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Synthesis of the Proposed Structure of Afzeliindanone.

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Abstract: A synthesis of the proposed structure of afzeliindanone has been achieved using an alkyne [2 + 2 + 2] cyclotrimerisation as a key step. The data for the synthetic material was found to not match the data for the natural material, indicating a structural misassignment.

Key words: alkyne, cyclotrimerisation, indanone, rhodium, catalysis.

Champy *et al.* reported the isolation of afzeliindanone **1** from the West African shrub *Uvaria afzelii* in 2009.¹ The structure shown in figure 1 was assigned based upon NMR studies. Afzeliindanone was found to have some activity against *Leishmania donovani* and *Leishmania major*, two of the parasites associated with leishmaniasis. It was pointed out that this structure is unusual as a natural product and represents the first indanone isolated from a plant.² Given the arrangement of the indanone moiety and the second aryl group as a 1,2,3-substitution pattern, we anticipated that this molecule could be amenable to synthesis by an alkyne [2 + 2 + 2] cyclotrimerisation³ from diyne **2**.

Figure 1 Afzeliindanone and a retrosynthesis. PG = protecting group.

To achieve this objective, guaiacol **3** was subjected to iodination.⁴ This reaction never went to completion. **Compounds 3 and 4 are separable by chromatography only with difficulty.** Rather than carry out a tedious separation of guaiacol **3** and 4-iodoguaiacol **4**, the mixture was carried forwards. The phenolic group was protected as a mesylate.⁵ We originally employed an acetate group, but this proved too labile in subsequent steps. Sonogashira coupling of mesylate **5** with 4-pentyn-1-ol yielded the alkyne **6** which could be separated from the guaiacol mesylate **4** arising from the incomplete iodination.⁶ Swern oxidation of the alcohol then yielded aldehyde **7** which was treated with ethynylmagnesium chloride to give diyne **2a**. At this point, we attempted the alkyne [2 + 2 + 2] cyclotrimerisation of diyne **2a** with acetylene gas, selecting tris(triphenylphosphine)rhodium(I) chloride^{3b-d} as the

catalyst (table 1). The simple reaction in ethanol yielded only 11-33% of the desired biaryl product **8**, depending on how thoroughly the solution was purged with acetylene (entries 1 and 2). In both cases, the product was accompanied by alkyne **9**, the product of a [2 + 2 + 2] dimerisation of diyne **2a**. To achieve pseudo high dilution of diyne **2a** in order to suppress dimerisation, a solution of this compound was added over an extended time period by syringe pump. Twelve hours proved too long as catalyst decomposition resulted in incomplete conversion, even if the temperature was reduced to room temperature (entries 3 and 4). Addition over 4 hours gave a better result (entry 5), especially with a higher catalyst loading (entry 6), giving a 75% yield of the desired indanol **8**.

Table 1 The [2 + 2 + 2] cyclotrimerisation^a

entry	slow addition time	T/ °C	yield		
			2a	8	9
1	none ^b	60	0	11	71
2	none ^c	60	0	33	48
3	12	60	22	35	0
4	12	25	32	13	0
5	4	60	trace	49	0
6	4 ^d	60	0	75	0

a: all reactions were carried out in ethanol using 4 mol% of Wilkinson's catalyst, except where stated otherwise; b: purging acetylene for 5 – 10 minutes before adding the reactants; c: 20 minutes of purging; d: 10 mol% of catalyst was used.

Deprotection of indanol **8** could be achieved using potassium hydroxide,⁵ but the resulting phenol **10** underwent decomposition during the subsequent oxidation (IBX), presumably due to the highly electron rich ring. In contrast, the mesyl protected compound **8** could be easily oxidised to the indanone **11** under Swern conditions. Now, however, decomposition occurred when deprotection was attempted using potassium hydroxide. To complete the synthesis, we resorted to a method that we earlier employed in our synthesis of γ -lycorane.⁷ Thus, treatment of indanone **11** with ethane thiol and sodium hydroxide in DMSO, generating a reagent that is less basic but more nucleophilic, yielded the target molecule **1** in 61% yield.

To our dismay, we observed significant differences between the ¹H NMR and ¹³C NMR spectra obtained for our synthetic material and those reported for the natural material. While the signals associated with the CH₂CH₂ moiety and the methoxy group were in good agreement, correlation of the signals of the aromatic rings was very

poor.⁸ To ensure that our synthetic material possessed the anticipated structure, an X-ray crystallographic study was carried out (figure 2), which confirmed the identity of the synthetic material as **1**.⁹ We, therefore, conclude that the structure of the natural product has been misassigned and is not as shown in figure 1. Errors in natural product structure assignments have been

discovered through total synthesis previously.¹⁰ Furthermore, closer inspection of the NMR data discussed in the original report¹ merely deepens the uncertainty. Given the rather scant data reported, it is not possible to assign a correct structure.¹¹

Scheme 1 Synthesis of the proposed structure of Afzeliindanone

In conclusion, we have completed the synthesis of the proposed structure **1** of afzeliindanone and shown that it is not the structure of the natural product. Nevertheless, this work shows that the [2 + 2 + 2] cyclotrimerisation of alkynes does provide rapid access to biaryls of this type, especially when slow addition is employed.

Figure 2 X-ray crystallographic structure of the proposed structure of afzeliindanone

4-(1-hydroxy-2,3-dihydro-1H-inden-4-yl)-2-methoxyphenyl methanesulfonate (**8**)

A solution of diyne **2a** (500 mg, 1.62 mmol) in ethanol (8 mL) was purged with nitrogen gas for 10 mins and subsequently with acetylene gas for 30 mins. A solution of $\text{RhCl}(\text{PPh}_3)_3$ (150 mg, 0.162 mmol, 10 mol%) in ethanol (12 mL) was similarly purged with nitrogen gas for 10 mins and subsequently with acetylene gas for 30 mins. The solution of diyne **2a** was then added slowly to the solution of Wilkinson's catalyst over 4 hours using a syringe pump while heating at 60 °C. The mixture was stirred overnight, then filtered through celite and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluent EtOAc/hexane 45:55) to give 4-(1-hydroxy-2,3-dihydro-1H-inden-4-yl)-2-methoxyphenyl methanesulfonate **8** as a yellow solid (407 mg, 75%).

^1H NMR (400 MHz, CDCl_3): δ 7.45 (d, J = 6.8 Hz, 1H), 7.37 – 7.28 (m, 3H), 7.05 – 7.01 (m, 2H), 5.31 (q, J = 5.9 Hz, 1H), 3.93 (s, 3H), 3.22 (s, 3H), 3.14 – 3.06 (m, 1H), 2.90 – 2.83 (m, 1H), 2.52 – 2.44 (m, 1H), 1.99 – 1.90 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 151.3, 146.2, 141.3, 141.1, 137.7, 137.6, 128.7, 127.7, 124.5, 123.9, 121.4, 113.5, 76.6, 56.2, 38.5, 36.3, 29.9; FTIR cm^{-1} : 3439; MS (ESI): $[\text{M} + \text{H}]^+$ m/z 335.18; HRMS: $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{17}\text{H}_{18}\text{O}_5\text{S}$: 335.0953; found: 335.1602, 335.2099; Melting point: 131–132 °C.

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Supporting Information

Experimental procedures, NMR spectra and table showing NMR data comparison for **1**.

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Afzeliindanone synthesis?

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