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Annulations of isoquinoline and β-carboline ring systems: synthesis of 8-oxoprotoberberine derivatives

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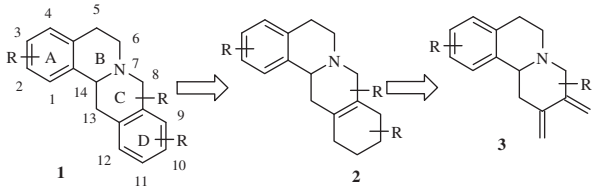
ABSTRACT

Annulation processes of isoquinoline and β-carboline compounds have been investigated leading to synthetic routes for the preparation of 8-oxoprotoberberine derivatives. The key steps combined a diene formation/Diels–Alder cycloaddition reaction to afford the targeted polycyclic skeletons. Further oxidative transformations of the cycloadducts produced the 8-oxoprotoberberine type products. The alkaloids of this class are important natural products with a wide range of biological activity and the synthethic methodology described in this paper could prove to be useful for the preparation of the D-ring functionalised derivatives.

Protoberberines are a large class of naturally occurring isoquinoline alkaloids derived from tetracyclic structure **1**.[1] The rings A and D are usually substituted and aromatised while the oxidation state of the ring C is variable. These compounds show a broad spectrum of biological properties and as such they have been the subject of intensive research.[2]



These structural variations have attracted attention from organic chemists and a number of methods for the preparation of these systems have been reported in the literature.[3] Formation of either ring B or C represents the key step in the majority of these synthetic procedures, while aromatic moieties A and D are usually incorporated into the structures of the starting materials.

Our interest in the anticancer properties[4] of these compounds, in particular 8-oxoprotoberberines (Fig. 1), has prompted us to design an approach that would allow straightforward functionalisation of the D ring. In addition, we anticipated the synthesis of an intermediate structure that potentially may be transformed into various classes of related alkaloids.

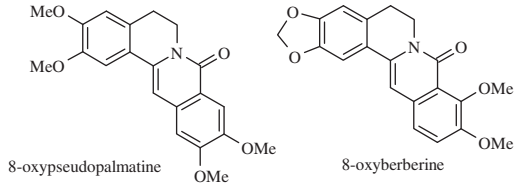


Figure 1. Structure of some 8-oxoprotoberberines.

The fact that protoberberines differ in the oxidation state of the C ring led us retrosynthetically to alkene 2, which was expected to undergo oxidative transformations to produce the 8-oxoprotoberberine skeleton. Cyclohexene derivative **2** may be accessible via Diels–Alder cycloaddition reaction of diene **3**.

To explore the above strategy, diene **4** was synthesised as outlined in Scheme 1. Quaternisation of the isoquinoline ring using an allyl bromide derivative afforded salt **5** in good yield.[5] A second allylation of the ring was achieved with the appropriate Grignard reagent producing compound **6**.[6] The enamino functionality of the crude product was then reduced under standard conditions to afford tetrahydroisoquinoline product **7** in 70% overall yield over two steps.[7]

Finally, the cyclisation process, carried out under typical Heck reaction conditions afforded diene **4**.[8] With diene **4** in hand, we

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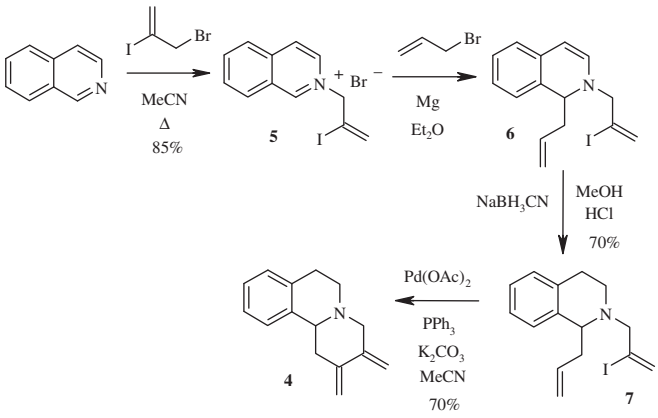
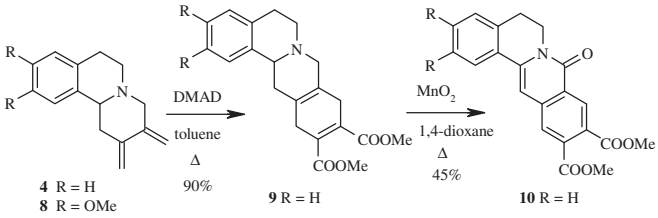


Scheme 1.



Scheme 2.

explored further transformations towards 8-oxoprotoberberine structures (Scheme 2).

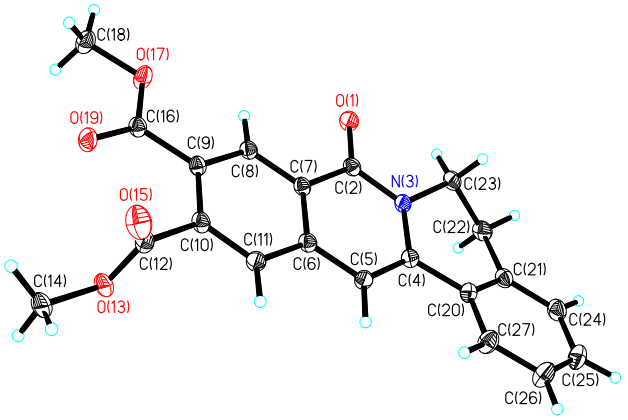
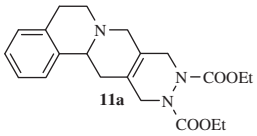
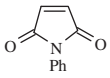
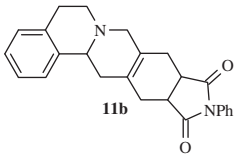
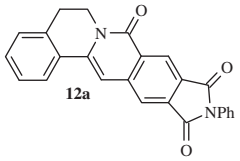
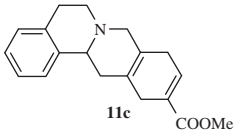
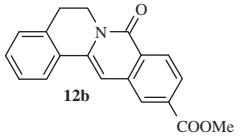
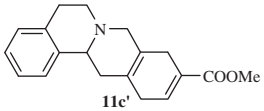
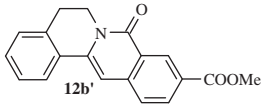
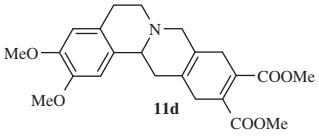
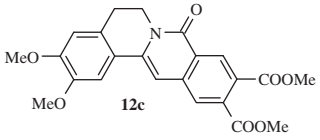


Figure 2. X-ray (SHELXL/XP) crystal structure of **10.**

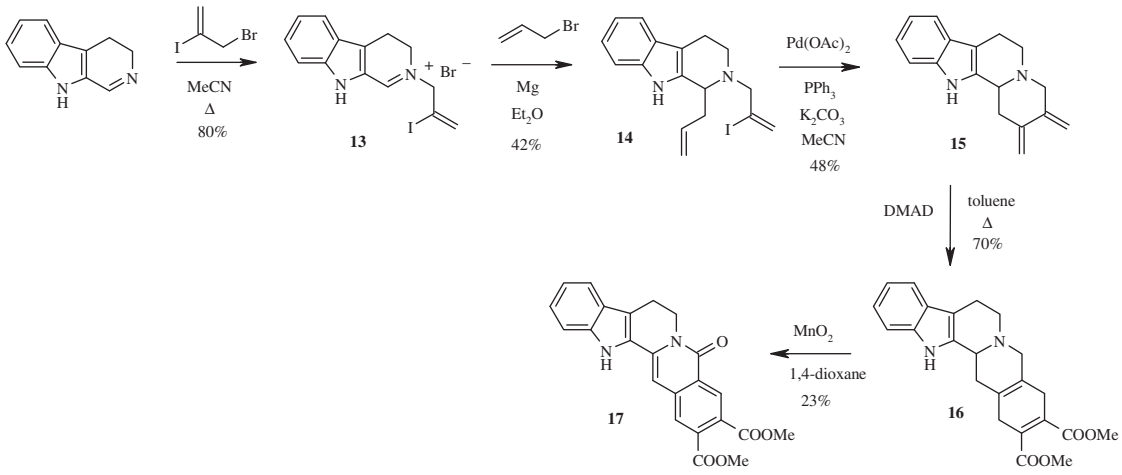
The Diels–Alder cycloaddition[9] reaction employing dimethyl acetylenedicarboxylate (DMAD) under thermal conditions afforded cyclohexadiene **9** which was then submitted to oxidative transformation in the presence of MnO_2.[10] This reaction produced 8-oxoprotoberberine derivative **10** in 45% yield. Analysis of the NMR data supported the above structure.

Compared to the starting material **9**, the ^{13}C NMR data of product **10** suggested the presence of an additional carbonyl group (δ 161.3). Analysis of the ^{1}H NMR spectrum showed three singlets for protons belonging to the rings C and D, with a signal at δ 7.03 (C13-H) which is typical for these compounds. The structure of compound **10** was also confirmed by single crystal X-ray analysis, Figure 2.[11]

Table 1
Synthesis of 8-oxoprotoberberine derivatives

Entry	Diene	Dienophile	Product[a]	Yield[c] (%)	Product[b]	Yield[c] (%)
a	4	EtOOC–N=N–COOEt	 **11a**	66		
b	4		 **11b**	85[d]	 **12a**	66
			 **11c**		 **12b**	45
c	4		 **11c'**	75[e]	 **12b'**	43
d	8		 **11d**	65	 **12c**	50

[a] Reaction conditions: diene (0.2 mmol), dienophile (0.24 mmol), toluene (5 mL), 12 h, 110 °C.
[b] Reaction conditions: **11** (0.1 mmol), MnO_2 (10 mmol), 1,4-dioxane (20 mL), 70 °C (oil bath temperature), 72 h.
[c] Isolated yield after column chromatography.
[d] Isolated as a mixture of diastereomers.
[e] **11c: 11c'** product ratio = 1:1.2.



Scheme 3.

Using the above described procedure, several 8-oxoprotoberberines were synthesised as outlined in Scheme 2 (Table 1). The cycloaddition steps were carried out with a slight excess of dienophile (1.2 equiv), under thermal conditions, affording the products in yields ranging from 65% to 85%. In the reaction with *N*-phenylmaleinimide (entry b, Table 1) a mixture of *exo* and *endo* cycloadducts was isolated. The products were obtained in a 2:1 ratio, but analysis of the NMR data did not suggest unambiguously the structure of the major component. The nonsymmetrical dienophile, methyl propiolate (entry c, Table 1), produced two regioisomeric products, 10- and 11-substituted, in a 1:1.2 ratio. The structures of the regioisomers were elucidated by NOESY experiments. The cycloaddition reaction with diethyl azodicarboxylate (entry a, Table 1) can also be performed at room temperature giving comparable results to those shown. The unoptimised oxidation step was carried out using an excess of MnO_2 to afford the 8-oxoprotoberberine products in moderate to good yields.

This transformation was also accomplished with reagents such as Pd/C or DDQ, but the yields were lower than those shown in Table 1. We also observed that cycloadduct **11d**, when exposed to air, was gradually converted into the product, but this process was very slow.

Compounds related to 8-oxoprotoberberines include β-carboline derivatives, alstonine oxide and degradation products of yohimbine such as ketoyobyrine.[12] This prompted studies towards application of the above methodology for the synthesis of oxocarboline derivatives (Scheme 3). Essentially, the reaction sequence is the same as previously discussed for the synthesis of the oxoprotoberberine compounds, although the yields were generally slightly lower.

The alkylation step afforded product **13** in good yield, which was then allylated as previously described. This step was performed with an excess of the Grignard reagent due to the presence of the acidic NH functionality. The following cyclisation step afforded the diene **15**, while the cycloaddition reaction employing DMAD as the dienophile afforded the polycyclic product **16**. Oxidation of diene **16** with MnO_2 produced the expected product **17**.

In conclusion, a simple synthetic procedure for the preparation of 8-oxoprotoberberines and related β-carboline derivatives has been developed. The polycyclic skeleton was assembled by the Diels–Alder cycloaddition reaction, while the required functionalities of the C ring were introduced during the oxidation step. Since these compounds are derivatives of naturally occurring products with a range of pharmacological properties, the described methodology could prove to be useful for their synthesis and further exploration of their properties.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.085.

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11. *Crystallographic data for* **10**: $C_{21}H_{17}NO_5$, M_r 1645.13, triclinic, P21/n, a = 6.89600(10), b = 8.64520(10), c = 28.7090(5) Å, β = 95.1184(6)°, V = 1704.73(4) Å^3, Z = 4, ρ_c = 1.416 Mg m^{-3}, T = 150 K, λ = 0.71073 Å. 22503 reflections collected, 3857 independent [R(int) = 0.035], which were used in all calculations. R_1 = 0.0502, wR_2 = 0.1273 for observed unique reflections [$I > 2\sigma(I)$] and R_1 = 0.0741, wR_2 = 0.1404 for all unique reflections. Max and min residual electron densities 0.38 and −0.38 e Å^{-3}. CCDC: 802445.
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