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Sequential Free Radical Synthesis of a Linear Triquinane Skeleton from an Acyclic Synthon

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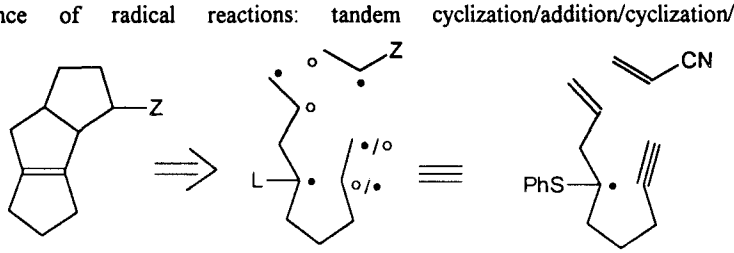
Abstract: Regio- and stereoselective synthesis of a linear triquinane derivative was accomplished by a sequential free radical reaction, starting from an acyclic precursor

Sequential free radical reactions offer a powerful method for the construction of complex polycyclic compounds[1]. Due to the ease of a free radical cyclopentane ring closure, polyquinanes have attracted much interest as potential targets for free radical methodology[2]. Existing synthetic approaches to triquinanes are based on tandem cyclizations, with formation of two new rings attached to a central cyclic unit already existing in the radical precursor[3]. Beckwith's studies showed that sequential cyclization of the simple open chain trienyl radical affords tricyclic products as a mixture of regio- and stereoisomers[4].

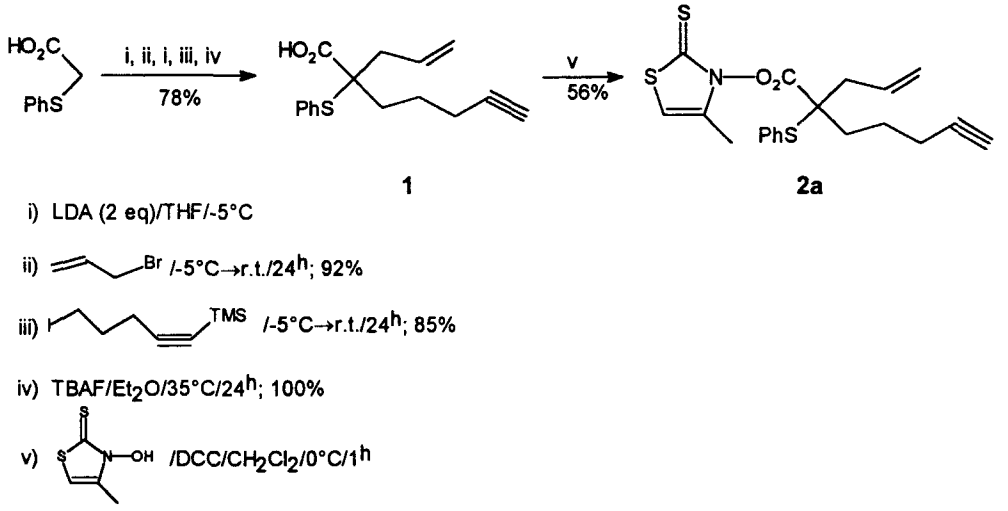
Recently, we reported a free radical annulation reaction leading to 2-vinyl substituted cyclopentane derivatives, where addition/cyclization/β-elimination sequence proceeds through the intermediacy of a 5-phenylthio-3-pentenyl radical[5]. In addition to this sequence of radical reactions for cyclopentane ring annulation, 5-*exo*-*dig* hexynyl radical cyclization[6] as well as 5-*exo*-*trig* cyclization of vinyl radicals[7] are also well known reactions for cyclopentane ring closure. Extending the scope of our method to the synthesis of polycyclic molecules, we designed a system where the same reactive unit, (emphasized substructure in **6**, Scheme 3), would be formed by two consecutive cyclizations, and further submitting to the already described reaction conditions eventually afford a tricyclic product[8]. From the retrosynthetic analysis of the linear triquinane skeleton (Scheme 1), it can be seen that starting from synthon **2** and applying the following sequence of radical reactions: tandem cyclization/addition/cyclization/β-elimination,



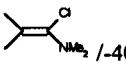
Scheme 1

the target molecule could be prepared from the easily available acyclic synthon.

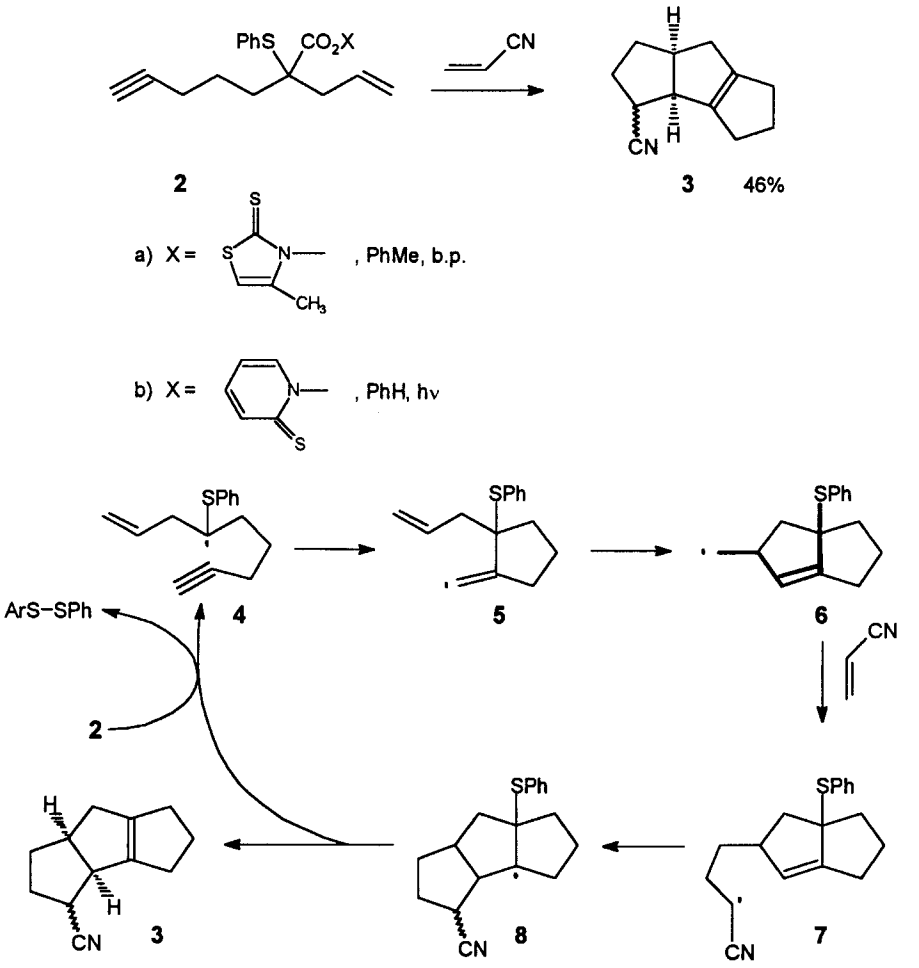
Here we report the first regio- and stereoselective formation of a linear triquinane framework by a sequential radical reaction of an open chain polyunsaturated radical. The acid **1** was prepared by two successive alkylations of phenylthioacetic acid dianion[9] followed by TMS group cleavage, in 78% overall yield (Scheme 2). Standard reagents for conversion of acid **1** into the corresponding acyl chloride



Scheme 2

($SOCl_2$/DMF; $(COCl)_2$/DMF;  /-40°C) were unsuccessful, and poor yields of thiohydroxamic ester **2b** were obtained. However, the thiohydroxamic ester **2a** was conveniently prepared by DCC method[10] (56% yield after column chromatography purification). When **2a** was submitted to the free radical conditions (CH_2=CHCN (22 eq), AIBN, boiling toluene, 0.5h), the unsaturated linear triquinane derivative **3** was obtained in 46% isolated yield (Scheme 3). The product was obtained as the inseparable mixture of two diastereoisomers in 2.2 : 1 ratio (determined by capillary GC and ^{13}C analyses)[11]. However, when the reaction sequence was performed with the precursor **2b** at lower temperature (benzene, 150W sunlamp, 70°C), the ratio of isomers was 3.7 : 1.

Several features of this sequential reaction are noteworthy. Cyclization of **4** proceeds regioselectively, although the sulphur-stabilized radical has the possibility of reversible or *endo* addition to the terminal (unactivated) alkyne[12]. The rate constant for vinyl radical addition to thione group of thiohydroxamic esters is not known, (although 5-alkenylvinyl radicals undergo rapid cyclization, premature trapping of the intermediate **5** by the precursor is a possible side reaction), but our results show that under appropriate conditions vinyl radical intermediates are compatible with the Barton method of radical generation[13]. By the cyclization of vinyl radical **5** the 5-phenyl-thio-3-pentenyl type radical **6** is formed, which is known to undergo



Scheme 3

intermolecular addition to acrylonitrile and subsequent cyclization/β-elimination reaction[5], thus furnishing the linear triquinane structure **3**[14]. The cyclization of **5** very likely gives rise to diastereoisomeric radicals **6**, but β-elimination of **8** destroys the stereochemistry at the ring juncture, giving a mixture of only two isomers, the predominant one being tentatively assigned as the *exo*.

To summarize, regio- and stereoselective synthesis of a linear triquinane framework can be achieved from readily available acyclic precursor under free radical conditions. Investigations concerning the syntheses of more functionalized triquinane molecules by this method are in progress.

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11. Spectral data for **3**:
    $^{13}C(CDCl_3)$, major isomer: 149.533 (C), 143.736 (C), 121.659 (C), 49.466 (CH), 47.526 (CH), 37.365 (CH_2), 34.01 (CH_2), 32.408 (CH), 31.06 (CH_2), 29.26 (CH_2), 28.58 (CH_2), 28.296 (CH_2)
    minor isomer: 147.691 (C), 144.612 (C), 123.154 (C), 52.546 (CH), 47.187 (CH), 36.758 (CH_2), 34.092 (CH_2), 32.296 (CH), 31.03 (CH_2), 29.26 (CH_2), 28.077 (CH_2), 27.571 (CH_2)
    ^1H NMR($CDCl_3$), the mixture of isomers: 3.2 (m, 1H); 0.8-2.8 (m, 14H)
    IR: 2940, 2847, 2236, 1448, 746
    MS(DCI/iso-butane): 174(9%, M+1), 173(73%,M^+), 172(100%,M-1), 145(70%), 119(84%), 105(56%), 92(33%), 91(70%), 79(30%), 77(29%), 65(27%), 51(14%), 41(29%), 39(24%)
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