Pergamon

Tetrahedron Letters 39 (1998) 6147–6150

TETRAHEDRON LETTERS

Studies Directed Toward the Total Synthesis of Kabiramide C: Asymmetric Synthesis of the C1-C19 Fragment

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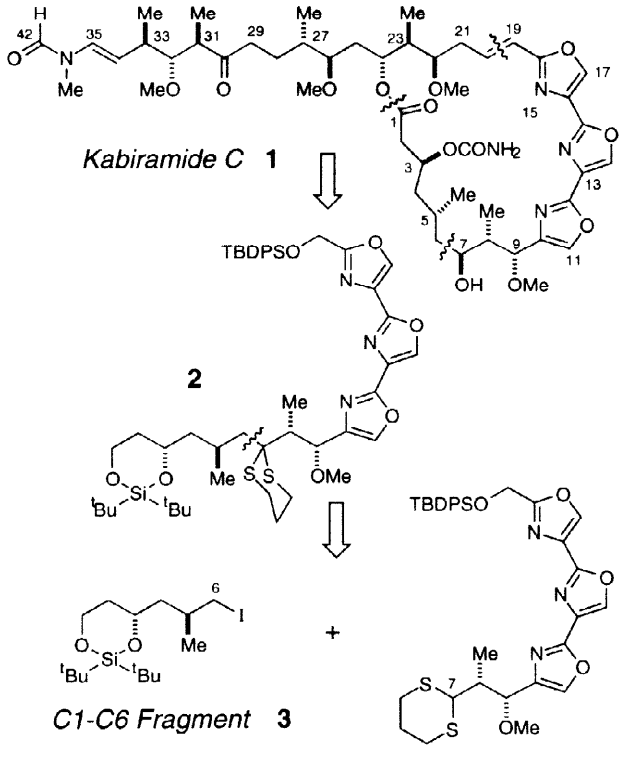
Received 11 June 1998; accepted 18 June 1998

Abstract: An efficient synthesis of the C1-C6 aliphatic fragment **3** and its coupling to the C7-C19 fragment **4** of kabiramide C is described. Key transformations include a $TiCl_4$ promoted condensation between aldehyde **5** and crotylsilane *(R)*-**6** and a Barton-McCombie deoxygenation of the homoallylic alcohol **9** to set the stereochemical array.

In the preceding paper, the asymmetric synthesis of the C7-C19 fragment of kabiramide C (**1**) was described.[1] Herein, we wish to report the asymmetric synthesis of the C1-C6 fragment **3** and its union with the C7-C19 fragment **4** completing the assembly of the central tris-oxazole core. Our general strategy for the construction of kabiramide C is based on the following considerations: (1) the approach should allow for a high degree of convergence; (2) the synthesis should permit the use of the chiral allylsilane-based bond construction methodology[2] for the introduction of the stereogenic centers; and (3) the strategic bond disconnections should be adaptable with regard to the order of fragment coupling. Therefore, it is our intention to employ a phosphorous-based olefination strategy during the formation of C19-C20 *trans* double bond[3] and to utilize a lithio-dithiane coupling for the C6-C7 bond construction (Scheme 1).

Scheme 1



Further retrosynthetic analysis of **3** suggested the use of a Lewis acid promoted condensation between aldehyde **5** and crotylsilane *(R)*-**6** as a straight forward protocol for the introduction of the C5 stereogenic center (Scheme 2).

Scheme 3 summarizes the construction of the C1-C6 fragment **3**, which began with the commercially available *(R)*-1,2,4-butanetriol **7**. The sequence was initiated by selective protection of the 1,3-diol as its di-^{t}butylsilyl ether [^{t}Bu$_2$Si(OTf)$_2$, 2,6-lutidine, CH_2Cl_2/DMF, 1:1 v/v, 0 °C, 86% yield) to afford the primary alcohol **8**, which was oxidized under Swern conditions[4] providing aldehyde **5** in 99% yield. The $TiCl_4$ promoted condensation between **5**

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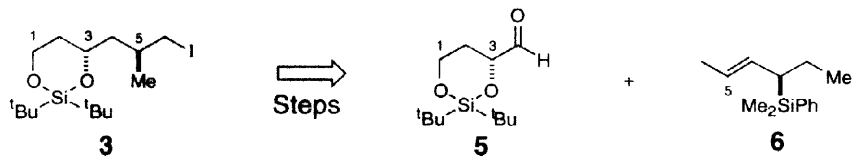
PII: S0040-4039(98)01300-8

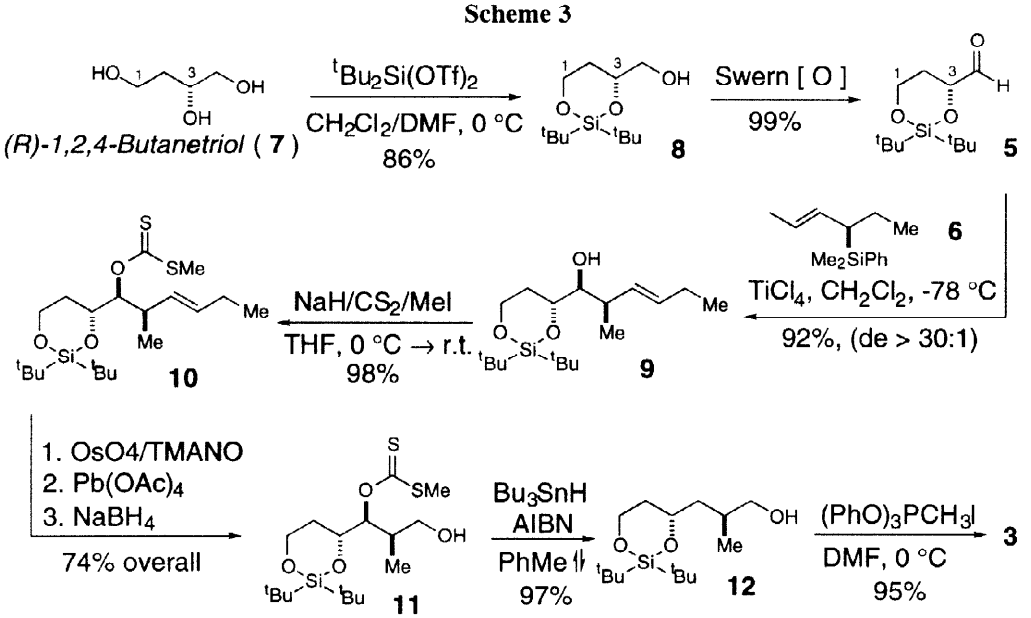
Scheme 2



3 **5** **6**

and crotylsilane *(R)*-**6** proceeded efficiently with high diastereoselectivity (*de* > 30:1 *syn/anti*), resulting in the formation of the homoallylic alcohol **9**[5] in 92% yield. With **9** in hand, a Barton-McCombie deoxygenation protocol[6] was employed to remove the secondary hydroxy group. Thus, alcohol **9** was converted to xanthate **10** (NaH, CS_2, MeI, 0 °C to rt, 98%), which was further elaborated to a new xanthate **11** in a three-step process, utilizing a catalytic dihydroxylation with OsO_4 (0.1 mol %) and TMANO (1.1 equiv).[7] The diol was used without purification in a subsequent oxidative cleavage using $Pb(OAc)_4$ (1.2 equiv)[8] to afford the intermediate aldehyde, which was reduced with $NaBH_4$ (2 equiv, MeOH, 0 °C) to give primary alcohol **11**. This three step reaction sequence to afford xanthate **11**, which is suitable for the deoxygenation,[9] proceeded in 74% overall yield. The xanthate functionality was then reductively removed using Bu_3SnH in the presence of a catalytic amount of AIBN (PhMe, reflux, 97%). Finally, alcohol **12** was directly converted to iodide **3**[10] by $(PhO)_3PCH_3I$ (DMF, 0 °C, 95%), thereby completing the synthesis of the C1-C6 aliphatic fragment **3** of kabiramide C.

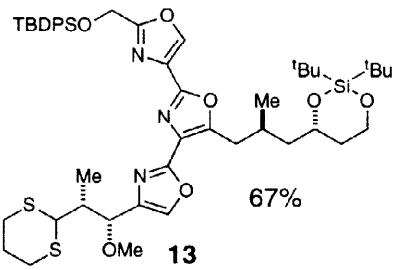
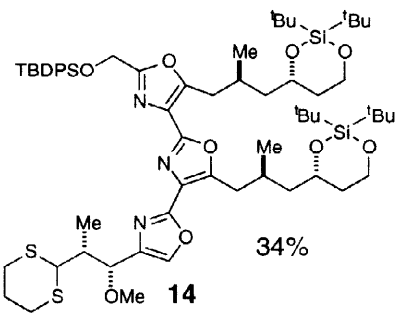
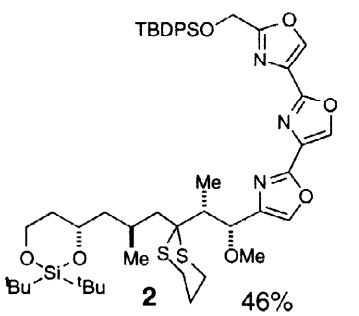
Scheme 3



Having accessed both fragments **3** and **4**[1], we now began to evaluate reaction conditions that would effect the crucial lithio-dithiane coupling. During the planning stages of this synthesis, the task of achieving a union between **3** and **4** was not regarded as a difficult one based on the fact that lithio-dithiane couplings are routinely carried out in organic synthesis.[11] However, lithium-deuterium exchange experiments have indicated that the protons on oxazole rings in **4** are much more acidic than the dithiane proton.[12] When **4** was treated with 1.2 equiv of ^{t}BuLi followed by addition of **3**, alkylation took place on the central oxazole ring, providing **13** in good yield (Table 1). When 2.2 equiv of base was used in the deprotonation step, dialkylation product **14** was obtained. At this stage, there were two

reasonable options ahead: (1) to devise an oxazole ring protection scheme, for example, by substituting trimethylsilyl groups for the acidic protons, which will add at least two more steps to the synthesis and require other protecting group modifications; (2) to remove all the acidic protons in **4** by simply using excessive base in the hope that the dithiane anion behaves more nucleophilicly than all other carbanions present in **4** affording the desired alkylation. Gratifyingly, when **4** was treated with 4.4 equiv of ^{t}BuLi and one equiv of **3** was added, the desired fragment union between **3** and **4** was successfully achieved providing **2** in modest yield (Entry 3).

Table 1. Lithio-Dithiane Coupling Results Between **3** and Tris-oxazole **4**

Entry	Reaction Conditions[a]	Major Product[b]
1	**4** (1 equiv) ^{t}BuLi (1.1 equiv) then **3** (2 equiv)	 67% **13**
2	**4** (1 equiv) ^{t}BuLi (2.2 equiv) then **3** (2 equiv)	 34% **14**
3	**4** (1 equiv) ^{t}BuLi (4.4 equiv) then **3** (1 equiv)	 **2** 46%

[a] All reactions were conducted in freshly distilled THF/HMPA (9:1 v/v) solvent system. [b] All yields refer to isolated yields after purification by chromatography on silica gel. All products gave satisfactory ^{1}H-NMR and MS data.

In summary, the synthesis of the C1-C6 fragment of kabiramide C was accomplished in 9 steps from the commercially available triol **7** with an overall yield of 52%. The carbon skeleton of the C1-C19 portion of kabiramide C was constructed in a convergent manner employing a lithio-dithiane coupling between the C1-C6 fragment and the C7-C19 fragment. The subsequent fragment manipulation, coupling and the completion of the total synthesis of kabiramide C will be reported at a later time.

Acknowledgment. We are grateful to Professor S. Matsunaga (University of Tokyo) for helpful discussions. This work has been financially supported by the National Institutes of Health (RO1 CA56304).

References and Notes.

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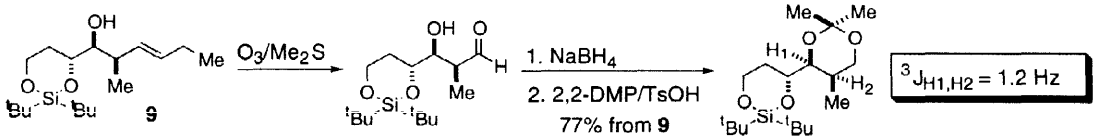
5. The *syn* relationship of the two newly formed stereogenic centers was assigned according to the transformations below followed by three-bond coupling constant analysis of the ^{1}H-NMR spectrum of the derived acetonide:



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9. The removal of the xanthate functionality in **11** was complicated due to the involvement of the proximal olefin bond, whereas the xanthate-removing operation of **12** proceeded smoothly.

10. Spectral data for **3**: ^{1}H-NMR ($CDCl_3$, 400 Hz): δ 4.14-4.06 (3H, m), 3.30 (dd, 1H, J_1 = 4.8 Hz, J_2 = 9.2 Hz), 3.25 (dd, 1H, J_1 = 5.2 Hz, J_2 = 9.2 Hz), 1.84-1.74 (m, 2H), 1.62-1.52 (m, 2H), 1.24-1.18 (m,1H), 1.01 (d, 3H, J = 5.2 Hz), 1.00 (s, 9H), 0.97 (s,9H). ^{13}C-NMR ($CDCl_3$, 75.5Hz): δ 72.0, 64.4, 45.3, 37.2, 31.3, 27.5, 27.2, 20.4, 19.3. IR (neat): υ_{max} 2933, 1635, 1473, 1377, 1247, 1212, 1194, 1069, 939, 903, 871 cm^{-1}. HRMS (CI, NH_3): $[M+H]^+$ Calcd. for $C_{15}H_{32}IO_2Si$: 399.1177. Found: 399.1211. $[\alpha]^{23}_D$ = -28.3° (c =1.4, $CHCl_3$).

11. For recent applications of lithio-dithiane coupling in natural product synthesis, see Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 947-961.

12. When **4** was treated with 5 equiv of LDA and quenched by D_2O, the following transformation was observed: