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A New Access to Spiro-isoxazolines Derivatives

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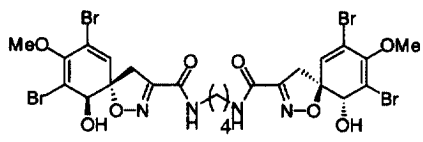
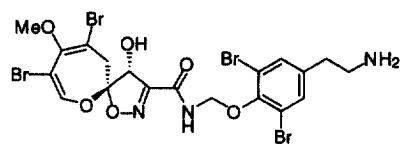
Abstract: A series of spiro-isoxazolines **1a-e** was prepared in an one-step procedure by treating the corresponding tricarbonyl **3a-e** derivatives with hydroxylamine hydrochloride.

Key words: spirooxazoline, cyclization

The isolation and structural determination of several bromotyrosine-derived natural marine metabolites containing the spirocyclohexadiene- or spirooxepin-isoxazoline system have been reported.[1] Aerothionin[2] and psammaplysin-A[3] are pertinent examples.



aerothionin



psammaplysin-A

The most interesting structural aspect of these molecules is the spirocyclic isoxazoline ring system. The oxidative cyclization of o-phenolic oxime acid derivatives serves as an efficient method for the construction of the spirocyclohexadiene-isoxazoline ring system that is present in aerothionin and its derivatives.[4] In contrast, to our knowledge, no methods were reported for the synthesis of the corresponding spirooxepin-isoxazole ring system. Therefore, the preparation of the core structure **1** constitutes the prime challenge en route to psammaplysin-A and its analogs (Scheme 1). In this paper, we report a general method to synthesise spiro-isoxazolines derivatives that constitute the core structure **1**.

It is well established in the literature that the acid-catalysed cyclisation of dihydroxyketones is the predominant ring-forming process for spiroketal synthesis.[5] Similar cyclisation was thus envisaged as the key step for the synthesis of spirocyclic isoxazoles of general structure **1**. Retrosynthetically, the structural prerequisites for such a spiroketalisation can be obtained from the α-hydroxyiminoesters **2** which are formed by treating the corresponding tricarbonyl derivatives **3** with hydroxylamine hydrochloride (Scheme 1).

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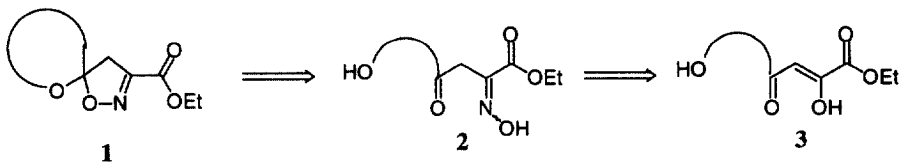
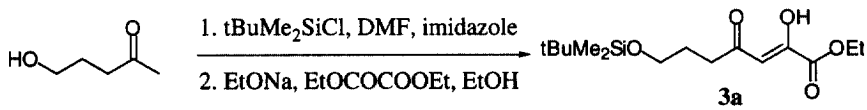


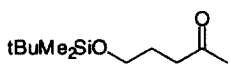
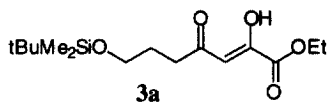
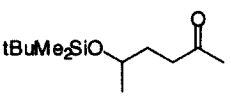
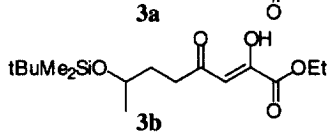
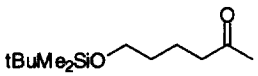
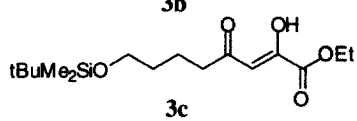
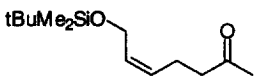
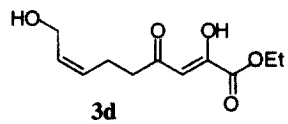
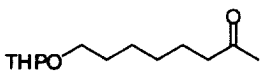
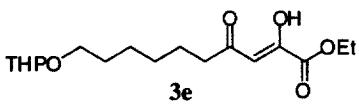
Scheme 1

A set of suitable substrates was prepared as shown in Scheme 2 and Table 1. The starting hydroxyketones were commercially available or easily obtained following known literature's procedures.[6] After protection of the alcohol as a t-butyldimethylsilyloxy- or a tetrahydropyran- derivative, the corresponding protected hydroxyketone was coupled with diethyloxalate in the presence of sodium ethanolate to afford compounds **3a-e** in good yields.[7] These were all easily purified by column chromatography apart from compound **3d** which underwent deprotection of the allylic t-butyldimethylsilyloxy group during purification.



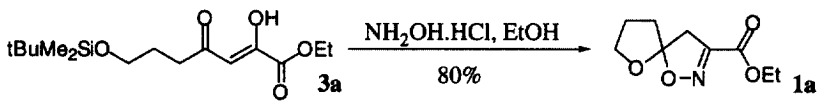
Scheme 2

Table 1 : Synthesis of compounds **3a-e**

Starting Material	Product	Yield [a]
	 **3a**	70%
	 **3b**	65%
	 **3c**	74%
	 **3d**	62%
	 **3e**	62%

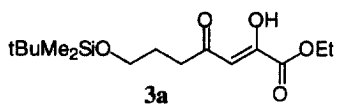
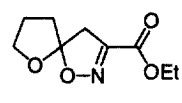
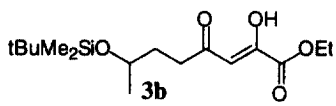
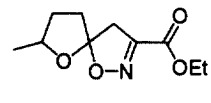
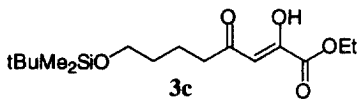
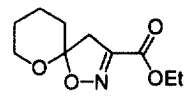
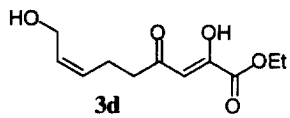
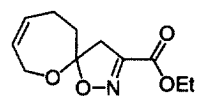
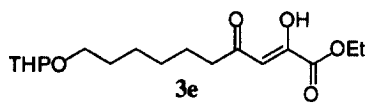
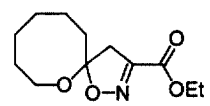
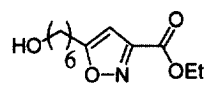
a: isolated yields

Compound **3a** was then exposed to a solution of hydroxylamine hydrochloride in ethanol for 2-3 hours at room temperature.[8] Under these conditions, the reaction proceeded to the desired spiro-isoxazoline **1a** in good yield without any trace of the intermediate α-hydroxyimino ester **2** as ascertained by NMR of the crude mixture (Scheme 3).[9] Similar results were obtained with compounds **3b-e** (Table 2). It is conceivable that the cleavage of the t-butyldimethylsilyl ether or THP group occurred with the concomitant formation of the hydroxyiminoether to give all the structural prerequisites for spontaneous spiroketalisation in this suitably acidic medium.



Scheme 3

Table 2 : Synthesis of the spiro-isoxazolines **1a-e**

Entry	Starting material	Product	Yield[a]
1	 **3a**	 **1a**	80%
2	 **3b**	 **1b**	72%
3	 **3c**	 **1c**	74%
4	 **3d**	 **1d**	68%
5	 **3e**	 **1e**	6%
		 **4**	60%

a: isolated yields

The novel methodology described in this paper is compatible with the formation of 1,6-dioxa-1-aza-spiro-[4,4] nonene, [4,5] decene and [4,6]undecene backbones (entries 1-4, Table 2). However, this strategy is not synthetically useful for the formation of 1,6-dioxa-1-aza-spiro-[4,7] dodecene **1e** as the major product formed was the corresponding isoxazole **1f** with a chemical yield of 60% with only traces of the desired spiro-isoxazoline **1e** (entry 5, Table 2). In this case, dehydration and aromatisation occurred prior to spiralisation to form the isoxazole ring directly.

Acknowledgments

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References and notes

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(7) Baraldi, P.G. ; Barco, A. ; Benitti, S. ; Moroder, F. ; Pollin, G.P. ; Simoni, D. ; *J. Org. Chem.* **1983**, *48*, 1297-1302.

(8) *Typical experimental procedure:* A solution of hydroxylamine hydrochloride (0.06g, 0.95mmol) and compound **3a** (0.1g, 0.32mmol) in 1ml of ethanol was stirred for three hours at room temperature. The mixture was then evaporated under reduced pressure, filtered on celite and purified by column chromatography. All compounds were fully characterized by ^{1}H, ^{13}C NMR, IR, mass spectroscopy.

(9) Reactions carried out at higher temperatures gave quantitatively the corresponding hydroxyisoxazoles; Bunnelle, X. ; Singam, P.R. ; Narayanan, B.A. ; Bradshaw, C.W. ; Liou, J.S. *Synthesis* **1997**, 439-442.