Studies Directed toward the Synthesis of Ulapualide A. Asymmetric Synthesis of the C8−C25 Tris-Oxazole Fragment

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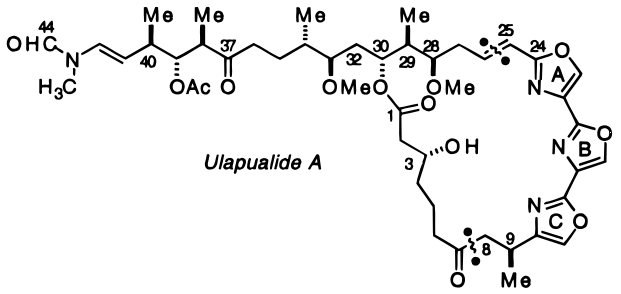
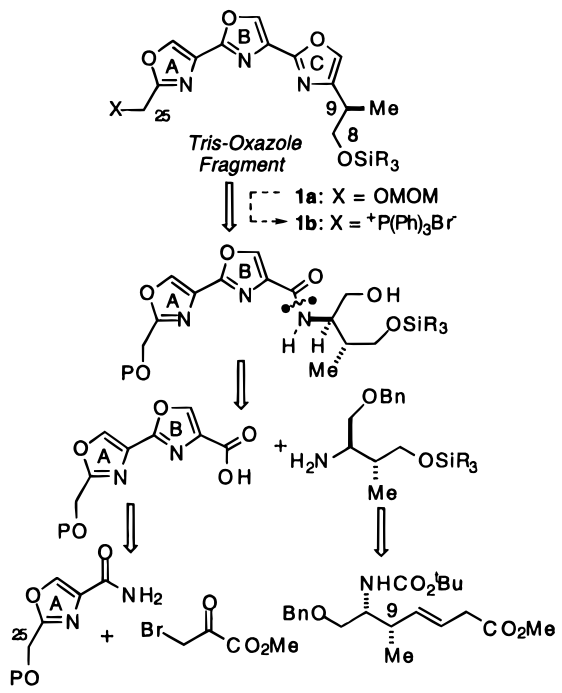
In the preceding paper, the asymmetric synthesis of the C26−C42 fragment of ulapualide A was reported.[1] In this communication we wish to report the first asymmetric synthesis of the C8−C25 tris-oxazole fragment containing the C9-methyl-bearing stereocenter which is suitably functionalized at both ends for subsequent fragment coupling.[2]

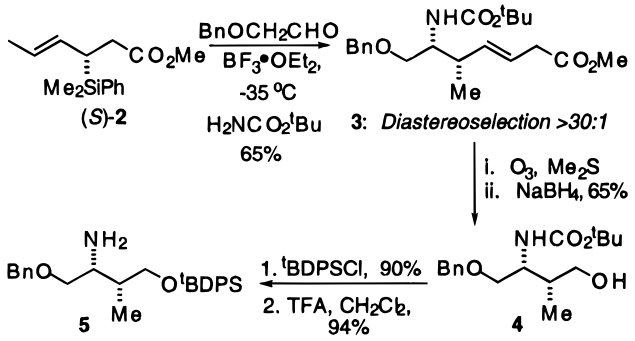


In connection with our synthetic plan for coupling of these two fragments during the construction of the C25−C26 *trans* double bond, it is our intention to rely on a phosphorus-based olefination strategy utilizing either phosphonium salts or the related phosphonate ester.[3] The synthetic analysis of the tris-oxazole, summarized in Scheme 1, involved the opening of the C-ring oxazole to give a bis-oxazole, bearing the chiral amino alcohol side chain. Disconnection at the amide linkage then affords the carboxylic acid bis-oxazole and the chiral amine. It was envisioned that with modified Hantzsch conditions, similar to those employed for thiazoles, an efficient bis-oxazole synthesis could be developed for the construction of the AB ring system.[4] Most published oxazole preparations rely on either a peptide-based two-step cyclization/oxidation sequence which is often times compromised by a competing elimination pathway and/or a low-yielding aromatization step.[5] Hantzsch methodology, centering on the treatment of an amide with a α-halo ketone, generates, in an efficient one-pot process, the oxazole that is suitably functionalized at the 4-position for the introduction of the second oxazole. The assembly of the AB-ring system and the chiral amine fragment, which was

Scheme 1



Scheme 2



derived from the homoallylic carbamate, whose syntheses are described below, represent the principal subunits of **1a**. We were attracted to the possibility of establishing the C9-methyl-bearing stereocenter and the nitrogen atom of the third oxazole (C-ring) through a *syn*-selective amino-crotylsilation. The importance of convergency and the fact that literature precedence for transformations of this type have been established prompted us to investigate such an approach.[6] The synthesis of the oxazole subunit bearing the C9-methyl stereocenter was initiated with a $BF_3{\cdot}OEt_2$-promoted addition of the (*S*)-**2** silane to an *in situ*-generated *tert*-butyl-*N*-acylimine derived from α-(benzyloxy)acetaldehyde afforded the homoallylic amine **3**, as a single diastereomer (>30:1, *syn*/*anti*) in 65% yield (Scheme 2).[7] Cleavage of the *trans* double bond by ozonolysis followed by immediate reduction with $NaBH_4$ afforded the chiral primary alcohol **4**, in 65% overall yield. The chiral subunit was then secured in two steps. Protection of the primary hydroxyl as its *tert*-butyldiphenylsilyl ether (90% yield), followed by removal of the Boc *N*-protecting group (TFA, CH_2Cl_2, rt), produced the amine **5**, in 94% yield. This series of transformations completed the synthesis of the chiral

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(4) Thiazoles and related oxazoles: (a) Aguilar, E.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 2473−2476. (b) Aguilar, E.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 2477−2480. (c) Schmidt. U.; Gleich, P.; Griesser, H.; Utz, G. R. *Synthesis* **1986**, 992−998. (d) Moody, C. J.; Swann, E. *J. Med. Chem.* **1995**, *38*, 1039−1043. (e) Kelly, T. R.; Lang, F. *Tetrahedron Lett.* **1995**, *36*, 5319−5322.

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(6) Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1994**, *59*, 2674−2676.

(7) Satisfactory spectroscopic data (^1H and ^{13}C NMR, IR, MS, and HRMS) were obtained for all new compounds.

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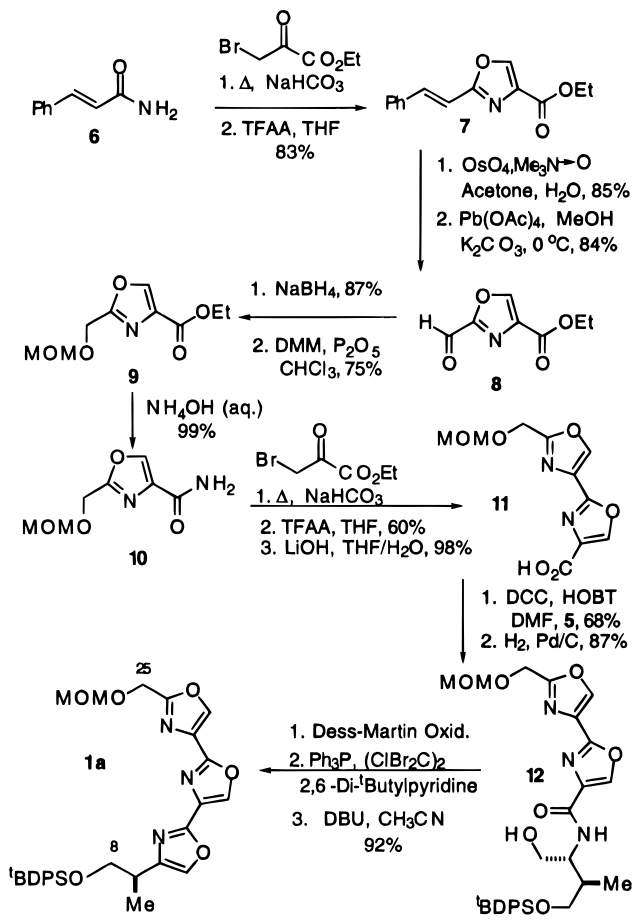
Scheme 3



fragment-containing methyl stereocenter, which was installed into the third oxazole as its side chain, and illustrates the versatility of chiral silane methodology for the construction small of chiral amine fragments.

The preparation of the bis-oxazole fragment **11**, coupling to the chiral amine **5**, and completion of the synthesis of chiral tris-oxazole fragment is summarized in Scheme 3. The synthesis of the bis-oxazole fragment began with the use of a modified Hantzsch synthesis.[8] Reaction of *trans*-cinnamamide with α-bromo ethyl pyruvate (2.2 equiv) using $NaHCO_3$-buffered conditions, followed by cyclodehydration (TFAA/THF, 1:1 v/v), afforded the functionalized oxazole **7** in 83% yield. It was our intention to utilize the *trans* double bond as an interchangeable functional group that would allow the introduction of a suitably modified side chain of the tris-oxazole for eventual coupling through a phosphorus-based olefination. The successful use of this intermediate in the synthesis required a selective oxidative cleavage of the *trans*-disubstituted double bond. Since it is known that the oxazole ring is sensitive to ozone,[5a] this transformation was accomplished via a two-step process, employing dihydroxylation with catalytic OsO_4, (10 mol %) and TMANO (1.5 equiv) in 85% yield.[9] The purified diol was subjected to oxidative cleavage using $Pb(OAc)_4$ (1.2 equiv), affording the corresponding aldehyde **8** in 84% yield which was subsequently reduced with $NaBH_4$ (2.0 equiv, EtOH) to give the primary alcohol in 87% yield. This alcohol was protected as the MOM ether (1:1 DMM/$CHCl_3$, P_2O_5) completing the construction of first oxazole unit (A-ring) **9** differentiated at the 2 and 4 positions. Conversion of the ethyl ester to the amide with aqueous NH_4OH afforded the amido-oxazole **10** and established the template for the construction of the second oxazole ring. The synthesis of the bis-oxazole subunit was carried out in 60% yield by subjecting the amide to the Hantzsch conditions as described above with recovery of starting amide. Hydrolysis of the ester by treatment with (LiOH, THF/H_2O) resulted in quantitative conversion to the bis-oxazole carboxylic acid **11**.

With the bis-oxazole **11** and chiral subunit **5** in hand, an efficient amide coupling and oxidation/cyclodehydration protocol was developed to complete the synthesis of the tris-oxazole fragment. Treatment of a solution of the carboxylic acid **11** with the chiral secondary amine **5** under standard amide coupling conditions DCC (1.1 equiv) and HOBT (0.1 equiv, DMF, rt) cleanly afforded the β-benzyloxy amide (68%) which was subjected to hydrogenolysis (H_2, 10% Pd−C, EtOH) to remove the benzyl ether protecting group (87% yield). This series of transformations gave the fully functionalized bis-oxazole **12** bearing the C9-methyl stereocenter which was now set for final conversion to the tris-oxazole fragment. This two-step oxidation/cyclodehydration sequence was completed through the intermediary bromo-oxazoline employing similar conditions previously described by Wipf.[10] Treatment of a solution of the β-hydroxy amide **12**, in CH_2Cl_2, with Dess−Martin periodinane[11] (3.0 equiv) resulted in the oxidation to the aldehyde that was directly cyclized to the oxazole. This aldehyde was converted to the bromooxazoline with $BrCl_2CCCl_2Br$ (5.0 equiv), and PPh_3 (5.0 equiv), 2,6-di-*tert*-butylpyridine (25.0 equiv) and without purification was dehydrohalogenated (DBU, 25.0 equiv; MeCN, rt), completing the formation of the tris-oxazole **1a** in 92% yield.

In summary, the first asymmetric synthesis of a suitably functionalized tris-oxazole fragment, identical to those of the ulapualides and with general application to the entire class of natural products, was accomplished in a convergent manner using 11 steps in 12% overall yield. An iterative Hantzsch-oxazole protocol was developed for the synthesis of the bis-oxazole subunit, while a new application of our chiral silane bond construction methodology was employed for the asymmetric synthesis of the chiral amine subunit. This chemistry played a key role in the synthesis of the third oxazole ring containing the methyl-bearing side chain. The coupling of the C26−C42 fragment described in the preceding paper to the tris-oxazole fragment and completion of the synthesis of ulapualide A will be reported at a later time.

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Supporting Information Available: General experimental procedures and spectral data for all intermediates and final product (7 pages).

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(8) The condensation of amide and α-halo ketone under Hantzsh conditions is typically driven either by heat or pressure, or through a buffer in order to remove generated acidic HX series. After surveying numerous reaction conditions involving changes in solvent (EtOH, CH_2Cl_2, THF, DME, acetone, CH_3CN, and toluene) and buffer (K_2CO_3, $CaCO_3$, $NaHCO_3$, Ag_2CO_3, and isoprene), the protocol was eventually optimized with ethyl bromopyruvate (1.3 equiv) and $NaHCO_3$ (5.0 equiv), in refluxing THF for 15 h followed by a second charge with ethyl bromopyruvate and an additional 8 h reflux period. Following filtration of solids and concentration under reduced pressure, the crude hydroxyoxazole was quantitatively converted to the oxazole through treatment with TFAA in THF at 0 °C.

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