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Studies Directed Toward the Synthesis of Ulapualide A: Phosphorus-Based Olefination as Model Studies for (Schlosser-like) Fragment Coupling

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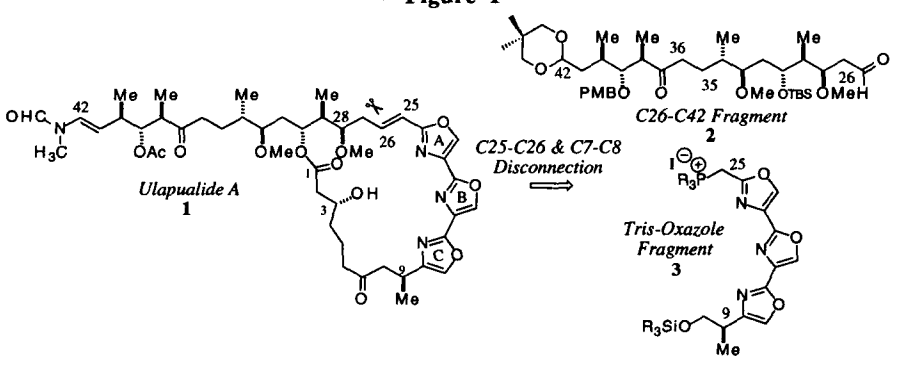
Abstract. Preliminary studies aimed at developing reaction conditions for the fragment coupling between the C_{26}-C_{42} fragment and the tris-oxazole fragment of ulapualide A are described. Our approach utilizes Schlosser-Wittig olefination conditions for the construction of a *trans*-double bond. In this study, seven different tri-alkyl and tri-aryl phosphines were evaluated in an attempt to determine the extent of *trans* / *cis* selectivity for the prospective construction of the *trans*-C_{25}-C_{26} double bond of ulapualide A. © 1997 Elsevier Science Ltd.

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. Presently, the stereochemistry is based on a correlation with related marine natural products, scytophycin C,[5] possessing a nearly identical side chain and whose stereostructure has been determined by X-ray crystallography and by NMR analysis of kabiramide C.[6]

Figure 1

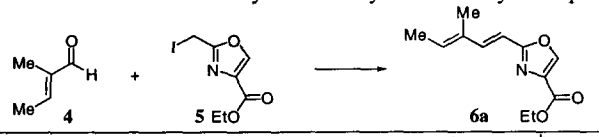


We have recently reported an efficient asymmetric synthesis of the fully elaborated C26-C42 fragment[7] as well as the first asymmetric synthesis of the C8-C25 tris-oxazole[8] unit of ulapualide A. A convergent route was designed which would permit the use of our developing chiral allylsilane bond

construction methodology[9] for the introduction of the stereogenic centers. The synthesis would be adaptable with regard to the order of fragment coupling. The first disconnections at the C25-C26 and C7-C8 bonds and cleavage of the C1-ester linkage produced three principal fragments including the aliphatic and tris-oxazole portions each possessing different synthetic challenges (Figure 1). The purpose of this communication is to report the results of our study concerning the use of a phosphorous-based fragment coupling strategy to be employed in the synthesis of ulapualide A.

Phosphorous-based olefination strategies were envisioned as a potential method for fragment coupling. This bond constuction methodology is partially precedented by the total synthesis of calyculin A, where a *trans*-4-alkenyl oxazole is prepared.[10] The present studies were designed to probe the fragment coupling strategy of the tris-oxazole unit with the C_{26}-C_{42} iodide fragment, to afford a *trans*-2-alkenyl oxazole. Good to excellent levels of selectivity in the construction of the C_{25}-C_{26} *trans* double bond has been established between a range of aldehydes with mono-, bis-, and tris-oxazole Wittig salts.[11] These model studies have proven the suitability of phosphorous based ylides for construction of the *trans*-C_{25}-C_{26} olefin in the synthesis of ulapualide A.

Table 1. Levels of Selectivity of Tri-Alkyl and Tri-Aryl Phosphines.



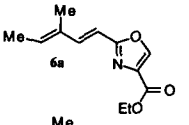
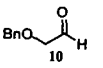
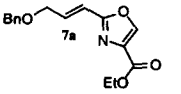
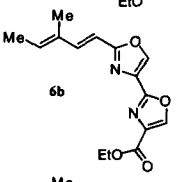
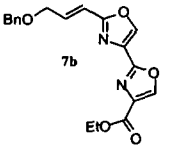
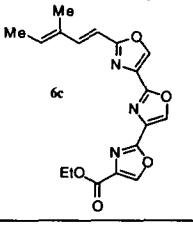
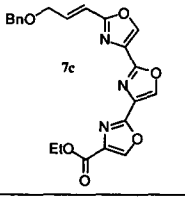
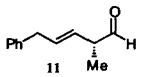
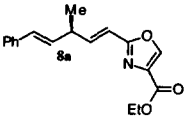
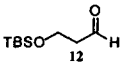
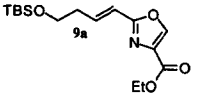
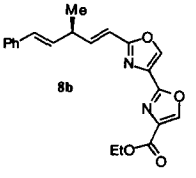
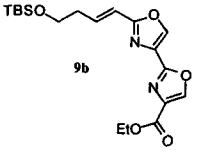
Entry	Phosphine	*trans : cis* ratio[a]	Yield[b]
1	$(Et)_3P$	100:0	97%
2	$(n\text{-}Bu)_3P$	100:0	98%
3	$(Ph)_3P$	4:1	69%
4	$(p\text{-}CH_3Ph)_3P$	5:1	67%
5	$(c\text{-hexyl})_3P$		no desired product
6	$(Bn)_3P$		no desired product
7	$(t\text{-}Bu)_3P$		no desired product

[a] Ratios were obtained by integration of ^{1}H-NMR. [b] Yields are of isolated product.

In this study, seven different tri-alkyl and tri-aryl phosphines[12] were evaluated to determine the extent of *trans* / *cis* selectivity in the olefination reaction under Schlosser-like conditions[13] with mono-oxazole **5** (Table 1).[14] The highest *trans* selectivity was established with unbranched alkyl phosphines (entries **1** and **2**), with no *cis* isomer detectable by ^{1}H-NMR.[15] Tri-butyl phosphine and tri-ethyl phosphine provided comprable results, with tri-ethyl phosphine proving to be more operationally convenient and was utilized in subsequent olefination reactions. The aryl phosphine stabilized ylides afforded a mixture of isomers (entries **3** and **4**), while branched alkyl phosphines, such as c-hexyl (entry **5**), benzyl (entry **6**), and *t*-butyl (entry **7**), resulted in no formation of the desired product.

With selectivity established, we then surveyed a range of aldehydes to assess the reactivity of mono-, bis-, and tris-oxazoles. The olefination reactions, summarized in Table 2, provided the desired products in moderate to good yields with excellent levels of *trans* : *cis* selectivity. It should be noted that reaction with the preformed phosphonium salts to yield **7a** and **8a** did not improve the yield, so the salt was generated *in situ* in all cases. Having established the utility of the Schlosser-Wittig olefination conditions to provide *trans*-2-alkenyl ozaxoles, we proceeded to coupling of a system that is structurally related to the natural product.

Table 2. Reactivity of Various Aldehydes with Mono-, Bis-, and Tris-Oxazoles.

Entry	Aldehyde	Major Product	Yield	Entry	Aldehyde	Major Product	Yield
1	 4	 6a	97%	4	 10	 7a	47%
2		 6b	67%	5		 7b	63%
3		 6c	82%	6		 7c	67%
Entry	Aldehyde	Major Product	Yield	Entry	Aldehyde	Major Product	Yield
7	 11	 8a	62%	9	 12	 9a	55%
8		 8b	66%	10		 9b	65%

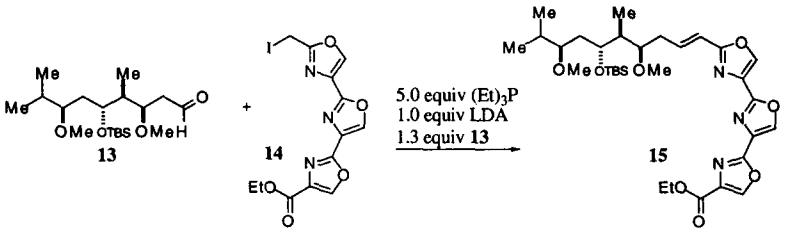
[a] A typical procedure is as follows: To a 0.08 **M** solution of iodo-oxazole in DMF at rt was added $(Et)_3P$ (5 equiv). After 30 min., the solution was cooled to 0 °C and LDA (1.0 equiv) was added, resulting in a yellow color. The solution was allowed to stir for 10 min. before addition of 1.3 eq. of the aldehyde. After 45 min. the reaction was diluted upon addition of saturated $NaHCO_3$.

There still remained the question of the viability of this approach to effectively condense a branched β-alkoxy aldehyde, especially with regard to β-eliminination.[16] An aldehyde bearing a stereogenic center at the β-position was designed to provide a closer analogy to the bond construction that will be encountered in the synthesis of the natural product. Subsequently we undertook coupling of a chiral β-alkoxy aldehyde **13** with the tris-oxazole subunit **14** (Scheme 1). This reaction proceeded in 83% yield under the defined conditions, affording **15** as a single olefin isomer. This process confirmed the utility of the Wittig coupling strategy for the installation of the C_{25}-C_{26} *trans* olefin of ulapualide A.

To summarize, we have developed an efficient method using Schlosser-Wittig olefination conditions for the coupling of oxazoles with α,β-unsaturated and branched aldehydes. The reaction is highly selective for the formation of a conjugated *trans*-olefin and provides good precedence for

extension to the natural system. The completion of the synthesis of ulapualide A is currently underway and will be reported at a later time.

Scheme 1



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References and Notes

1. (a) Roesener, J. A.; Scheuer, P. J. *J. Am. Chem. Soc.* **1986**, *108*, 846-847. (b) Matsunaga, S.; Fusetani, N.; Hashimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 847-849.
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 the reference1a, reporting its isolation.
4. Matsunaga, S.; Fusetani, N.; Hashimoto, K.; Koseke, K.; Noma, M. *J. Am. Chem. Soc.* **1986**, *108*, 847-849.
5. Kiefel, M. J.; Maddock, J.; Pattenden, G. *Tetrahedron Lett.* **1992**, *22*, 3227-3230.
6. Professor N. Fusetani and Dr. S. Matsunaga Personal communication.
7. Panek, J. S.; Beresis, R. T.; Celatka, C. A. *J. Org. Chem.* **1996**, *61*, 6494-6495.
8. Panek, J. S.; Beresis, R. T. *J. Org. Chem.* **1996**, *61*, 6496-6497.
9. Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293-1316.
10. Zhao, Z.; Scarlato, G. R.; Armstrong, R. W. *Tetrahedron Lett.* **1991**, *32*, 1609-1612.
11. Oxazole synthesis: Turchi, I. J. *Ind. Eng. Chem. Prod. Res. Dev.* **1981**, *20*, 32-76.
12. Vedejs, E.; Marth, C. F. *J. Am. Chem. Soc.* **1988**, *110*, 3948-3958.
13. Schlosser, M.; Schaub, B. *J. Am. Chem. Soc.* **1982**, *104*, 5821-5823.
14. Liu, P; Celatka, C. A.; Panek, J. S. Preceeding paper in this issue.
15. Satisfactory spectroscopic data (^{1}H and ^{13}C NMR, IR, MS, and HRMS) were obtained for all new compounds.
16. Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Org. Chem.* **1992**, *57*, 1964-1966.

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