Synlett Rita et al. Letter

Synthesis of the Proposed Structure of Afzeliindanone

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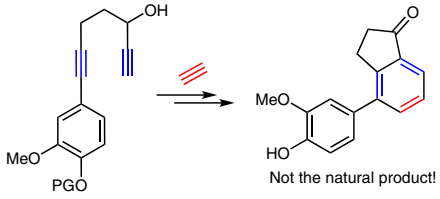

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Abstract A synthesis of the proposed structure of afzeliindanone was achieved by using an alkyne [2+2+2]-cyclotrimerization as a key step. The data for the synthetic material were found not to match those for the natural material, indicating a structural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

Key words alkynes, cyclotrimerization, indanones, rhodium catalysis, afzeliindanone

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 on the basis of NMR studies. Afzeliindanone was found to have some activity against *Leishmania donovani* and *L. major*, two of the parasites associated with leishmaniasis. It was pointed out that this structure is unusual for a natural product and that it 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 surmised that this molecule might be amenable to synthesis by an alkyne [2+2+2] cyclotrimerization[3] from diyne **2**.

To achieve this objective, guaiacol (**3**) was subjected to iodination (Scheme 1).[4] However, this reaction never went to completion. Compounds **3** and the iodo derivative **4** are separable by chromatography only with difficulty. Rather than carry out a laborious separation of guaicol **3** and its iodo derivative **4**, we carried the mixture forward, and 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 pent-4-yn-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 gave aldehyde **7**, which was treated with ethynylmagnesium

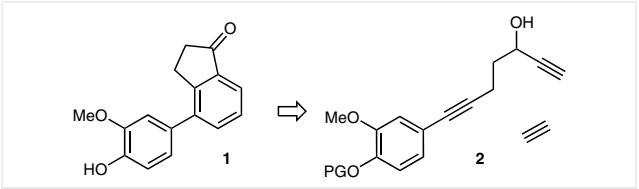

Figure 1 Afzeliindanone (**1**) and a retrosynthesis. PG = protecting group.

chloride to give diyne **2a**. At this point, we attempted the alkyne [2+2+2] cyclotrimerization of diyne **2a** with acetylene gas in the presence of tris(triphenylphosphine)rhodium(I) chloride[3b–d] as a catalyst (Table 1). The simple reaction in ethanol gave only 11–33% of the desired biaryl product **8**, depending on how thoroughly the solution had been purged with acetylene (Table 1, entries 1 and 2). In both cases, the product was accompanied by alkyne **9**, the product of [2+2+2] dimerization of diyne **2a**. To achieve pseudo high dilution of diyne **2a** to suppress this dimerization, a solution of **2a** was added over an extended 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 four hours gave a better result (entry 5), especially with a higher catalyst loading (entry 6), and a 75% yield of the desired indanol **8** was obtained.[7]

Deprotection of indanol **8** could be achieved by using potassium hydroxide,[5] but the resulting phenol **10** underwent decomposition during a subsequent oxidation by IBX, presumably due to the highly electron-rich ring. In contrast, the mesyl-protected compound **8** could be easily oxidized to the indanone **11** under Swern conditions. However, decomposition occurred when deprotection was attempted using potassium hydroxide. To complete the synthesis, we resorted to a method that we previously employed in our synthesis of γ-lycorane.[8] Thus, treatment of indanone **11**

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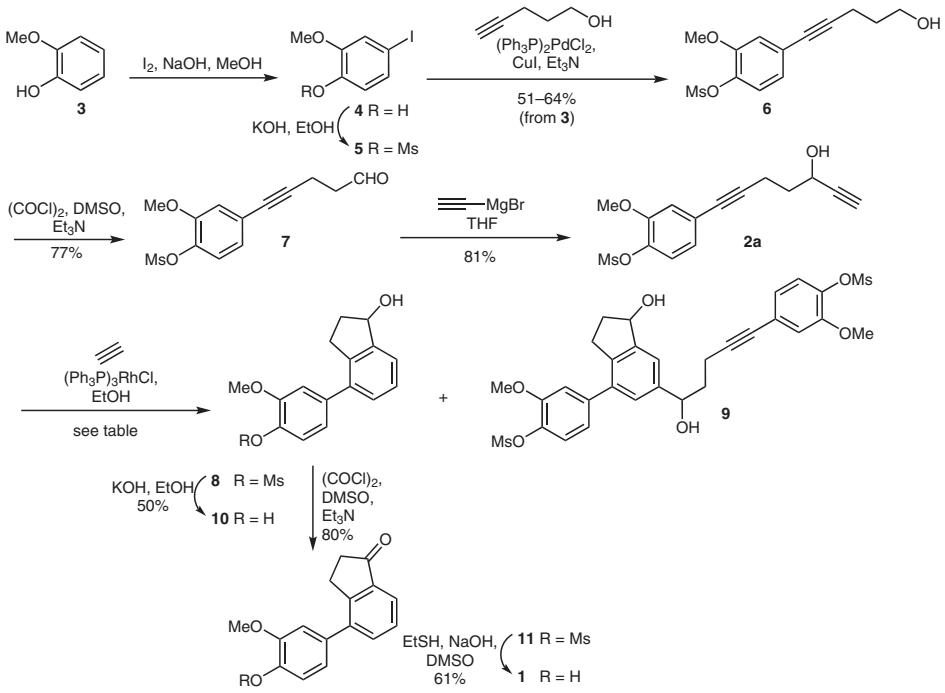

Scheme 1 Synthesis of the proposed structure of afzeliindanone

Table 1 Optimization of the [2+2+2] Cyclotrimerization[a]

Entry	Slow addition time (h)	Temp (°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 EtOH using 4 mol% of Wilkinson's catalyst, except where otherwise stated.
[b] Acetylene was purged for 5–10 min before adding the reactants.
[c] Acetylene was purged for 20 min.
[d] 10 mol% of the catalyst was used.

with ethanethiol and sodium hydroxide in DMSO, to generate a reagent that was less basic but more nucleophilic, gave the target molecule **1** in 61% yield.

To our dismay, however, we observed significant differences between the ^{1}H NMR and ^{13}C NMR spectra of our synthetic material and those reported for the natural material. Whereas the signals associated with the CH_2CH_2 moiety and the methoxy group were in good agreement, correlation of the signals of the aromatic rings was poor.[9] To ensure that our synthetic material possessed the expected structure, we performed an X-ray crystallographic study (Figure 2), which confirmed the identity of the synthetic material as **1**.[10] We, therefore, conclude that the structure of the natural product had been misassigned, and is not that shown in Figure 1. Errors in natural-product structure assignments have been discovered through total synthesis previously.[11] Furthermore, closer inspection of the NMR data discussed in the original report[1] merely deepens the uncertainty; given the rather scant data reported, it is not possible to assign a correct structure.[12]

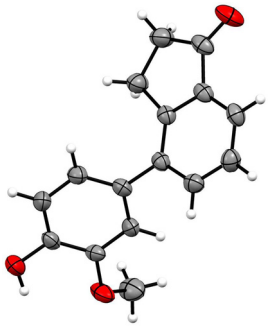

Figure 2 X-ray crystallographic structure of the proposed structure of afzeliindanone

In conclusion, we have completed a synthesis of the proposed structure **1** of afzeliindanone and have shown that this is not the structure of the natural product. Nevertheless, this work showed that the [2+2+2] cyclotrimerization

of alkynes provides rapid access to biaryls of this type, especially when slow addition is employed.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707470.

References and Notes

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(4) Fryatt, T.; Botting, N. P. *J. Labelled Compd. Radiopharm.* **2005**, *48*, 951.

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(6) In some runs, alkyne **6** was contaminated with the product of Glaser coupling of the pentynol. This could be easily separated after the subsequent Swern oxidation.

(7) **4-(1-Hydroxy-2,3-dihydro-1*H*-inden-4-yl)-2-methoxyphenyl Methanesulfonate (8)**
A solution of diyne **2a** (500 mg, 1.62 mmol) in EtOH (8 mL) was purged with N_2 gas for 10 min and then with acetylene gas for 30 min. A solution of $RhCl(PPh_3)_3$ (150 mg, 0.162 mmol, 10 mol%) in EtOH (12 mL) was similarly purged with N_2 gas for 10 min and then with acetylene gas for 30 min. The solution of diyne **2a** was then slowly added to the solution of Wilkinson's catalyst at 60 °C over 4 h by using a syringe pump. The mixture was stirred overnight then filtered through Celite and concentrated in vacuo. The residue was purified by column chromatography [silica gel, EtOAc–hexane (45:55)] to give a yellow solid; yield: 407 mg (75%); mp 131–132 °C.
FTIR (nujol): 3439 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 6.8 Hz, 1 H), 7.37–7.28 (m, 3 H), 7.05–7.01 (m, 2 H), 5.31 (q, *J* = 5.9 Hz, 1 H), 3.93 (s, 3 H), 3.22 (s, 3 H), 3.14–3.06 (m, 1 H), 2.90–2.83 (m, 1 H), 2.52–2.44 (m, 1 H), 1.99–1.90 (m, 1 H). ^{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. MS (ESI): *m/z* = 335.18 $[M + H]^+$. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{19}O_5S$: 335.0953; found: 335.1602, 335.2099.

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(9) For a comparison of all of the NMR data, see the Supporting Information.

(10) CCDC 1913019 contains the supplementary crystallographic data for compound **1**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(11) Maier, M. E. *Nat. Prod. Rep.* **2009**, *26*, 1105.

(12) Attempts to contact the corresponding author of Ref. 1 met with no reply.