Studies Directed toward the Synthesis of Ulapualide A. Asymmetric Synthesis of the C26−C42 Fragment

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Ulapualide A belongs to an emerging class of secondary metabolites, first isolated from the egg masses of marine nudibranches (sea slugs).[1] Subsequent reports identified structurally related members possessing a tris-oxazole fragment, which include the halichondramides,[2] mycalolides,[3] and kabiramides.[4] Ulapualide A exhibits inhibitory activity against L1210 leukemia cell proliferation and antifungal activity. Although the relative and absolute stereochemical relationships of the ulapualides have not been established, structural similarities between these macrolides provide circumstantial evidence for a common stereochemical assignment. The stereochemistry is based on a correlation with related marine natural products, scytophycin C,[5] whose stereostructure has been determined by X-ray crystallography, and by NMR analysis of kabiramide C.[6] Molecular modeling studies reported by Pattenden are consistent with the illustrated stereochemistry and support the notion of a common absolute stereochemistry.[7] This prediction has not been confirmed experimentally. It should be noted that there is an apparent discrepancy in the ulapualide stereochemical relationships originating from the assignment of the C34 methyl group of scytophycin and kabiramide C. To address this issue we have incorporated into our synthesis a set of double stereodifferentiating crotylation reactions capable of providing either a *syn*- or *anti*-bond construction across C33−C34.

As a result of their complex stereostructure and diverse architecture these macrolides provide challenges to the organic chemist.[8] Herein we wish to report the asymmetric synthesis of the C26−C42 fragment, and in the accompanying communication we describe the preparation of the C8−C25 tris-oxazole fragment.

It was our intention to design a convergent route using our chiral allylsilane bond construction methodology[9] for the introduction of the stereochemical relationships. The synthesis would be adaptable with regard to the order of fragment coupling. The first disconnection at the

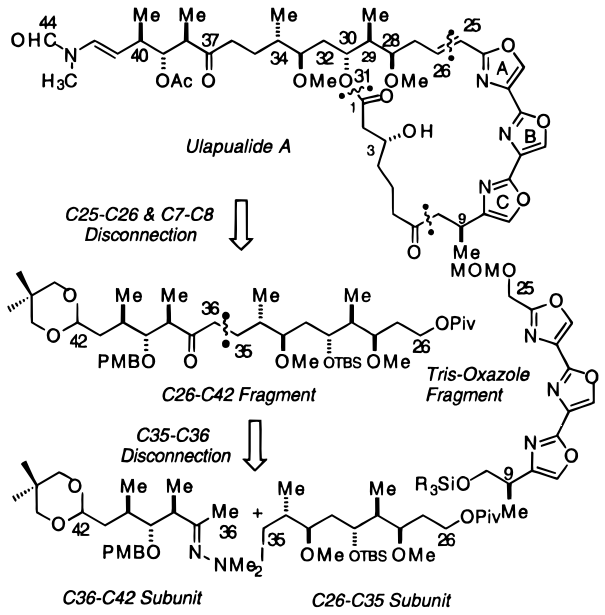
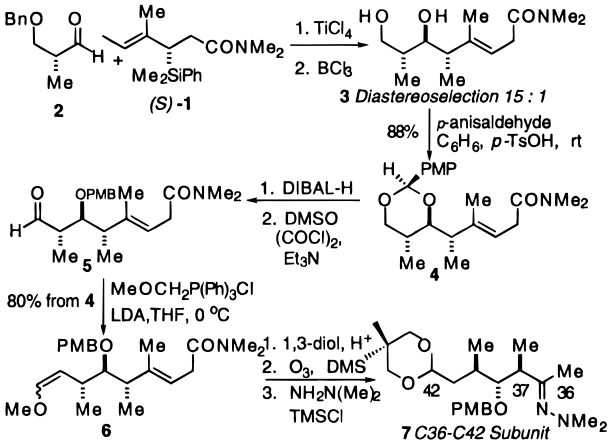


Figure 1.

Scheme 1



C25−C26 and C7−C8 bonds and cleavage of the C1-ester linkage produced three principal fragments including the aliphatic and tris-oxazole portions (Figure 1). Further disconnection of the C35−C36 bond produces two smaller subunits which served as our initial subgoals.

C36−C42 Subunit. The preparation of this subunit relied on the installation of three contiguous stereocenters through a chelation-controlled condensation of a *β*-methyl-substituted (*E*)-crotylsilane with (*R*)-3-(benzyloxy)-2-methylpropanal, followed by a one-carbon homologation of the benzyloxy terminus and cleavage of the trisubstituted olefin to give the protected methyl ketone equivalent. The synthesis was initiated with a Lewis acid-promoted condensation of silane (*S*)-**1**[10] with aldehyde **2** (Scheme 1). In the presence of $TiCl_4$ (1.2 equiv) this *anti*-selective crotylsilation (15:1 *anti*/*syn*) results from a matched double stereodifferentiating pairing and proceeds through a transition state involving a chelated aldehyde to give the homoallylic alcohol in 76% yield.[11] Deprotection of the primary hydroxyl group with BCl_3 (2 equiv) in PhMe provided the 1,3-diol **3** in 90% isolated

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(2) (a) Matsunaga, S.; Fusetani, N.; Hashimoto, K.; Koseki, K.; Noma, M.; Noguchi, H.; Sankawa, U. *J. Org. Chem.* **1989**, *54*, 1360−1363. (b) Kernan, M. R.; Molinski, T. F.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 5014−5020.

(3) Fusentani, N.; Yasumuro, K.; Matsunaga, S.; Hashimoto, K. *Tetrahedron Lett.* **1989**, *30*, 2809−2813. The carbon skeleton of ulapualide A is numbered according to reference 1a, reporting its isolation.

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(10) For preparation of silane (*S*)-**1** and (*S*)-**15**, see supporting information.

(11) (a) Jain, N. F.; Cirillo, P. F.; Pelletier, R. *Tetrahedron Lett.* **1995**, *36*, 8728−8730. (b) Panek, J. S.; Beresis, R. T. *J. Org. Chem.* **1993**, *58*, 809−810.

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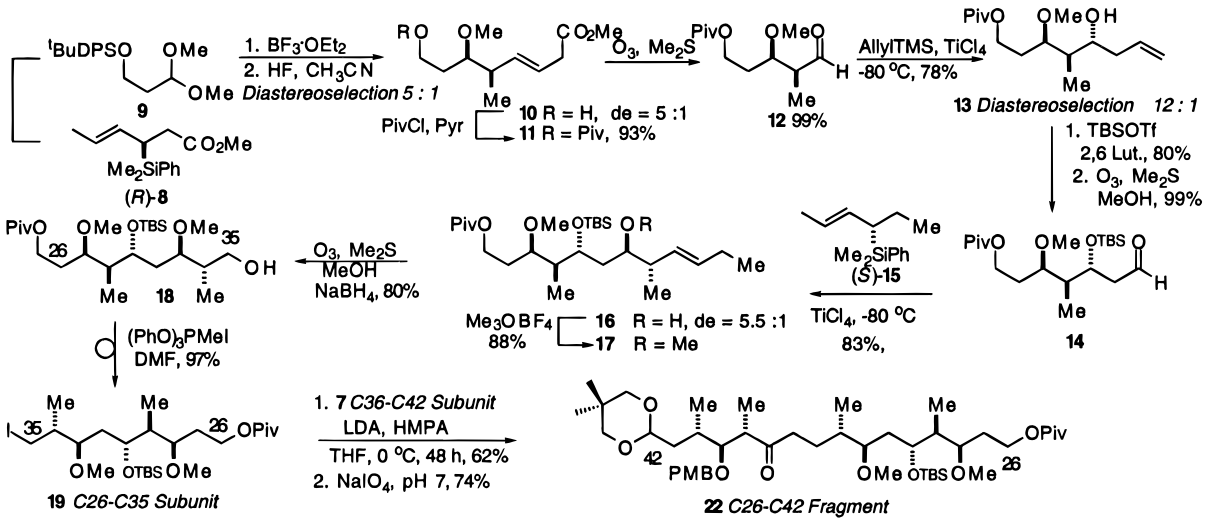
Scheme 2



yield.[12] Acetal formation with (PMBCHO, 1.3 equiv, cat. *p*-TsOH) afforded the *p*-methoxybenzylidene **4** (88%) which was subjected to nucleophilic opening (DIBAL-H, 5.0 equiv, CH_2Cl_2 −50 °C, 15 h) giving the primary alcohol in 100% yield as a single diastereomer. With the protection of the secondary hydroxyl group, the remaining primary hydroxyl was oxidized under Swern conditions providing aldehyde **5**.[13] A one-carbon homologation with (methoxymethyl)triphenylphosphonium ylide resulted in the formation of enol ether **6** (80% yield two-steps) which was directly converted to the C42 acetal (2,2-methyl-1,3-propanediol, PPTS, C_6H_6, Δ) in 90% yield. This ketalization established a stable carbonyl synthon for eventual elaboration to the terminal *N*-formyl enamine. Cleavage of the trisubstituted olefin by ozonolysis afforded the methyl ketone in 70% yield, which was converted to the *N*,*N*-dimethylhydrazone **7** in 87% yield through treatment with TMSCl (2.0 equiv) in *N*,*N*-dimethylhydrazine.[14] This sequence completed the synthesis of **7** in nine steps, 26% overall yield from (*S*)-**1**.

C26−C35 Subunit. The synthesis of this subunit (Scheme 2) relies on three sequential asymmetric crotyl- and allylation reactions to establish the stereochemical relationships at *syn*-C28−C29, *anti*-C29−C30, and *anti*-C33−C34. In accord with previous reports from this laboratory,[15] the synthesis began with the addition of silane (*R*)-**8**[10] to acetal **9** (BF_3·OEt_2, 2.0 equiv, −50 °C) to afford the *syn* homoallylic ether that was, without purification, deprotected (aqueous HF−CH_3CN) providing the primary alcohol **10** (75%, two steps). After chromatographic removal of the minor diastereomer, the primary hydroxyl group was protected as the pivalate ester (PivCl, 2.0 equiv, CH_2Cl_2−pyridine 3:2) which gave **11** in 93% yield. Cleavage of the (*E*)-olefin with ozone yielded the aldehyde **12** in quantitative yield which was subjected to a chelate-controlled[16] allylsilane addition ($TiCl_4$, 1.2 equiv, −80 °C, CH_2Cl_2) affording the homoallylic alcohol **13** (78%). Protection of the secondary alcohol (TBSOTf, 1.5 equiv, 2,6-lutidine, 3.0 equiv, 0 °C) followed by oxidative cleavage (O_3, SMe_2) gave **14** in 89% yield (two steps). At this stage the C26−C33 synthon of this subunit is prepared for a second crotylation reaction to install the final two stereocenters. Accordingly, silane (*S*)-**15**[10] (2.0 equiv) condensed with **14** in the presence of $TiCl_4$ (1.2 equiv, −80 °C, 15 h) to provide the homoallylic alcohol **16** in 83% yield. The useful level of diastereoselection (5.5:1 *anti*/*syn*) in this reaction is consistent with a nonchelation-controlled, partially mismatched process which exhibits 1,3-induction.[17] In this case, the stereochemical bias of the aldehyde overrides the normal *syn* preference of the (*E*)-silane reagent.[11a]

Methylation of **16** with Me_3OBF_4 (6.0 equiv) and proton sponge (6.0 equiv) gave the homoallylic ether **17** in 85% yield. Cleavage of the *trans* olefin under ozonolysis conditions was immediately followed by reduction of the crude aldehyde with $NaBH_4$ (2.0 equiv) to give the primary alcohol **18** in 80% yield. The synthesis of C26−C35 subunit **19** was achieved in a 10-step sequence with an overall yield of 24% by iodination (97%) utilizing $(PhO)_3PMeI$ (1.2 equiv) in DMF at 0 °C.[18]

C26−C42 Fragment. This fragment was prepared by coupling of the hydrazone-derived methyl ketone enolate **7** to the C26−C35 subunit **19** by displacement of the primary iodide. Hydrazone **7** was lithiated (LDA, 1.3 equiv, HMPA, 1.5 equiv, THF, 0 °C, 30 min) before the addition of iodide **19** (1.5 equiv). The reaction was maintained at 0 °C for 48 h to yield the C26−C42 segment **22** in 62% isolated yield (84% yield based on recovered hydrazone). The hydrazone was oxidatively removed with $NaIO_4$ affording the ketone. The synthesis of the C26−C42 fragment of ulapualide A was accomplished using chiral allylsilane bond construction methodology for the introduction of the stereochemical relationships. In the following paper, the synthesis of the tris-oxazole fragment is described.

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Supporting Information Available: General experimental procedures and stereochemical proofs as well as spectral data for all intermediates and final products (15 pages).

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(12) Satisfactory spectroscopic data (^1H and ^{13}C NMR, IR, CIMS, CIHRMS) were obtained for all new compounds. Ratios of diastereomers were determined by ^1H-NMR.

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(16) Chelation-controlled carbonyl additions see Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462−468.

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(18) Aldehyde **14** was condensed with silane (*R*)-**15** under similar conditions, to afford **20** in 84% yield and excellent *syn* diastereoselection.