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Studies Directed Toward the Total Synthesis of Kabiramide C: Asymmetric Synthesis of the C7-C19 Fragment

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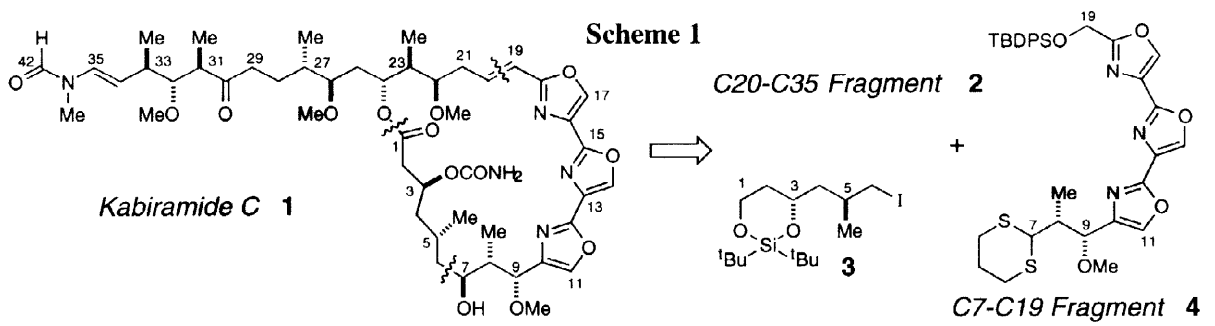
Abstract: The synthesis of the C7-C19 tris-oxazole fragment **4** of kabiramide C via a BF_3•OEt_2 promoted condensation between dimethyl acetal **12** and *(S)*-silane **6** as the crucial synthetic step is described. © 1998 Elsevier Science Ltd. All rights reserved.

Kabiramide C (**1**) was first isolated in 1986 by Fusetani and coworkers from the egg masses of marine nudibranches (sea slugs).[1] It belongs to an emerging class of secondary metabolites including the ulapualides,[2] halichondramides,[3] and mycalolides,[4] which share similar molecular architecture and an exciting biological profile. Subsequent studies revealed that these tris-oxazole containing macrolides exhibit a broad range of biological activities, including antileukemic, antifungal, and ichthyotoxic properties.[5] Kabiramide C, which is an extremely potent antifungal agent[1] as well as a novel actin depolymerizing agent, may serve as a new pharmacological tool for analyzing actin-mediated cell functions, such as muscle contraction, cell motility, and cell division. Structurally, kabiramide C is

Scheme 1



constructed from a 28-membered lactone which incorporates a tris-oxazole motif and a *N*-methyl formyl group bearing sidechain. Although the relative and absolute stereochemistry of **1** has not been unambiguously assigned, structural similarities among these macrolides provide compelling circumstantial evidence for a common stereochemical assignment consistent within this class. The illustrated stereochemistry rests primarily on spectroscopic analysis[6] and a correlation with a related marine natural product, scytophycin C,[7] whose stereostructure has been established by X-ray crystallography. The unique molecular structure of kabiramide C, in conjunction with its activity profile, has attracted considerable interest of certain members of the synthetic organic community.[8] In this paper, we wish to report the asymmetric synthesis of the C7-C19 tris-oxazole fragment **4**.

The bond disconnections at the C6-C7 and C19-C20 and cleavage of the lactone linkage produced three principal fragments including the known C20-C35 polypropionate fragment **2**,[8d] the C1-C6 aliphatic fragment **3**, and the C7-C19 tris-oxazole fragment **4** (Scheme 1).

It was envisioned that the *syn* stereochemical relationship at the C8 and C9 in **4** could be established using chiral allylsilane based bond construction methodology.[9] Since the formyl oxazoles are

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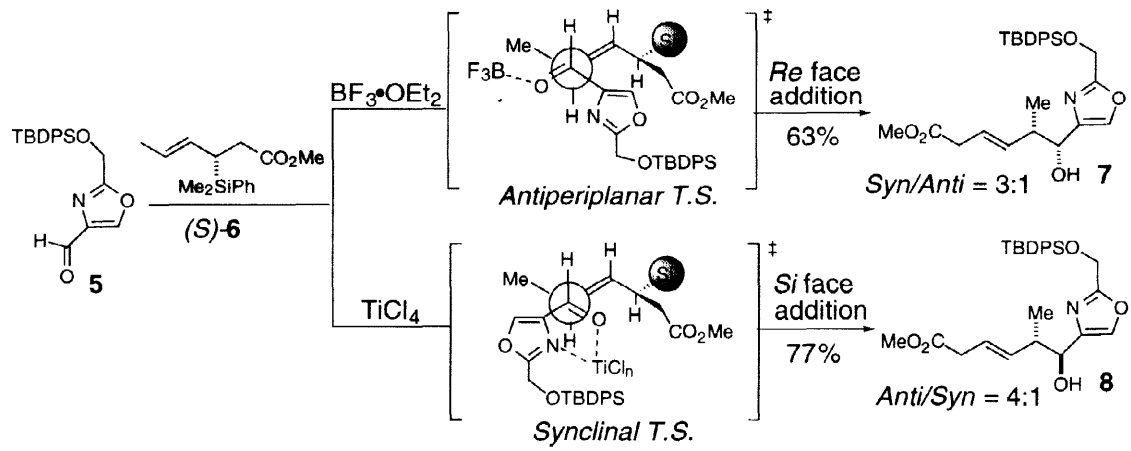
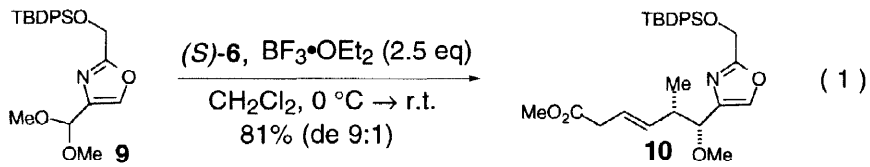
previously unreported substrates for the Lewis acid promoted condensations with chiral crotylsilane reagents, we designed model studies that would define reaction conditions and suitability of the formyl oxazoles in the asymmetric crotylation reactions.

Model Studies. Oxazole-aldehyde **5**, which is easily accessible from the corresponding 4-ethoxycarbonyl oxazole,[8e] was chosen as the substrate to evaluate the sense and level of the asymmetric induction by chiral silane *(S)*-**6**. Among the many Lewis acids examined, BF_3•OEt_2 and $TiCl_4$ proved to be the only Lewis acids that can promote the condensation between **5** and **6** in synthetically useful yields. More interestingly, it was found that the sense of 1,2-asymmetric induction in the Lewis acid promoted addition of *(S)*-**6** to oxazole aldehydes can be turned over by proper choice of the Lewis acid, albeit, with modest diastereoselection (Scheme 2). If the monodentate Lewis acid BF_3•OEt_2 is employed, a *syn* bond construction predominates, presumably via an antiperiplaner transition state. Whereas the complimentary *anti* bond construction can be achieved when $TiCl_4$, a bidentate Lewis acid, is used to promote the condensation presumably through simultaneous coordination of the aldehyde carbonyl and the nitrogen of the oxazole ring. The 1,3-relationship of the heteroatoms of the oxazole ideally prediposes the more Lewis basic nitrogen with the aldehyde carbonyl to generate a 5-membered chelate with $TiCl_4$ (see illustrated synclinal transition state), which is responsible for the turn over of the stereochemical course of the crotylation.

Scheme 2[10]



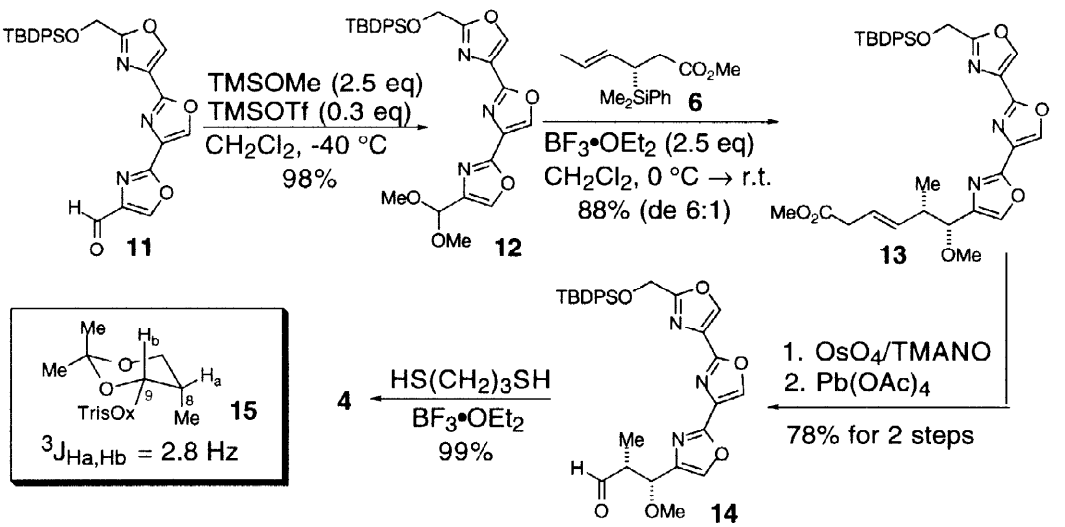
In an effort to increase the level of diastereoselectivity, we then turned our focus on the crotylation with the oxocarbonium ion derived from dimethyl acetal **9**. Gratifyingly, BF_3•OEt_2 promoted condensation between **9** and **6** proceeded smoothly with a useful level of diastereoselectivity (*de* 9:1 *syn/anti*), resulting in the formation of the homoallylic ether **10**[11] in 81% yield (eq 1). The conditions developed for this reaction were used in the synthesis of the C7-C19 fragment.



(1)

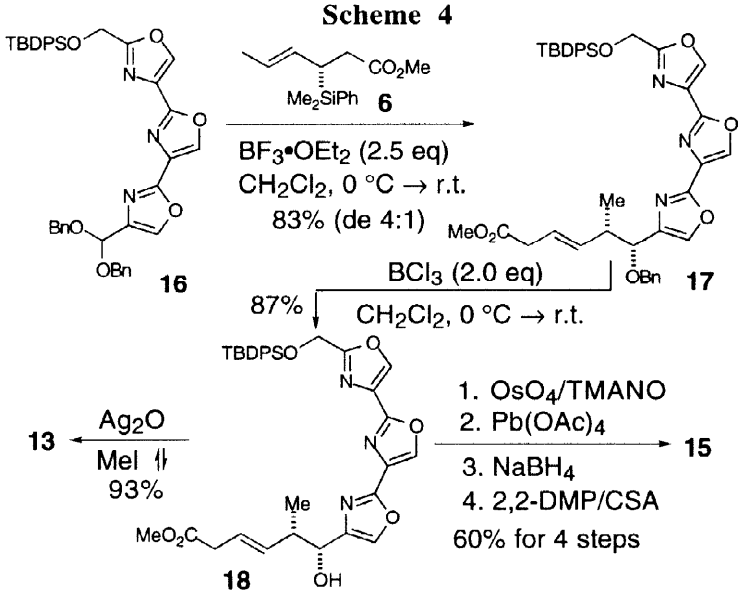
The C7-C19 Fragment. The previously reported tris-oxazole aldehyde **11**[8f] served as the starting point for the synthesis of the C7-C19 fragment **4** (Scheme 3). Conversion of the aldehyde **11** to the corresponding dimethyl acetal **12** (TMSOMe/TMSOTf, 98%), followed by BF_3•OEt_2 promoted crotylation using *(S)*-**6** (2.5 equiv BF_3•OEt_2, CH_2Cl_2, 0 °C to rt) afforded the homoallylic methyl ether **13** in 88% yield with a moderate degree of diastereoselection (*syn/anti* 6:1). Through a two step process, (1) a catalytic dihydroxylation with OsO_4 (0.1 mol %), (2) an oxidative diol cleavage by $Pb(OAc)_4$ (1.2 equiv), the methyl ether **13** was converted to aldehyde **14** (78% for two steps), which was converted to the dithiane under standard conditions [$HS(CH_2)_3SH$, BF_3•OEt_2],[12] providing **4**[13] in nearly quantitative yield. Thus, the synthesis of the C7-C19 fragment **4** was achieved by an efficient, five-step sequence with 67% overall yield from **11**.

Scheme 3



In order to assign the stereochemical outcome of the C8/C9 bond construction, a correlation study was designed which is illustrated by Scheme 4. Thus, condensation between dibenzyl acetal **16** (prepared from **11** using TMSOBn/TMSOTf) and *(S)*-**6**, followed by debenzylation of benzyl ether **17**, afforded the homoallylic alcohol **18**, which was used for C8/C9 stereochemical assignment. From **18**, the acetonide **15** was prepared via a four-step sequence (dihydroxylation, diol cleavage, aldehyde reduction, and ketalization), and at the same time, methylation[14] of **18** provided the C-9 methyl ether, which is identical to **13** obtained from the direct crotylation with **12**.

Scheme 4



By measuring the three-bond coupling constant of H_a and H_b in **15** ($^3J_{Ha,\ Hb}$ = 2.8Hz), the *syn* relationship at C8/C9 was unambiguously assigned.

In summary, a concise synthesis of the C7-C19 tris-oxazole fragment of kabiramide C has been developed. The following paper in this issue describes the synthesis of the C1-C6 fragment and its union with the C7-C19 fragment.

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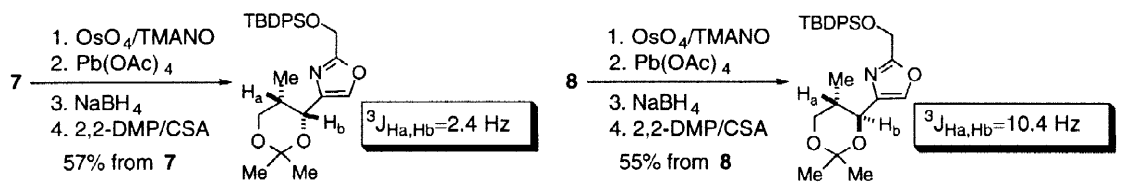
10. The stereochemistry of **7** and **8** was assigned according to the transformations below followed by three-bond coupling constant analysis of the ^{1}H-NMR spectra of the derived acetonides:



11. The stereochemistry of **11** was assigned by correlation with **8**: methylation of **8** gave **11**.
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13. Spectral data for **4**: ^{1}H-NMR ($CDCl_3$, 400 Hz): δ 8.34 (s, 1H), 8.29 (s, 1H), 7.70-7.69 (m, 5H), 7.44-7.36 (m, 6H), 4.80 (s, 2H), 4.54 (d, 1H, *J* = 5.6 Hz), 3.98 (d, 1H, *J* = 6.4 Hz), 3.35 (s, 3H), 2.88-2.72 (m, 4H), 2.46-2.37 (m, 1H), 2.08-1.91 (m, 1H), 1.91-1.80 (m, 1H), 1.14 (d, 3H, *J* = 6.8 Hz), 1.06 (s, 9H). ^{13}C-NMR ($CDCl_3$, 75.5Hz): δ 163.5, 156.0, 155.2, 141.5, 139.9, 138.4, 136.6, 135.6, 132.4, 131.7, 130.1, 129.8, 127.9, 77.3, 58.8, 57.8, 51.6, 41.9, 30.5, 30.1, 26.7, 26.2, 19.3, 12.0. IR (neat): υ_{max} 3164, 3072, 2934, 2898, 1646, 1588, 1428, 1378, 1112 cm^{-1}. HRMS (CI, NH_3): $[M+H]^+$ Calcd. for $C_{34}H_{40}N_3O_5S_2Si$: 662.2180. Found: 662.2160. $[\alpha]^{23}_D$ = +3.62° (c = 1.85, $CHCl_3$).
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