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Synthesis of the Enantiopure C15-C26 Segment of Phorboxazole A and B

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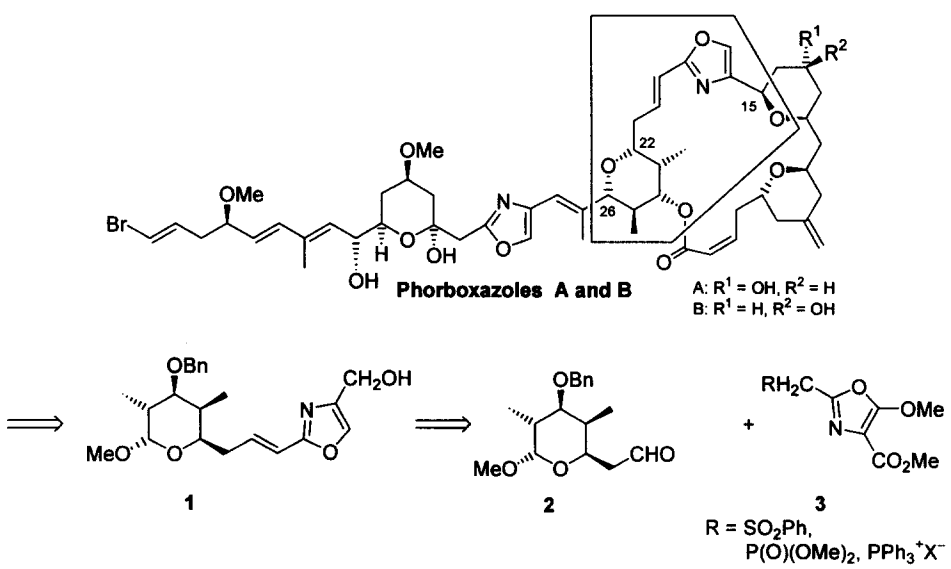
Abstract: Two approaches towards an enantiopure C15-C26 segment of the phorboxazoles starting from the corresponding C20-C26 aldehyde are presented. A variety of functionalized oxazoles have been synthesized *via* the rhodium(II) acetate catalyzed cycloaddition of dimethyl diazomalonate to substituted nitriles.

Keywords: marine macrolides; oxazole synthesis; stereocontrol; HWE olefination

The phorboxazoles A and B are two new highly cytotoxic macrolides containing two 2,4-disubstituted oxazole rings.[1] They inhibit growth of tumor cells at subnanomolar concentrations *in vitro* (mean GI_{50} 1.58 × 10^{-9} M). In contrast to antimitotic natural products they arrest the cell cycle during S phase.[1c] The enormous biological activity and the fascinating molecule structure have stimulated synthetic efforts by a number of research groups.[2] As yet, only one total synthesis by Forsyth has been achieved.[2a] From our group the syntheses of a C3-C13 segment,[3] a C20-C26 segment[4] and a C28-C41 segment[5] of the phorboxazoles have already been disclosed. The C15-C26 segment contains the *E*-configurated C19-C20 olefinic double bond and a 2,4-disubstituted oxazole moiety. No less than 5 of the total of 15 stereocentres are crowded on the central C22-C26 tetrahydropyran ring. Herein we describe two stereoselective approaches to a C15-C26 segment.

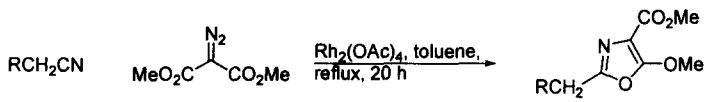


Scheme 1

PII: S0040-4039(99)00803-5

Our retrosynthetic analysis of the phorboxazole skeleton (Scheme 1) included disconnections between the C14/C15 bond and the C26/C27 bond providing a C15-C26 segment **1**, which in turn was to be generated by an olefination reaction from C20-C26 aldehyde **2** and an oxazole building block **3**.

In the course of this project we prepared various highly functionalized oxazoles. Most of the known methods for the synthesis of functionalized 2-methylated oxazoles require multistep procedures.[6] The rhodium(II) catalyzed cycloaddition reaction of diazo compounds to nitriles, developed especially by Helquist and his coworkers, is a well established one step pathway.[7] By allowing substituted acetonitriles **4a-d** to react with dimethyl diazomalonate **5** in the presence of catalytic amounts of rhodium(II) acetate we obtained new oxazoles **3a–3d** in reasonable yields (Scheme 2, Table 1).



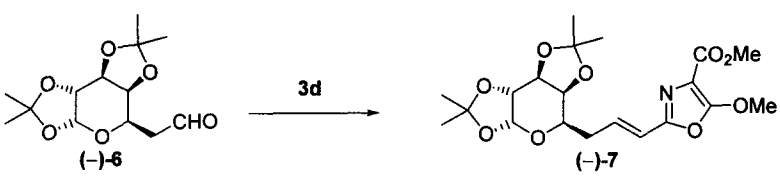
Scheme 2

Table 1. Rh(II) mediated synthesis of oxazoles 3a-d

3	R	Yield [%]
a	Cl	61
b	Br	37
c	$PhSO_2$	48
d	$(EtO)_2P(O)$	18

Starting from methyl substitituted oxazoles **3a** and **3b** all attempts to prepare the corresponding phosphonium salts failed. In general, no reaction took place or the starting material was destroyed when heated with triphenylphosphine in various solvents. Furthermore, attempts to couple sulphonylmethyl oxazole **3c** with a variety of aldehydes under typical reaction conditions[8] did not yield any α-hydroxy sulphonylmethyl oxazoles.

However, when diethyl phosphonylmethyl oxazole **3d** was allowed to react with aldehyde **(–)-6**[9] the C15-C26 phorboxazole analogue **(–)-7** was formed in good chemical yield (Scheme 3). The stereochemical outcome was dependent on the choice of solvent (Table 2). Interestingly, Paterson has recently reported the failure for the stereoselective installation of the C19/C20 olefinic double bond of the phorboxazoles when using a diethyl phosphonylmethyl oxazole while the corresponding Wittig triphenylphosphonium analogue gave good stereoselectivities.[2d]

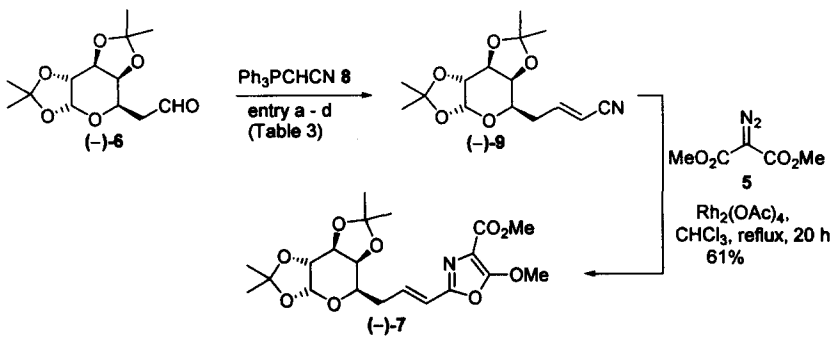


Scheme 3

Table 2. Horner-Wadsworth-Emmons reaction to phorboxazole analogue (-)-7

Entry	Conditions	Yield	*E:Z*
a	LDA, THF, -78°C → RT, 3h	65%	1:6
b	NaH, DCM, -78°C, 1h	no reaction	–
c	NaH, RT, DCM, 1 h	82%	4.7:1

A second two step strategy (Scheme 4) for the *E*-selective construction of the C19/C20 double bond started with an optimized Wittig olefination between aldehyde **(–)-6** and ylide **8**[10] to give predominantly acrylonitrile ***E*-(–)-9** in excellent yield and stereoselectivity (95%; *E*:*Z* = 6.3:1). Again the stereochemical outcome was significantly dependent on the choice of the solvent. In this case the use of toluene and addition of lithium chloride gave the best result (Table 3). The rhodium(II) acetate catalyzed cycloaddition of acrylonitrile ***E*-(–)-9** to dimethyl diazomalonate **5** led to the C15-C26 analogue ***E*-(–)-7** in a yield of 55%, the configuration of the *E*-double bond being left intact (Scheme 4).

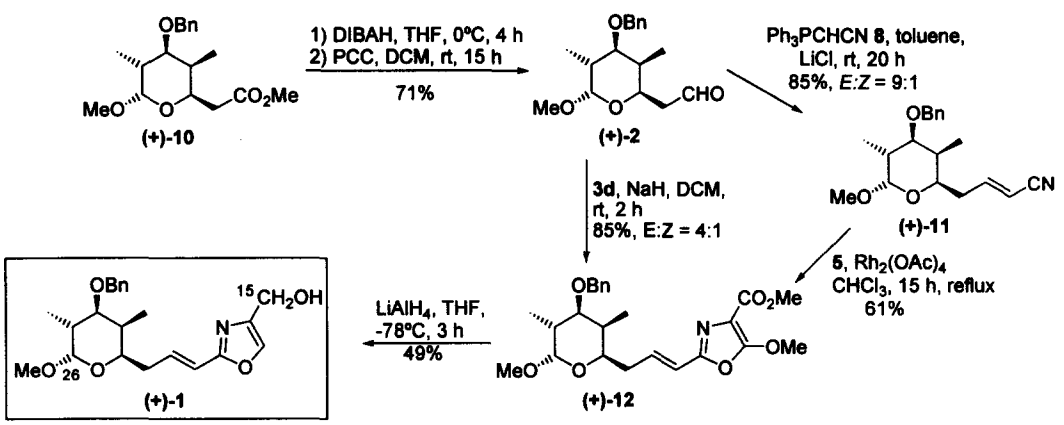


Scheme 4

Table 3. Optimization for the Wittig olefination to nitrile (-)-9

Entry	Conditions	Yield [%]	*E*:*Z*
a	DMF, LiCl, rt, 18 h,	92	1:1
b	DCM, rt, 5 h	96	2.2:1
c	DCM, LiCl, rt, 5 h	94	2.5:1
d	toluene, LiCl, rt, 18 h	95	6.3:1

Using the optimized reaction conditions for both strategies (Tables 2 and 3) we prepared the C15-C26 segment of the phorboxazoles (Scheme 5) starting from aldehyde **(+)-2**,[4] which was available from the corresponding ester **(+)-10** under typical reaction conditions (DIBAH reduction and subsequent PCC oxidation). The 2,4,5-trisubstituted oxazole ester **(+)-12** was reduced completely to the 2,4-disubstituted oxazole target **(+)-1** with $LiAlH_4$. For this difficult reduction step all other common reducing reagents failed.[11]



Scheme 5

In conclusion, we have developed two new reaction sequences towards a C15-C26 segment of the phorboxazoles starting from the C20-C26 ester (+)-**10**. For both routes the rhodium(II) catalyzed cycloaddition of nitriles and dimethyl diazomalonate was the key step. All new compounds gave satisfactory spectroscopic and analytical data.[12]

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12. Data for 2,4-disubstituted oxazole target (+)-**1**: colourless oil; $[\alpha]_D^{20}$ +68.9° (c = 1; $CHCl_3$); IR ($CHCl_3$): ν = 3604, 3064, 2972, 2932, 2892, 1740, 1664, 1596, 1532, 1496, 1452, 1392, 1352, 1264, 1228, 1160, 1072, 1028, 988, 964, 908 and 552 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.52 (1 H, s); 7.36-7.26 (5 H, m); 6.80-6.72 (1 H, dt, ^3J = 16.1 Hz and ^3J = 7.2 Hz); 6.33 (1 H, d, ^3J = 16.1 Hz); 4.61 (1 H, d, ^2J = 11.5 Hz); 4.60 (2 H, s); 4.54 (1 H, d, ^3J = 3.9 Hz); 4.37 (1 H, d, ^2J = 11.5 Hz); 3.94-3.89 (1 H, m); 3.60-3.56 (1 H, m); 3.30 (3 H, s); 2.61-2.53 and 2.39-2.30 (2 H, 2 × m); 2.18-2.12 (1 H, m); 2.03-1.96 (1 H, m); 1.01 (3 H, d, ^3J = 6.8 Hz) and 0.95 (3 H, d, ^3J = 6.9 Hz); ^{13}C NMR (100 MHz; DEPT, $CDCl_3$): δ = 161.5; 141.0; 138.7; 136.9; 134.3; 128.3; 127.6; 127.5; 118.3; 102.5; 79.0; 70.2; 69.2; 56.6; 55.1; 36.1; 35.0; 34.4; 12.8 and 5.1; HR-MS: calc. for $C_{21}H_{26}NO_4$ = (M^+-OCH_3): 356.1862, found: 356.1862.