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An efficient total synthesis of (±)-*ar*-tenuifolene

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ABSTRACT

(±)-*ar*-Tenuifolene was synthesized using a ring expansion mediated by a formal 1,3-alkyl shift reaction on a *trans*-1-aryl-2-propenyl-cyclobutancarbonitrile as the key step to generating the cyclohexene moiety. The conditions for this rearrangement are described.

A range of marine and terrestrial sources continue to provide interesting and structurally inspiring natural products that attract the interest of medicinal and synthetic organic chemists alike.

Our research group focuses on the synthesis of biologically active natural products. We recently developed an interest in 1-aryl-2-propenylcyclobutanecarbonitrile rearrangements as an approach to a variety of carbocyclic derivatives.

Prior studies revealed the formation of benzocyclooctene ring adducts upon treatment of substrate **1** under certain conditions.[1] Later studies revealed that the application of different conditions to substrate **1** yielded a six-membered ring instead of the anticipated eight-membered ring (Scheme 1).

After elucidating the structure of the unexpected product **2**, we realized that the connectivity conversion displayed by **1** could be viewed as a formal 1,3-alkyl shift. Such rearrangements, although rare, have been described in the past, and they are known mechanistically to proceed by various pathways, depending on the nature of the substrate.[2] Methodologies involving this kind of transformation have been implemented in total syntheses.[3] Data that could elucidate the pathway through which our reaction proceeded were not previously available; however, systems with similar functionalities have been studied, and the determining steps of those reactions were shown to depend on the particular system functionality present.[2f]

As we ascertained the structure of compound **2**, we set out to explore rearrangements that expanded template substrates. At the same time, we realized that the sesquiterpenoid character on structure **2** was prevalent, leading us to recognize the close resemblance between the core of the natural products *ar*-tenuifolene and tenuifolene (Fig. 1). In view of this insight, we focused our efforts on achieving on the first place the total synthesis of the natural product using an appropriate raw material.

As described for the first time in 2004 by König[4], *ar*-tenuifolene is found in the essential oil of *Olearia tenuifolia*, together with its reduced analog tenuifolene. *O. tenuifolia* presents pharmacological properties and has been used by the Masai tribe in East Africa as a medicine against gonorrhea[5] and as an antipyretic in cattle.[6] *ar*-Tenuifolene has also been identified in the essential oils of *Radula perrottetii*[7] and *Callitris sulcata*.[8]

The first and only synthesis of (±)-*ar*-tenuifolene was reported by Srikrishna and Beeraiah in 2005.[9] These researchers proposed using a key ring-closing metathesis (RCM) step to form the cyclohexene moiety.

In view of the evidence supporting a ring expansion mechanism, we envisaged an (±)-*ar*-tenuifolene synthesis through a Wolff–Kishner reduction of the aldehyde (**3**), which could be reached through the chemoselective reduction of nitrile **4**. This cyclohexenecarbonitrile was affordable after a 1,3-alkyl shift in 1-(4-methylbenzene)-2-propenyl-cyclobutancarbonitrile (**5**) (Fig. 2).

Our synthetic approach began from 4-methylbenzylcyanide **7**, which was first treated with *n*-BuLi in THF at a temperature of −78 °C, followed by treatment with 5-iodo-2-methylpent-2-ene as an alkylating agent, to generate the homoisoprenylic moiety. Subsequently, an epoxidation protocol[10] with dimethyldioxirane (DMDO), generated in situ by Oxone®, was used to produce epoxynitrile **6** in an 80% global yield.

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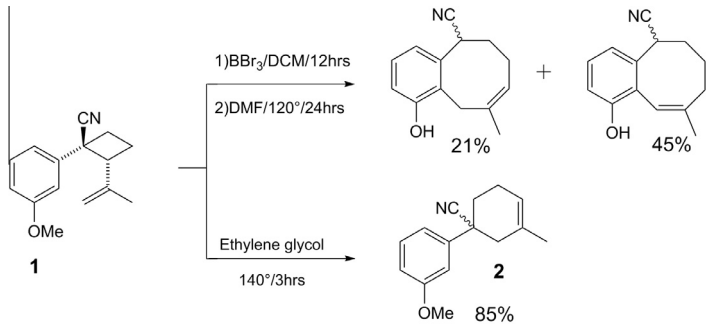


Scheme 1. Possible reaction outcomes for substrate **1**.

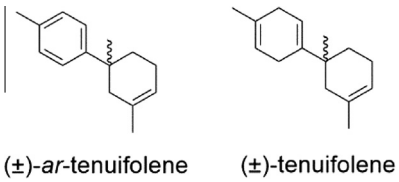


Figure 1. Structures of (±)-*ar*-tenuifolene and (±)-tenuifolene.

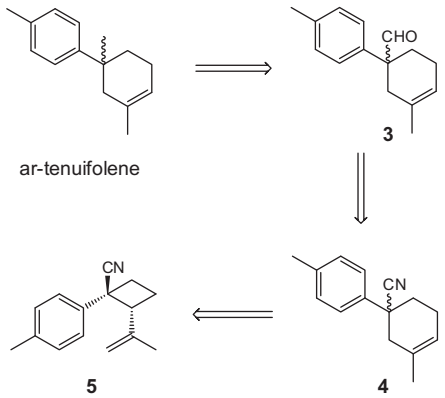


Figure 2. Retrosynthetic analysis of (±)-*ar*-tenuifolene.

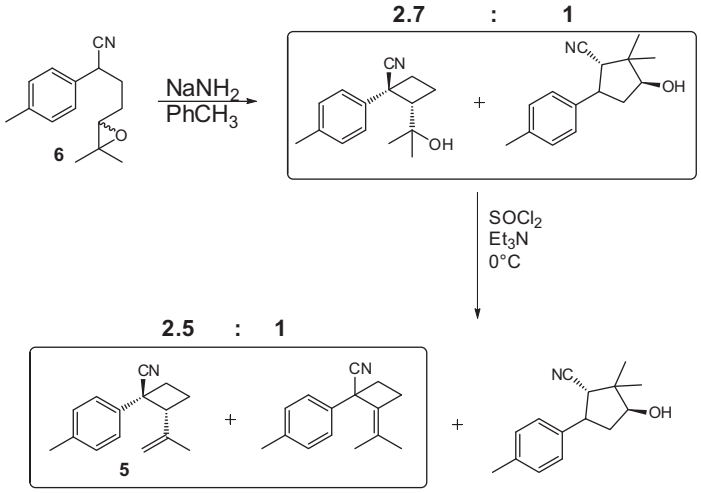
The next step effectuated an intramolecular anionic cyclization according to a variant of a methodology reported previously by our group.[11] This approach was suited for the construction of this type of carbocyclic system. The variant methodology involved the treatment of **6** with sodium amide in benzene under reflux.

This approach yielded two *trans*-regioisomers: cyclopentane- and cyclobutanecarbinols. The regioisomeric mixture was dehydrated with thionyl chloride and Et_3N in toluene at 0 °C. This protocol allowed us to synthesize the *trans*-1-(4-methylbenzene)-2-propenylcyclobutanecarbonitrile (**5**), in 45% yield.

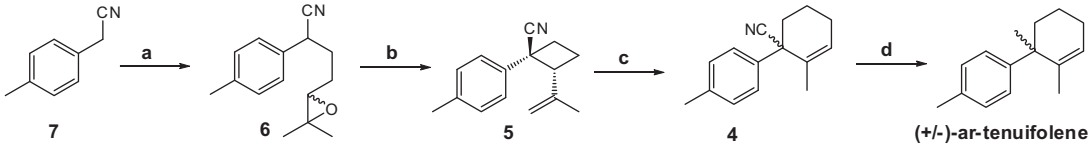
We observed an interesting effect involving isomeric selectivity during the dehydration step. Only the cyclobutanic adduct reacted to produce an isomeric mixture of alkenes, leaving the cyclopentanic adduct unaffected (Scheme 2). This allowed us to make the conversion of **6** to **5** without purifying the isomeric mixture of alcohols.

The key step of the synthesis involved the rearrangement described above, which depended significantly on the temperature. The reaction did not proceed at temperatures below 115 °C, and increases in the temperature were found to reduce the necessary reaction time. We concluded that the energetic barrier to the transformation could only be overcome at temperatures exceeding 115 °C. Solvents, such as chlorobenzene and DMF, were evaluated for their ability to reduce the reaction barrier, and ultimately ethylene glycol was selected for the easy work-up that it enabled. Treatment of **5** in ethylene glycol at 140 °C was found to yield the cyclohexenecarbonitrile **4** in a 90% yield.

Finally, a two-step reduction was performed on the nitrile **4**. DIBAL-H was first used on DCM at 0 °C to generate the aldehyde



Scheme 2. Reaction pathway from **6** to **5** through a selective dehydration.



Scheme 3. Synthesis of (±)-*ar*-tenuifolene. Reaction conditions: (a) (i) nBuLi, THF, −78 °C, 15 min; (ii) 5-iodo-2-methylpent-2-ene, −78 °C to rt, 30 min; (iii) Oxone®, $NaHCO_3$, acetone, H_2O, rt. 2 h, 80% yield. (b) (i) $NaNH_2$, PhH, reflux, 2 h; (ii) $SOCl_2$, Et_3N, toluene, 0 °C, 15 min, 45% yield. (c) Ethylene glycol, 140 °C, 3 h, 90% yield. (d) (i) DIBAL-H, DCM, 0 °C, 6 h; (ii) NH_2-NH_2·H_2O, diethylene glycol, 150 °C, 1 h; (iii) KOH powder, 200 °C, 1 h, 71% yield.

3, which was subsequently subjected to a Wolff–Kishner–Huang reaction with NH_2-NH_2·H_2O in diethylene glycol at 150 °C. KOH powder was added at 200 °C to finally give the (±)-*ar*-tenuifolene in a 71% yield (Scheme 3). The spectral data obtained from the product agreed well with the spectra obtained from the natural product.

It is worth noting that Srikrishna and Beeraiah also synthesized (±)-tenuifolene via a Birch reduction on (±)-*ar*-tenuifolene, which entitles us to say that our route also provides a formal synthesis of (±)-tenuifolene.

The methods described here provide a novel total synthesis of (±)-*ar*-tenuifolene through a formal 1,3-alkyl shift over *trans*-1-(4-methylbenzene)-2-propenylcyclobutanecarbonitrile with a global yield of 23%. This approach constitutes the most efficient synthesis of (±)-*ar*-tenuifolene reported to date.

We are currently developing a deeper exploration of this type of rearrangement, obtaining consistent results with the formation of cyclohexane moieties. We hope these results will improve our understanding of the reaction involved in producing (±)-*ar*-tenuifolene and the possible mechanisms through which this reaction proceeds.

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