **7** to an in situ generated *tert*-butyl-*N*-acyliminium ion of α-benzyloxyacetaldehyde **8** (Scheme 2).[18] This three component crotylation proceeds in 73% yield and affords the *syn*-homoallylic carbamate **9** with a dr >30:1. Oxidative cleavage of the *trans*-olefin with ozone and homologation with the ylide of triphenylphosphonium methyl bromide provided the terminal olefin **10** in 64% yield (two steps). Subsequent hydroboration (9-BBN-H_2O_2) afforded the primary alcohol in 84% yield, which was protected as its *tert*-butyldiphenylsilyl ether **11** in 98% yield. Removal of the benzyl protecting group with BCl_3 in 82% yield was followed by protection as a benzoate in 94% yield, which proved necessary as the benzyl ether was difficult to remove from bis-oxazole **14**. Finally, treatment with TFA in CH_2Cl_2 provided the secondary amine fragment **12**, suitable for coupling with the bis-oxazole fragment **13**, whose preparation has been previously described using modified-Hantzsch methodology.[19] The intermediate secondary amine was obtained in eight steps in 30% overall yield.

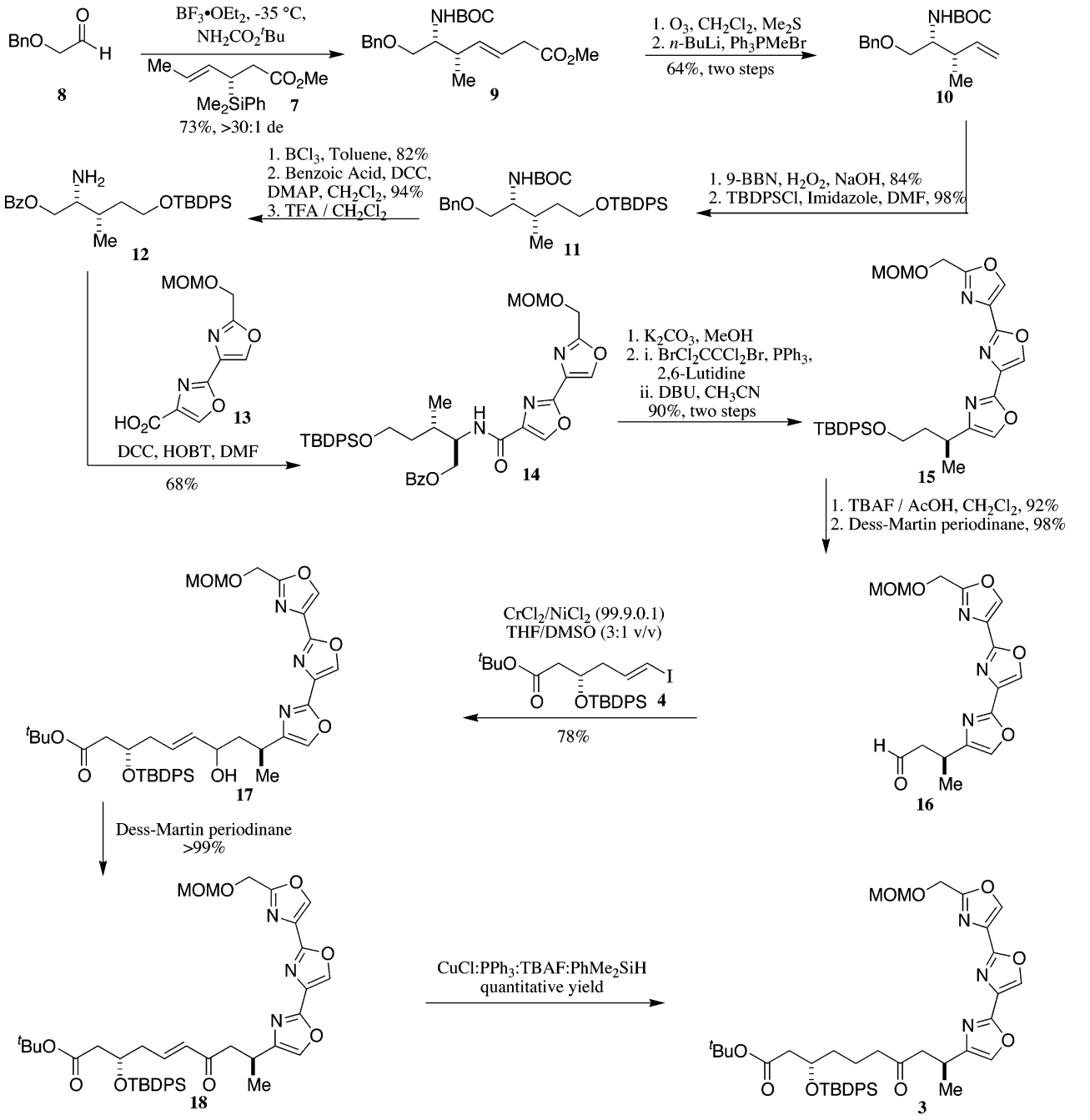
Introduction of the third oxazole ring was accomplished through the oxidation, cyclization, dehydrohalogenation protocol developed by Wipf.[20] This sequence was initiated with peptide coupling of the secondary amine **12** and the bis-oxazole carboxylic acid **13** using DCC and HOBT in DMF to afford the amide–oxazole **14** in 68% yield. The benzoate group was hydrolyzed in the presence of K_2CO_3 in MeOH in quantitative yield, and the resultant alcohol oxidized to its aldehyde with Dess–Martin periodinane, readying the fragment for cyclization.[21] Treatment with dibromotetrachloroethane, triphenylphosphine, and 2,6-lutidine gave the 5-bromo-oxazoline, which is directly dehydrohalogenated with DBU in 90% yield to provide the tris-oxazole **15**. Removal of the *tert*-butyldiphenylsilyl ether was effected with AcOH buffered TBAF in 92% yield. Oxidation of the primary alcohol to the corresponding aldehyde **16** with Dess–Martin periodinane in 98% yield provided the C7–C19 fragment.

Coupling of the C1–C6 **4** and C7–C19 **16** subunits by a Kishi–Nozaki coupling with $CrCl_2/NiCl_2$ in THF/DMSO afforded the C1–C19 fragment **17** in 78% yield as a 1:1 mixture of diastereomers.[22] Treatment with Dess–Martin periodinane provided the enone **18** in >99% yield. The synthesis was completed by conjugate addition of hydride to the enone using CuCl, PPh_3, TBAF, $PhMe_2SiH$.[23] This reaction proceeded in quantitative yield, affording the fully protected C1–C19 fragment **2**.

In summary, an advanced C1–C19 fragment of ulapualide A was synthesized in 17 steps from **8** in 13% overall yield. The C3-hydroxyl bearing stereocenter was installed using Jacobsen's HKR methodology while the C9-methyl bearing stereocenter was introduced through use of chiral (*E*)-crotylsilane bond construction methodology. The completion of the synthesis and stereochemical assignment of ulapualide A is currently underway in our laboratory and will be reported in due course.



Scheme 1. Synthesis of the C1–C6 subunit.



Scheme 2. Synthesis of the C1–C19 fragment.

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