

A Highly Abbreviated Synthesis of Pentalenene by Means of the Squarate Ester Cascade

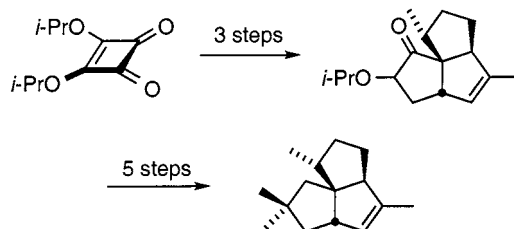
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ABSTRACT



The sequential addition of 5-methylcyclopentyllithium and propynyllithium to diisopropyl squarate results in the efficient formation of a functionalized angular triquinane having two of its five-membered rings substituted precisely as in the target sesquiterpene. Only seven additional steps are then required to access pentalenene.

Pentalenene (**1**), whose isolation from *Streptomyces griseochromogenes* was reported by Seto and Yonehara in 1980,¹ is the parent hydrocarbon of the pentalenone antibiotic family of fungal metabolites. The unusual tricyclo[6.3.0.0^{4,8}]-undecane structural motif common to **1** and its oxygenated congeners has elicited considerable synthetic² and biosyn-

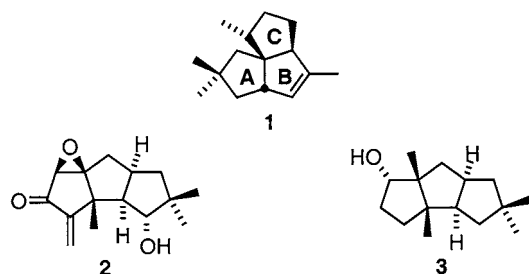
thetic interest.³ Since the first de novo approach to pentalenene reported by our group in 1982,⁴ almost 30 total^{5–19} and formal syntheses^{20–26} of **1** have been defined. Some of the more effective means for accessing this sesquiterpenoid

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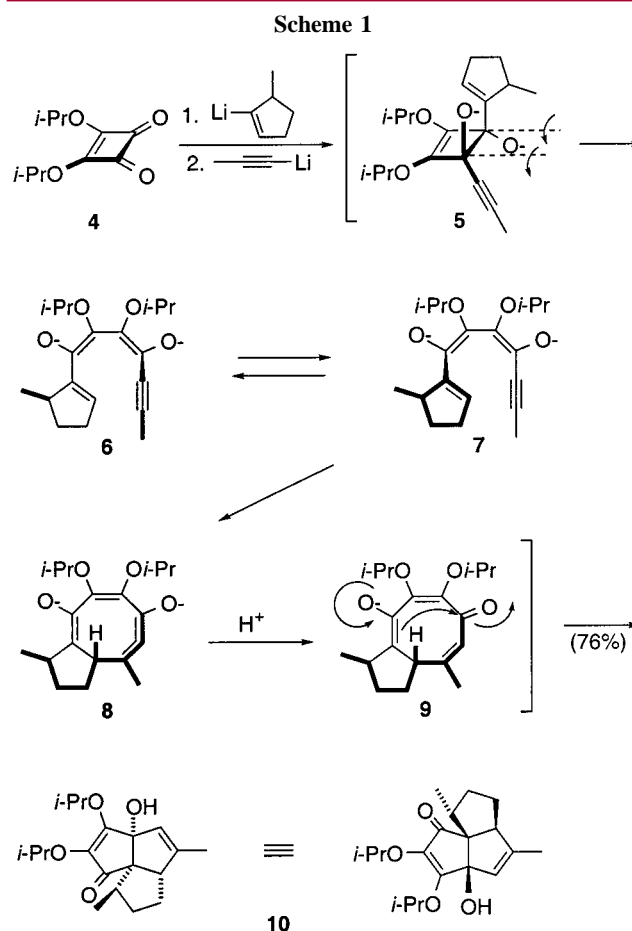
include thermal and photochemical cycloadditions,^{4,7,11,17} transannular cyclizations,^{5,8} tandem radical-mediated ring closures,^{18,19} metal-catalyzed transformations (Zr,²⁶ Co,¹² Fe,²² Ni²⁵), and the use of cyclopropane and cyclobutane intermediates.^{6,10,16}

In making use of the extensive bond reorganization that accompanies the so-called “squarate ester cascade”,²⁷ we previously found it possible to apply this deep-seated rearrangement to the expeditious synthesis of the naturally occurring linear triquinanes hypnophilin (**2**),^{28,29} coriolin,²⁹ and ceratopicanol (**3**).²⁹ Presently, we describe the first successful undertaking that transforms diisopropyl squarate (**4**)³⁰ in an equally convenient and concise manner into the alternative angularly fused architecture, as is present, for example, in **1**.



The pentalenene framework features a bridged spirane arrangement of three cyclopentane rings. To arrive at this carbocyclic skeleton from the direction of **4**, it becomes necessary to achieve regioselective protonation within a strained 1,2,4,6-cyclooctatetraene intermediate such as **8**. To this end, we found it productive to treat **4** first with 5-methylcyclopentenyllithium and then propynyllithium (Scheme 1). Under these circumstances, trans addition likely predominates to furnish **5** as the principal bis-adduct.³¹ The doubly charged nature of **5** and the strong donor character of the two oxido anions combine to promote outward conrotatory movement of the oxygen atoms during opening of the cyclobutene ring.³²

Equilibration between the two helical dienolates **6** and **7** so formed was anticipated to be facile.³³ Participation of the



constituent triple bond in the second (now 8π conrotatory) electrocyclization proceeds more slowly and delivers the strained intermediate **8**.³⁴ Beyond that, the presence of a methyl group on the cyclopentene subunit should sufficiently impede the rate of ring closure in **6** because of its placement on the interior of the coil in this case.³⁵ Comparable kinetic retardation should not accompany the conversion of **7** to **8**, thereby resulting in good overall stereochemical control at this stage. At the experimental level, **10** was isolated in 76% yield following acidification and transannular aldolization (see **9**). We note specifically that the stereoselectivity and steric constraints operational while proceeding from **6** to **10** result in the direct, one-pot assembly of a tricycloundecane product having rings B and C of the target pentalenene structure completely elaborated.

The chemical modification of ring A began by activation of the hydroxyl group in **10** as the acetate (Scheme 2). When

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(31) Diastereoselective cis addition would also give rise to **8** via dianionic oxy-Cope rearrangement.

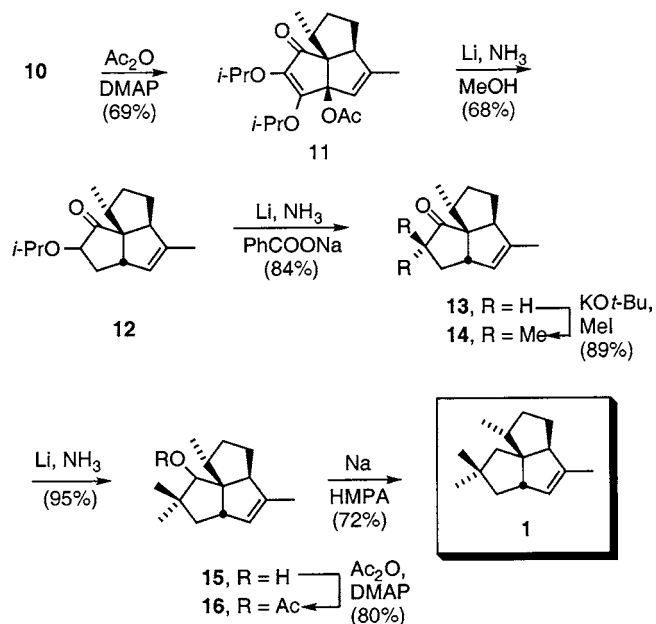
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(35) Carefully executed experiments and quantitation of chromatographic fractions following workup have shown **10** to dominate over its diastereomer (formed analogously from **6**) by a ratio of 8.8:1. Since racemic 5-methylcyclopentenyllithium was employed in this study and the other reagents are achiral, the enantiomeric representations of **6–10** are also involved.

Scheme 2



11 was reduced with approximately 50 mol equiv of lithium metal in liquid ammonia at -78°C and excess methanol was slowly added over 1 h, the transfer of six electrons was made possible and **12** was formed in 68% yield.³⁶ Although conditions for cleavage of the second isopropoxy substituent in this step were not found, the independent dissolving metal reduction of **12** did lead efficiently to ketone **13**. Sodium benzoate was invariably introduced prior to workup for the purpose of quenching the excess lithium reagent, thus

(36) Although a single isomer of **12** was produced in this manner, the relative orientation of its isopropoxy group was not definitively established, although it is expected that it is on the β -face.

guarding against possible overreduction. With rapid arrival at **13**, it was now possible to undertake the α,α -dimethylation of its enolate anion. This transformation was best achieved with potassium *tert*-butoxide and methyl iodide in that contamination involving the difficultly separable monomethyl derivative was not seen.

The doubly neopentyl nature of the carbonyl group in **14** brought an assortment of challenges to the fore. For example, no reaction was observed whenever nucleophilic attack at the sp^2 -hybridized carbon was a matter of consideration. Two such processes include attempted Wolff–Kishner and $\text{LiAlH}_4/\text{THF}$ reduction at elevated temperature. In contrast, dissolving metal reduction was well suited to the task, providing alcohol **15** in near-quantitative yield. Once its derived acetate **16** was reached, recourse to C–O bond cleavage with sodium metal in HMPA³⁷ gave pentalenene (**1**), which was spectroscopically identical to an authentic sample.³⁸

The use of the squarate ester cascade as a device for rapid assembly of a naturally occurring angular triquinane has thus been demonstrated. The hydrocarbon nature of the target also provided a forum for evaluating the power of dissolving metal reduction. Three distinctively different transformations involving Li/NH_3 can be identified at various stages of the synthesis, this routing making possible an economic eight-step sequence to arrive at **1** from **4**.

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Supporting Information Available: Experimental details and characterization data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(38) All compounds are considered to be of $>97\%$ purity on the basis of NMR and TLC analyses.