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LETTERS

A new approach to the total synthesis of the unusual diterpenoid tropone, harringtonolide.

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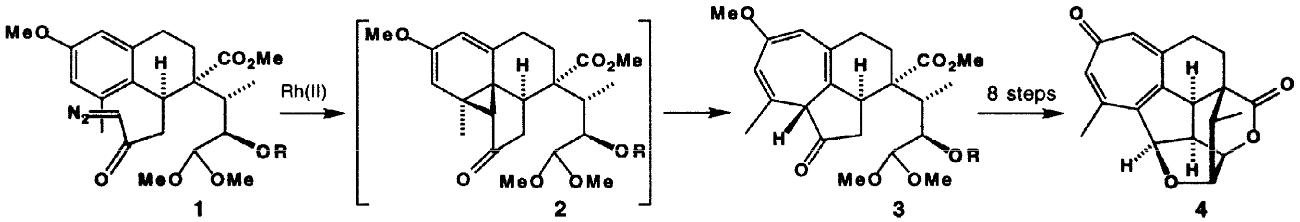
Abstract

The Diels Alder reactions of 5-methoxyindenone followed by intramolecular cyclopropanation provide the basis for a new and more efficient approach to the synthesis of the unusual diterpenoid tropone, harringtonolide.

Keywords: Cycloadditions; Cyclopropanation; Diazo compounds; Troponoids.

The unusual diterpenoid tropone, harringtonolide (**4**), first isolated in North America from seeds of *Cephalotaxus harringtonia* (Taxaceae) [1], and independently from the bark of the related Chinese species *Cephalotaxus hainanensis* [2] has been shown to have promising anti-neoplastic and anti-viral properties [3]. In order to explore its chemistry and therapeutic potential, we have examined a number of strategies for the preparation of **4**, culminating in the successful completion of the sequence outlined in Scheme 1 [4]. A shortcoming of this approach, however, was the need to carry out extensive manipulations in the presence of the highly reactive cycloheptatriene moiety so as to effect the conversion of **3** into **4**.

In seeking a more efficient synthesis of **4** and its analogues, we have now designed the alternative route outlined in Scheme 2 that should require fewer steps and that postpones the assembly of the cycloheptatriene array to a much later stage, as had been planned in our very first approach [5]. Although the initial [4+2] cycloaddition between the indenone and a suitable α-pyrone [6] is problematical, we were more concerned about the feasibility of the



Scheme 1

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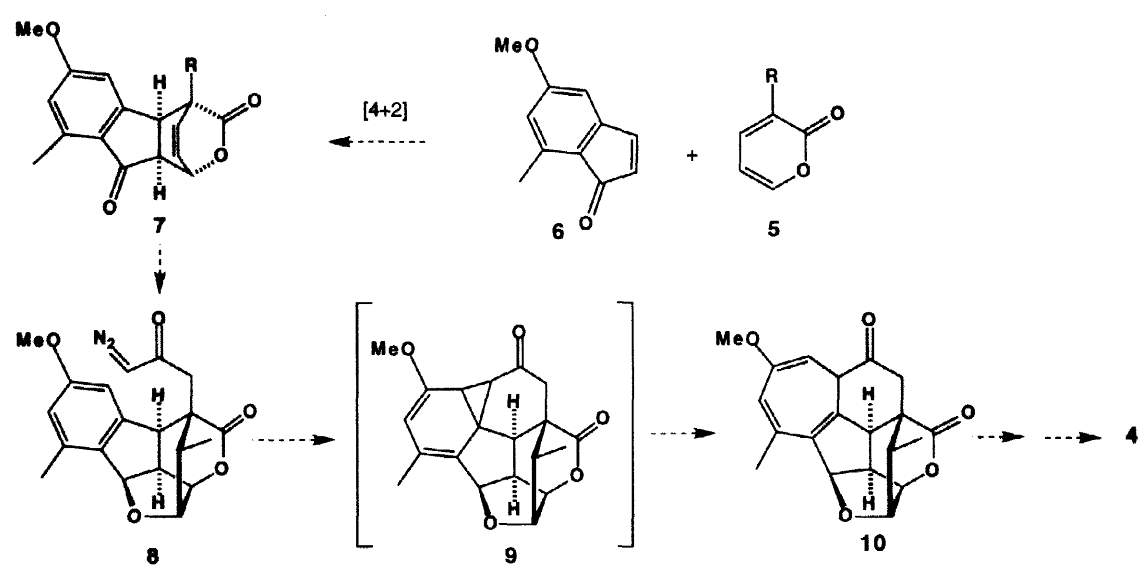
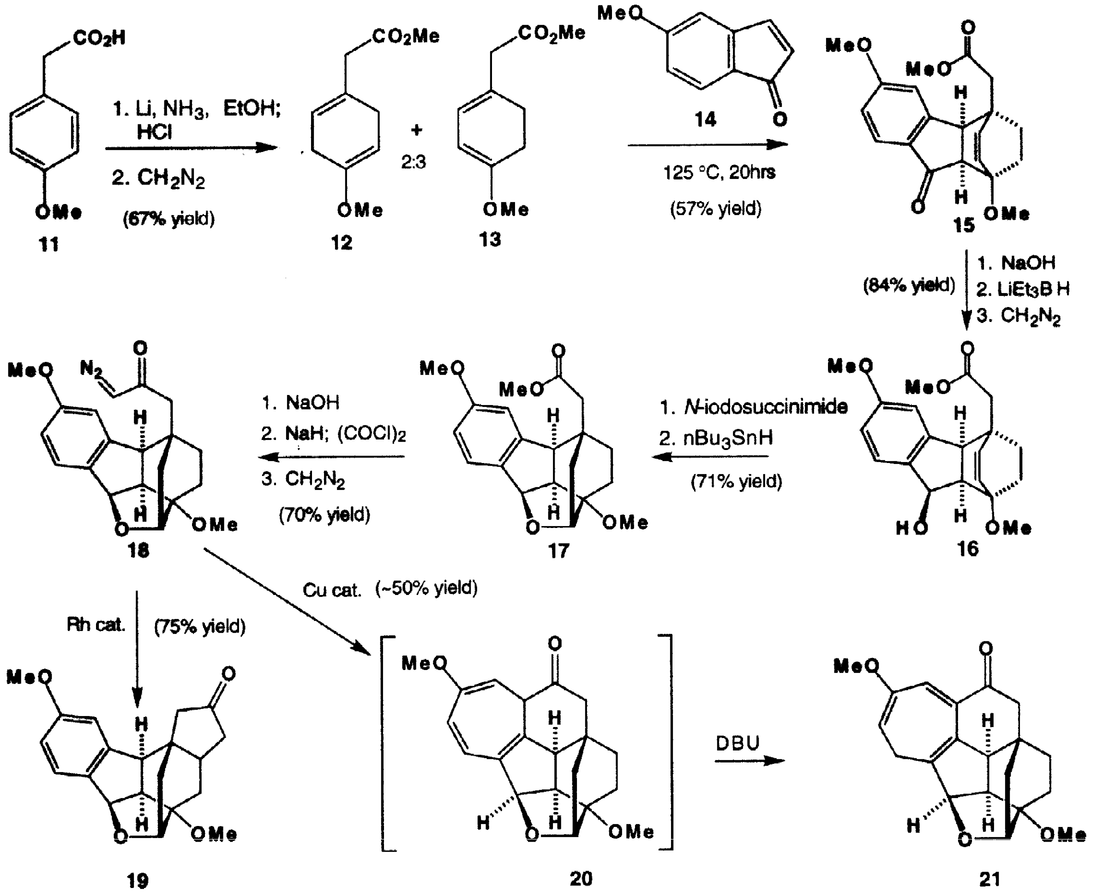


Scheme 2

cyclopropanation step **8** → **9**, which was not expected to be as favourable as the conversion of **1** to **2**, given the different ring size and the potential for competing reactions, *i.e.* CH insertion [7,8] and/or ylide formation with the lactone carbonyl group [9]. We therefore undertook a model study in order to study this pivotal conversion as well as other aspects of the proposed synthesis, the results from which are described in this Letter.

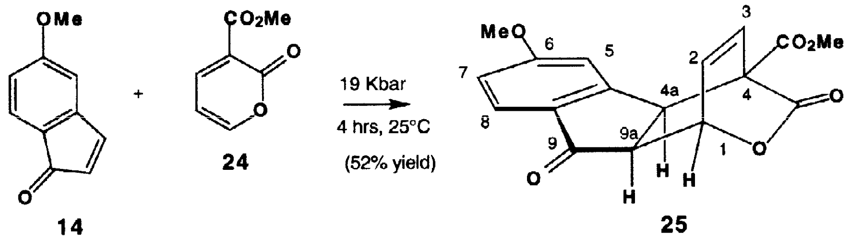
The assembly of a suitable analogue of diazoketone **8**, namely **18**, and its reactions with a range of rhodium and copper catalysts are summarised in Scheme 3. Although indenones are prone to dimerisation and polymerisation [10], a 56% yield of tetracyclic **15** could be obtained by heating a neat 1:2 mixture of indenone **14** [11] with diene **13** at 125°C. Ester **13**, obtained as a 3:2 mixture with **12** from the Birch reduction of **11** (presumably as a consequence of brief exposure to acid during isolation of the initial reduction product), was chosen in the expectation that the methoxyl would provide sufficient activation and ensure the correct regiochemistry. The gross structure of **15** was confirmed by HSC and HMBC spectra [12] while the *endo* stereochemistry was evident from NOE correlations between the protons of the ethane bridge with the cyclopentanone ring protons.

For the next phase of the synthesis, it was necessary to reduce **15** to carbinol **16**, but the indanone carbonyl was surprisingly inert to $NaBH_4$ treatment. Ketone **15** was therefore hydrolysed to the corresponding acid and reduced with $LiEt_3BH$ [13]. After restoration of the ester function with diazomethane, **16** was obtained in good overall yield and converted smoothly to the cyclic ether **17** by treatment with *N*-iodosuccinimide, followed by tri-*n*-butylstannane reduction. After hydrolysis of the ester function, diazoketone **18** was prepared [4] by formation of the sodium salt (NaH), conversion to the acyl chloride (oxalyl chloride plus a molar equivalent of DMF) and then treatment with diazomethane. A range of rhodium and copper catalysts was employed to generate the metallocarbenoid, resulting in a considerable variation in outcomes. No discreet products were obtained with $Rh_2(OAc)_4$, while the use of $Rh_2(acam)_4$ [14] returned mainly starting material. The epimeric CH insertion products **19** were obtained in 75% yield when $Rh_2(tpa)_4$ [15] was used, and were the only detectable products with rhodium mandelate [16] (40-50% yield). Treatment with $Cu(acac)_2$, which had proven to be an effective catalyst for other arene cyclopropanations [17], or copper-bronze afforded a complex mixture. A moderate yield of cyclopropanation product (50% yield) was obtained with bis(*N*-*t*.-butylsalicyl-aldiminato) copper(II) [18], however, provided that toluene was used as solvent; a complex mixture was obtained when the reaction was conducted in 1,2-dichloroethane. No attempt was made to isolate the very labile cycloheptatriene **20**, but instead, the reaction mixture was treated *in situ* with DBU so



Scheme 3.

as to afford the somewhat more stable isomer **21**. Having established that formation of the harringtonolide skeleton by this approach appeared to be feasible, we returned to the question of whether the [4+2] cycloaddition of a suitable α-pyrone with the indenyl system could be used to assemble a suitable tetracyclic intermediate (*cf.* Scheme 2). Although it appeared unlikely that good regiochemical control would be obtained in the reaction of indenone **6** with an α-pyrone derivative such as **5** (R = CH_2CO_2R'), ester **24** has been shown to afford good *syn*-regioselectivity with electron-rich dienophiles [6,19]. It was therefore of considerable interest to determine the outcome from treating **24** with an electron-deficient dienophile such as indenone **14**. A reaction was carried out at 19 Kbar and resulted in a 52% yield (unoptimised) of a cycloadduct (Scheme 4) that furnished ^{1}H NMR data consistent with those expected for structure **25**: namely, the benzylic proton H4a (δ 4.32, d), was coupled



Scheme 4

(J = 7.1 Hz) only to H9a (δ 3.63, dd), whereas this proton was also coupled to H1 (δ 5.56), the magnitude of $J_{1,9a}$ (5.0 Hz) showing that the *endo* adduct had been formed [19]. Confirmation of structure **25** was established by determining an X-ray crystal structure (Figure 1).[1] With the successful preparation of **21** and **25**, it appears that the synthesis of harringtonolide **4** by means of the strategy outlined in Scheme 2 is indeed feasible. There is also an excellent prospect of establishing an enantioselective route by employing a chiral variant of **24** in the cycloaddition step [6].

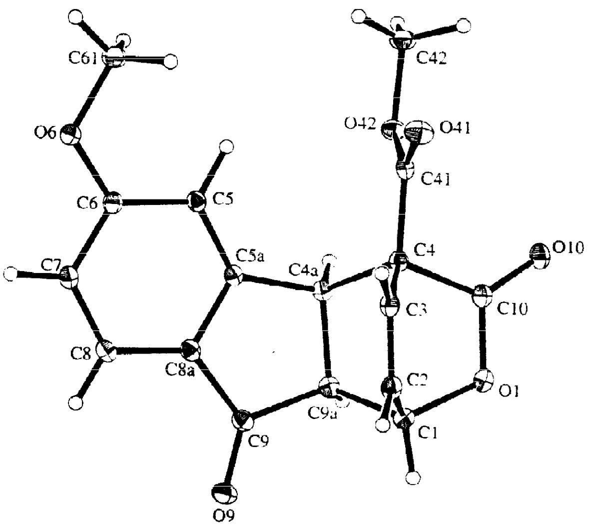


Figure 1. ORTEP view of lactone **25**; thermal ellipsoids enclose 20% probability levels.

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[1] Crystal data: $C_{17}H_{14}O_6$, M = 314.29, T = 296(1) K, triclinic, space group $P\bar{1}$, a = 7.877(2), b = 9.080(1), c = 10.721(2) Å, U = 691.8(2) $Å^3$, D_c (Z = 2) = 1.509 g cm^{-3}, F(000) = 328, $\mu(CuK_\alpha)$ = 9.24 cm^{-1}, semi-empirical absorption correction; 2057 unique data ($2\Theta_{max}$ = 120.2°), 1938 with $I > 3\sigma(I)$; R = 0.037, wR = 0.054, GOF = 3.28. Data were measured on a Rigaku AFC6R rotating anode diffractometer (graphite crystal monochromator, λ = 1.54178 Å). Data were corrected for Lorentz/polarization effects and absorption [20]. The structure was solved by direct methods [21] and expanded using Fourier techniques [22]. Refinement was by full-matrix least squares analysis on F using the teXsan Structure analysis Software of Molecular Structure Corporation [23]. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited by the editor at the Cambridge Crystallographic Data Centre.