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Synthesis of Poly-oxazole Systems Found in Marine Metabolites

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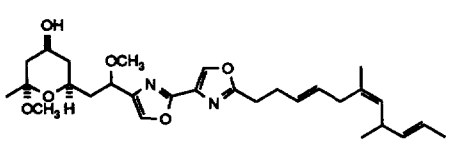
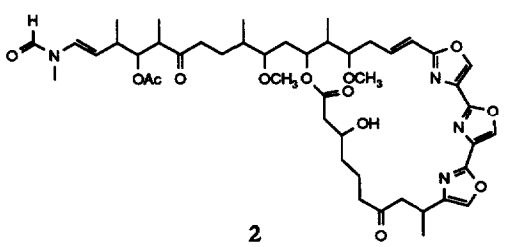
Abstract: *Synthesis of contiguous bis- and tris-oxazole systems was achieved via repetitive rhodium acetate catalyzed cycloaddition reactions of diazomalonates with nitriles.*

Oxazole-containing marine metabolites, first described in 1986 from nudibranch egg masses[1,2] and subsequently from sponges[3-8], possess significant bioactivities including antifungal, cytotoxic, anthelmintic, tumor-promoting, antiviral, and peripheral analgesic properties. These marine metabolites possess 2,4-disubstituted oxazole moieties. Particularly, hennoxazoles[8] and ulapualides[1] (also known as kabiramides[2], halichondramides[2b,3], and mycalolides[4]) incorporate unprecedented contiguous bis- or tris-oxazole units in their structures. The structures of hennoxazole A(**1**) and ulapualide A(**2**) are shown as representative examples.

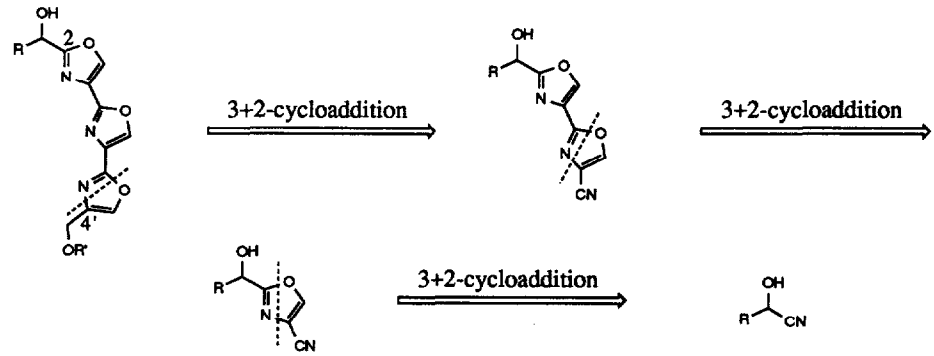


1



2

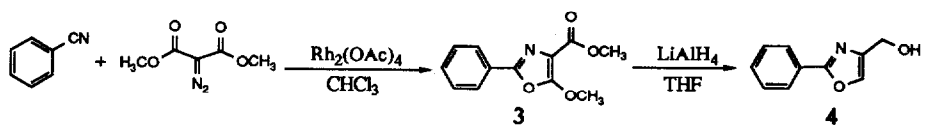
The probable biogenetic pathway to the tris-oxazole moiety involves cyclization and oxidation of a substituted tris-serine peptide intermediate, and the first synthesis[9] of a contiguous tris-oxazole used three molecules of serine in three sequential oxazoline cyclization-oxidation steps according to the method of Meyers et. al.[10] A new approach to contiguous bis- and tris-oxazole systems with appropriate appendages at C-2 and C-4' position for further elaboration to the oxazole-containing natural products or their derivatives was realized by sequential 3+2-cycloaddition of an appropriate acylcarbene with nitriles (Scheme I).



(Scheme I)

Acylcarbenes, or functionally equivalent species have been found to undergo oxazole ring formation in the desired manner with nitriles[11]. Diazomalonates react with nitriles in the presence of rhodium acetate catalyst[11f] and this reaction may provide an efficient route to 2,4-disubstituted oxazoles and 2,4'-disubstituted poly-oxazoles, if the reductive removal of the 5-methoxy moiety and the conversion of the 4-methoxycarbonyl moiety to nitrile are possible.

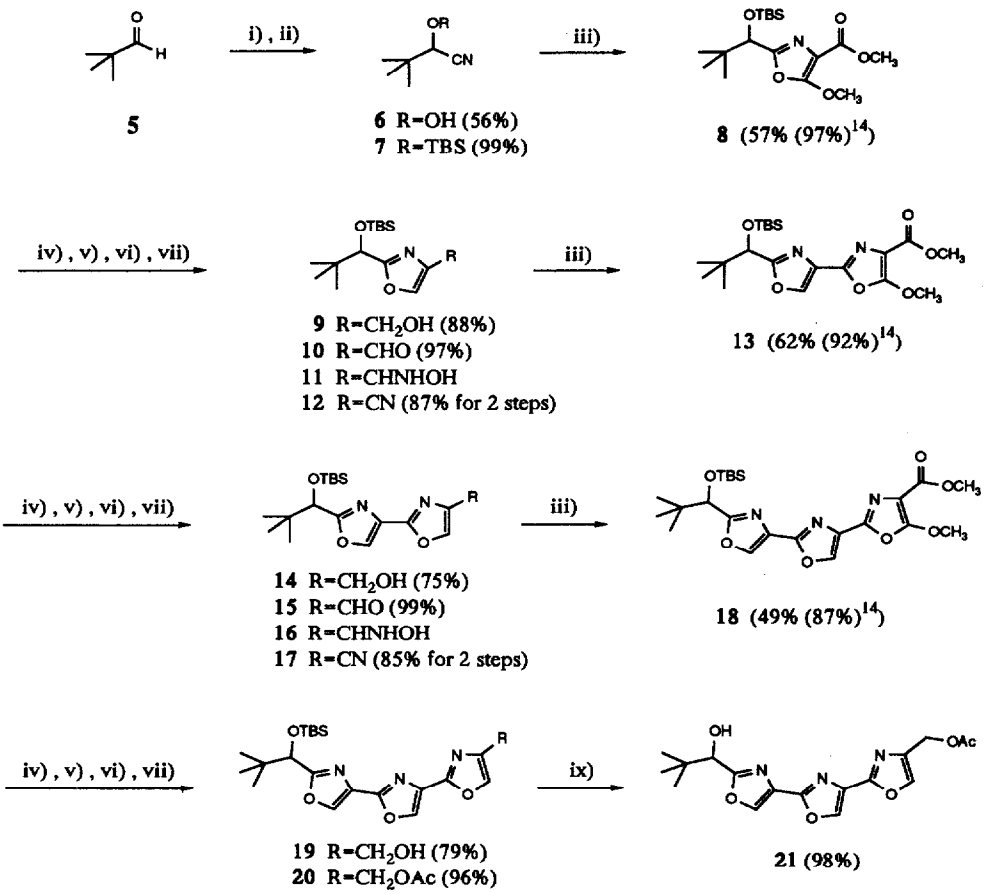
Oxazole **3** was prepared by the literature method.[11f] Reductive removal of the 5-methoxy moiety of **3** with some reducing agents was extremely problematic under typical conditions.[11f] Lithium aluminum hydride was found to be the best reducing agent (**3** was added to $LiAlH_4$ (0.8eq.) suspension in THF at -78°C, the reaction mixture was stirred for 3 hours, and then it was slowly warmed to room temperature.) which led to the reduction of both 5-methoxy and 4-methoxycarbonyl moieties giving 2,4-disubstituted oxazole **4**[12] in 87% yield (Scheme II).



(Scheme II)

In order to test the functionalization of C-2 substituent, cyanohydrin silyl ether **7** prepared from pivaldehyde (**5**) was used as the starting material. Cycloaddition reaction was carried out by slow addition of dimethyl diazomalonate over 12 hours period to a refluxing chloroform solution of **7** containing rhodium acetate (2 mole%). The product **8** was reduced to **9** using $LiAlH_4$ under the previously established conditions. Conversion of **9** to nitrile **12** was achieved following 3-pot procedure, i.e., Swern oxidation to aldehyde **10**, preparation of aldoxime **11**, and then dehydration to nitrile **12** using triflic anhydride.[13] The straightforward repetition of this sequence (i.e., $Rh_2(OAc)_4$ catalyzed cycloaddition, $LiAlH_4$ reduction, Swern oxidation, nitrile preparation via aldoxime) afforded C-2 and C-4' disubstituted bis-oxazoles

(**13**,**14**,**15**,**16**,**17**) and tris-oxazoles(**18**,**19**). Finally, acetylation (Ac_2O, TEA, CH_2Cl_2) and desilylation (n-Bu_4NF, THF) of **19** proceeded well to give **21**,[15] thus completing the construction of the appropriately functionalized tris-oxazole system via bis-oxazole system (Scheme III). Applications of this method in poly-oxazole containing natural product synthesis are currently being pursued in our laboratory.



i) KCN, EtOH, H_2O ii) $^tBuMe_2SiCl$, imidazole, DMF iii) Dimethyl diazomalonate(1.5eq), $Rh_2(OAc)_4$ (2mole%), $CHCl_3$, reflux iv) $LiAlH_4$(0.8eq), THF (-78°C for 3 hours, and then slowly warmed to room temperature) v) Oxalyl chloride, DMSO, TEA, CH_2Cl_2 vi) $NH_2OH{\cdot}HCl$, K_2CO_3, EtOH vii) triflic anhydride, TEA, CH_2Cl_2 (-78°C→0°C) viii) Ac_2O, TEA, CH_2Cl_2
ix) n-Bu_4NF, THF.

(Scheme III)

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References and Notes

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12. ^{1}**H-NMR**($CDCl_3$, TMS) δ 8.03(m, 2H), 7.65(s, 1H), 7.46(m, 3H), 4.69(s, 2H), 2.8(b,1H). ^{13}**C-NMR**($CDCl_3$) δ 161.99, 141.73, 135.08, 130.32, 128.58, 127.06, 126.29, 56.32. **IR**(KBr) 3236, 1550, 1485, 1450 cm^{-1}. **MS**(m/z) 175(100), 146(17), 117(21), 104(49), 77(28).
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14. Yields based on consumed starting materials.
15. ^{1}**H-NMR**($CDCl_3$, TMS) δ 8.38(s, 1H), 8.32(s, 1H), 7.76(s, 1H), 5.09(s, 2H), 4.59(d, 1H), 3.06(d, 1H), 2.12(s, 3H), 1.04(s, 9H). ^{13}**C-NMR**($CDCl_3$) δ 170.68, 166.21, 155.93, 155.08, 139.44, 138.35, 137.39, 137.17, 131.36, 129.41, 75.82, 57.85, 36.13, 25.47, 20.81. **IR**(KBr) 3350, 1736, 1517 cm^{-1}. **MS**(m/z) 361(19), 305(52), 245(100), 232(20).

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