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A Novel Diels-Alder Approach to Hydroisoquinolines

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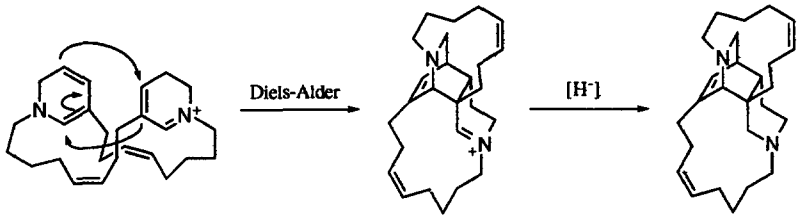
Abstract

A synthetic approach to functionalised hydroisoquinoline rings, using dihydropyridinium ions as dienophiles in the Diels-Alder reaction, is described.

Keywords: Diels-Alder reactions; iminium salts; isoquinolines; marine metabolites.

1. Introduction

The biogenetic pathway leading to an increasing number of cytotoxic marine alkaloids is believed to proceed *via* the intramolecular Diels-Alder cycloaddition of a partially-reduced *bis*-pyridinium species (Scheme 1), wherein the dienophile is an electron-deficient dihydropyridinium ion [1]. Included among these alkaloids are the manzamines and keramaphidin B [2-4].



Scheme 1

Although activated imines and iminium ions have been exploited previously as dienophiles in Diels-Alder approaches to heterocycles [5], their conjugated counterparts have attracted little attention in this context. Dihydropyridinium ions are cyclic, conjugated iminium ions

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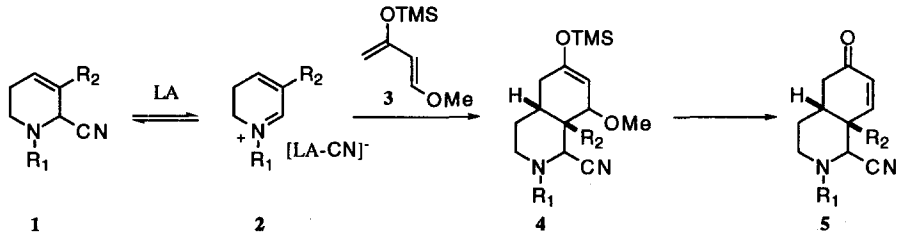
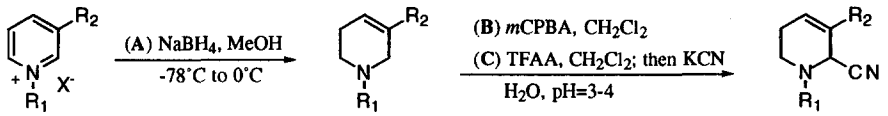
and their use as dienophiles would provide a synthetic approach to hydroisoquinolines. The hydroisoquinoline ring system is not only present in the skeletal framework of the manzamines and keramaphidin B, but also in other important natural products including reserpine and morphine. The principle short-coming of dihydropyridinium ions as synthetic intermediates is their propensity to undergo oxidation and disproportionation reactions. *In situ* generation of the dihydropyridinium ion from the corresponding α-aminonitrile, *e.g.* **1**, with a Lewis acid (LA) minimises the problem (Scheme 2). It was our aim to *reversibly* generate a 3-alkyl substituted dihydropyridinium ion **2** and trap this species with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**3**). Re-introduction of cyanide would then furnish a *cis*-fused cyanohydroisoquinoline **4**, which on hydrolysis would provide enone **5**.



Scheme 2

2. Results and discussion

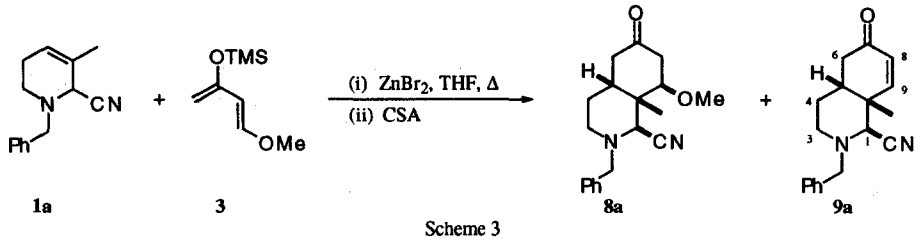
The tetrahydropyridines **7a-7d** were prepared by regioselective reduction of the appropriate pyridinium salts **6a-6d** (X=Br or I) at low temperature (Table 1). *N*-Oxidation and subsequent treatment with trifluoroacetic anhydride (TFAA) yielded the conjugated iminium ions which were trapped with KCN to give α-aminonitriles **1a-1d** [6].



Series	R_1	R_2	Yield (%) A	B	C
a	$PhCH_2$	CH_3	94	98	80
b	CH_3CH_2	CH_3	95	96	86
c	CH_3CH_2	$PhCH_2O(CH_2)_3$	92	94	83
d	$H_2C{=}CH(CH_2)_4$	$H_2C{=}CH(CH_2)_2$	83	99	87

Table 1

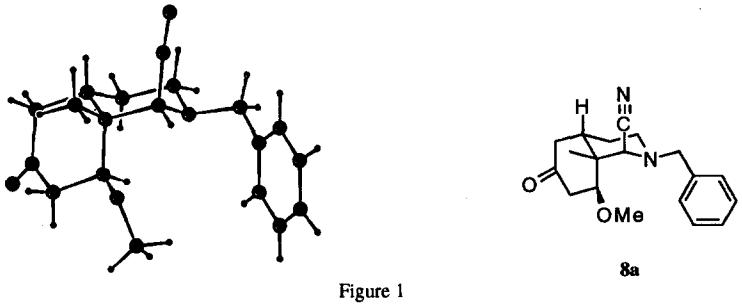
Treatment of **1a** with diene **3** and a catalytic amount of $ZnBr_2$ in refluxing tetrahydrofuran (THF) for 2 hours, followed by acid hydrolysis with 10-camphorsulfonic acid (CSA), furnished an inseparable 1:1 mixture of the methoxy-ketone **8a** and the enone **9a** in a 66% combined yield (Scheme 3).



1a 3 8a 9a

Scheme 3

There was no apparent reaction between the Diels-Alder partners in the absence of Lewis acid, indicating that a species similar to **2** is required for a successful reaction. Unambiguous assignment of the *exo* nature of the cycloadduct **8a** was possible by extensive NMR analysis and subsequently by X-ray crystallographic analysis (Figure 1). Conversion of the initial product mixture (**8a** and **9a**) into a single component enone (*i.e.* only **9a**) could be achieved by treatment of the mixture of cycloadducts with KO^{t}Bu in ^{t}BuOH for 2 hours, followed by addition of EtOH and stirring for a further 12 hours. This procedure furnished **9a** in 89% yield from **1a**. The structure of **9a** was also confirmed by NMR and X-ray analyses.[1]



8a

Figure 1

We have successfully applied this reaction to the other α-aminonitriles (**1b-1d**). Exchange of the *N*-benzyl group in **1a** for an *N*-ethyl group (**1b**) had little effect on the yield of **9b** (Scheme 4), although some epimerisation occurred at the C1 centre to give a 20:1 mixture of products. Selective reductive removal of the cyanide substituent, using $NaBH_3CN$ in refluxing MeOH, gave a single product **10b** in 91% yield.

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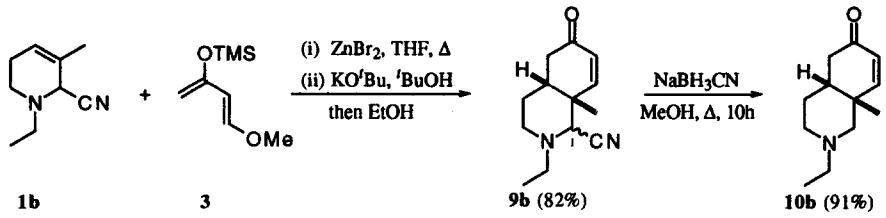
[1] Data for compound **9a**; mp 106-107°C; (Found C, 76.9; H, 7.45; N, 10.0. $C_{18}H_{20}N_2O$ requires C, 77.1; H, 7.20; N, 10.0%); R_f 0.30 (Al_2O_3; petroleum ether 40-60: ethyl acetate; 8:2); ν_{max} (KBr disc)/cm^{-1} 2930s, 2822s, 2221w (CN), 1677s (C=O, enone), 1454s, 1130s, 914s, 737s, 701s; δ_H (500MHz; $CDCl_3$) 1.35 (3H, s, C$\underline{H}_3$), 1.59-1.61 (1H, m, C(4)$\underline{H}$), 1.77 (1H, qd, *J*12.5, 5Hz, C(4)$\underline{H}$'), 2.21-2.25 (1H, m, C(5)$\underline{H}$), 2.28 (1H, d, *J*17.5Hz, C(6)$\underline{H}$), 2.63 (1H, td, *J*12.5, 3.5Hz, C(3)$\underline{H}$), 2.82 (1H, dd, *J*17.5, 5Hz, C(6)$\underline{H}$'), 2.88 (1H, br dd, *J*12, 5Hz, C(3)$\underline{H}$'), 3.49 (1H, s, C(1)$\underline{H}$), 3.51-3.77 (2H, ABq, J_{AB}13Hz, C$\underline{H}_2$Ph), 5.96* (1H, d, *J*10Hz, C(8)$\underline{H}$), 6.37* (1H, dd, *J*10, 2.5Hz, C(9)$\underline{H}$), 7.33-7.40 (5H, m, phenyl C$\underline{H}$); *the assignments at these resonances can be interchanged; δ_C (50.3MHz; $CDCl_3$) 24.2 (C$\underline{H}_3$), 27.1 (C$\underline{H}_2$), 36.8 (C$\underline{H}$), 39.2 (quaternary), 39.8, 48.7 and 60.1 (3 x C$\underline{H}_2$), 62.2 (C$\underline{H}$), 114.4 (quaternary), 127.9, 128.3, 128.6 and 128.8 (4 x C$\underline{H}$), 136.6 (quaternary), 153.8 (C$\underline{H}$), 197.3 (C=O); *m/z* (chemical ionisation, NH_3) 281 (MH^+, 4%), 254 ([M-CN]$^+$, 36), 186 (72), 94 (32), 91 (100).

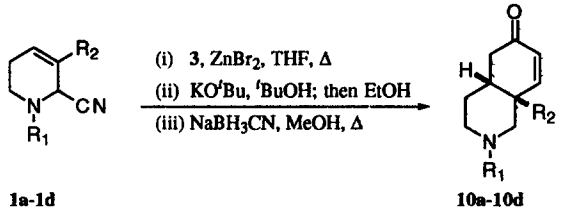


1b 3 9b (82%) 10b (91%)

Scheme 4

Application of this three step sequence to α-aminonitriles bearing more functionalised R_1 and R_2 substituents has allowed the preparation of hydroisoquinolines **10c** and **10d**, which may provide access to the central core of the manzamine alkaloids. Although the increase in steric bulk resulted in a reduction in overall yield, the desired hydroisoquinolines were still obtained in greater than 60% yield over the three steps (Table 2).

Series	Yield of enone (10)
a	80%
b	75%
c	62%
d	62%



1a-1d 10a-10d

Table 2

In summary, we have developed a novel Diels-Alder approach to the synthesis of functionalised hydroisoquinolines using dihydropyridinium ions as dienophiles. The feasibility of applying this methodology to the synthesis of a variety of alkaloids is currently under investigation.

Acknowledgements

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