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Synthesis of the Fully Functionalized Tris-oxazole Fragment Found in Metabolites Derived from Marine Organisms

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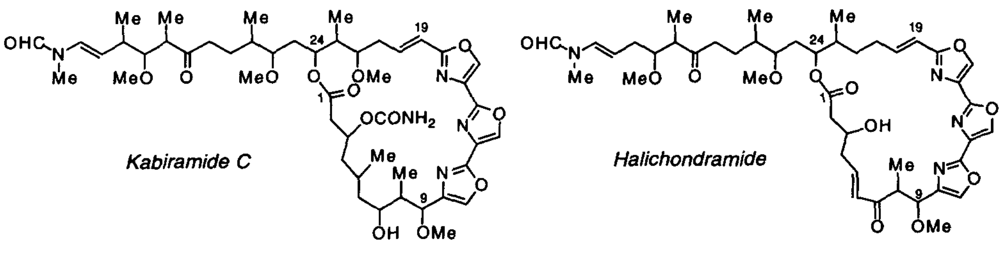
Abstract: The synthesis of the fully functionalized tris-oxazole fragment **9** found in marine metabolites kabiramide C and halichondramide is reported employing modified Hantzsch methodology. Starting with the condensation reaction between cinnamamide **1** and ethyl bromopyruvate **2**, the synthetic sequence leading to **9** was carried out in 13 steps with an overall yield of 26%.

Tris-oxazole containing marine natural products, examples of which are the ulapualides,[1] halichondramides,[2] mycalolides,[3] and kabiramides[4], are members of an emerging class of secondary metabolites. These extraordinarily interesting macrolides, first isolated from the egg masses of marine nudibranches (sea slugs), exhibit a wide variety of biologic activities, including antileukemic, antifungal, and ichthyotoxic properties. Such a biologic profile may in part be associated with the capacity of the metabolites to sequester and transport metal ions *in vivo* using the curve-linear array of the oxygen and nitrogen bearing ligand binding sites in their structures.[5] The members of this family of macrolides were shown to contain a 28-membered lactone which incorporates a common tris-oxazole subunit. The structures of kabiramide C and halichondramide[6] are shown here as representative examples of this class of natural products.

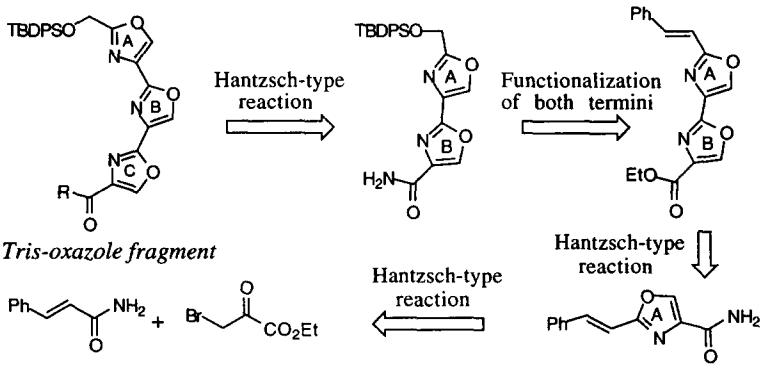


The unprecedented C-2 and C-4' disubstituted tris-oxazole fragment has attracted considerable interest of organic chemists and continues to be a challenging synthetic target.[7-9] The first synthesis of a tris-oxazole fragment, by Pattenden and co-workers,[7] which was completed in 14 steps with an overall yield of 6%, began with the condensation reaction between L-serine ethyl ester hydrochloride and ethyl acetimidate hydrochloride followed by three sequential oxazoline formation-oxidation steps. The approach described by Yoo[8] utilized a rhodium(II)-catalyzed cycloaddition reaction of dimethyl diazomalonate and a cyanohydrin in the oxazole-forming step which, when employed sequentially, furnished the tris-oxazole system in 16 steps with an overall yield of 3.3%. It was realized that in order

to embark on a total synthesis of the tris-oxazole containing natural products, a more efficient and practical synthetic approach to the heterocyclic fragment would be required. In this communication, we report a practical and operationally simple synthesis, which utilizes inexpensive and readily available starting materials. With regard to our total synthesis objectives, it allows for the preparation of gram quantities of the tris-oxazole **9** which is suitably functionalized at both termini.

The retrosynthetic analysis of the tris-oxazole, summarized in Scheme 1, involved the sequential opening of the C-ring, B-ring, and A-ring oxazoles. Hantzsch-type methodology was employed in a linear reaction sequence to generate all three oxazole rings.[10] It is worth pointing out that the order of the terminus functionalization was crucial to the efficiency of the synthesis; and that the cleavage of the styrenyl olefin bond at the bis-oxazole stage provided the most efficient synthetic pathway to the tris-oxazole fragment. If the styrenyl olefin bond was cleaved at the mono-oxazole stage, the yield of the bis-oxazole generating step was relatively low (20% lower); while the cleavage of the olefin bond at the tris-oxazole stage and elaboration of the opposing end was difficult due to the poor solubility of the styrenyl bearing tris-oxazole.

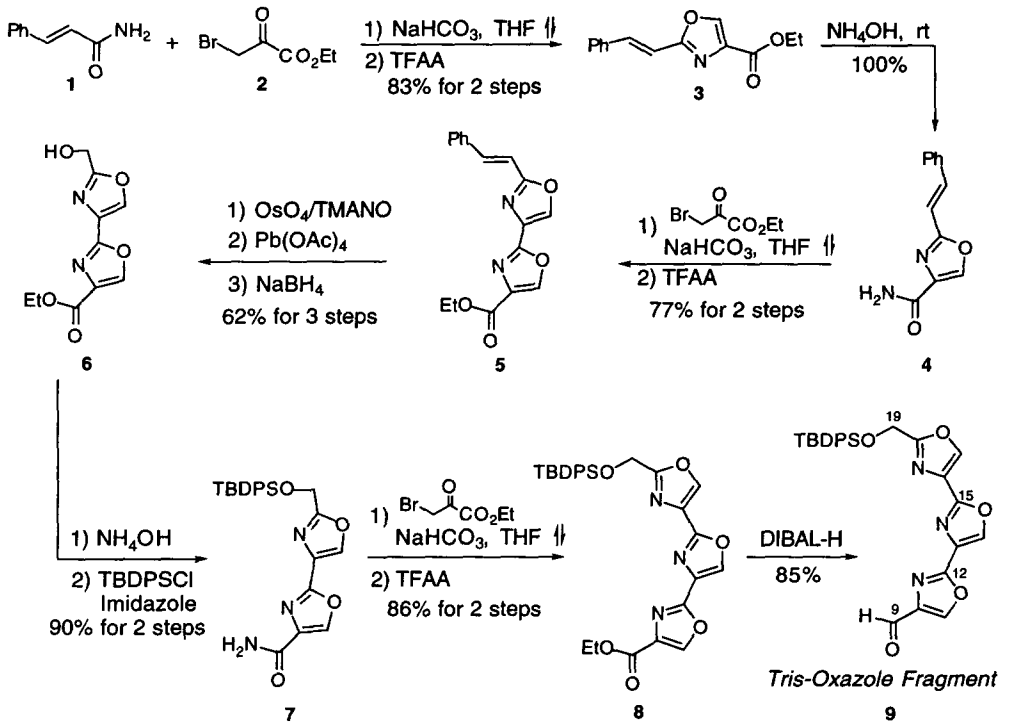
Scheme 1



The synthetic sequence of the tris-oxazole **9** was initiated with the condensation between cinnamamide **1**[11] and ethyl bromopyruvate **2** using Hantzsch-type conditions (Scheme 2). Thus, the reaction of **1** with **2** in a $NaHCO_3$ buffered medium gave the corresponding hydroxyl oxazoline. This condensation was immediately followed by dehydration (TFAA/THF, 1:1 v/v) affording the fuctionalized oxazole **3** in 83% yield. Conversion of the ethyl ester to the corresponding amide with aqueous NH_4OH quantitatively gave the amido-oxazole **4** which underwent a second Hantzsch reaction resulting in the formation of bis-oxazole **5**. The upper end of bis-oxazole 5 was elaborated in a three-step process, employing a catalytic dihydroxylation with OsO_4 (0.1 mol%) and TMANO (1.1 equiv) as the secondary oxidant.[12] The diol was used without purification in a subsequent oxidative cleavage using $Pb(OAc)_4$ (1.2 equiv) to afford the corresponding aldehyde, which was reduced with $NaBH_4$ (2 equiv, EtOH, 0

°C) to give the primary alcohol **6**. This three step reaction sequence to afford the alcohol proceeded in 62% overall yield. Amidation of the ester followed by protection of the primary alcohol as its *t*-butyldiphenylsilyl ether provided the silylated bis-oxazole **7** in 90% yield. This material was subjected to a third Hantzsch reaction to give the tris-oxazole **8**.[13] Finally, the ethoxycarbonyl group was directly transformed to the formyl functionality by DIBAL-H reduction[14] [DIBAL-H (2.5 equiv) / PhMe, -78 °C, 7 min.] thereby completing the synthesis of the fully elaborated tris-oxazole fragment **9**.[15]

Scheme 2



In summary, a practical synthetic method of the C-2 and C-4' disubstituted tris-oxazole system contained in the associated natural products has been developed. The synthesis was accomplished in 13 steps from cinnamamide and ethyl bromopyruvate with an overall yield of 26%. Utilization of this method in the total synthesis of tris-oxazole containing natural products is currently being pursued in our laboratory.

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11 The α,β-unsaturation of the amide was found to play a pivotal role in the formation of oxazoles, as alkyl and α-alkoxy amides did not effectively participate in the oxazole synthesis.

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13 Mp 169-171 °C (white solid). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.396 (s, 1H), 8.321 (s,1H), 8.290 (s, 1H), 7.694 (m, 4H), 7.411 (m, 6H), 4.807 (s, 2H), 4.419 (q, 2H, J=7.2 Hz), 1.388 (t, 3H, J=7.2 Hz), 1.060 (s, 9H). ^{13}C-NMR ($CDCl_3$, 67.5 MHz): δ 163.5, 160.9, 156.1, 155.4, 143.7, 139.8, 139.2, 135.5, 134.7, 132.3, 130.8, 130.0, 129.6, 127.8, 61.4, 58.7, 26.6, 19.2, 14.2. IR (neat): ν 3125, 2929, 1722, 1643, 1539, 1168, 987 cm^{-1}. HRMS (CI, NH_3): M^+ Calcd. for $C_{29}H_{29}N_3O_6Si$: 543.1825. Found: 543.1782.

14 The control of the reaction time for this reduction step is critical. If the reaction time was less than 5 minutes, approximately 20% of starting material ester remained intact; while if the reaction was allowed to proceed for more than 10 minutes, approximately 20% of the ester was over-reduced to the alcohol. A reaction time of 7-8 minutes gave the best results.

15 Mp 167-169 °C (white solid). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 10.01 (s, 1H), 8.365 (s, 1H), 8.350 (s, 1H), 8.317 (s, 1H), 7.696 (m, 4H), 7.412 (m, 6H), 4.810 (s, 2H), 1.062 (s, 9H). ^{13}C-NMR ($CDCl_3$, 67.5 MHz): δ 183.9, 163.4, 156.2, 155.8, 143.7, 141.4, 140.0, 139.3, 135.4, 132.2, 130.5, 129.9, 129.5, 127.8, 58.6, 26.5, 19.1. IR (neat): ν 3178, 3150, 3084, 2998, 2931, 1734, 1647, 1589, 1847, 1255 cm^{-1}. HRMS (CI, NH_3): $[M+NH_4]^+$ Calcd. for $C_{27}H_{29}N_4O_5Si$: 517.6365. Found: 517.1932.

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