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

ORGANIC LETTERS 2002 Vol. 4, No. 25 4547-4549

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Received October 14, 2002

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-

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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

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



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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⁽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-methyl-cyclopentenyllithium was employed in this study and the other reagents are achiral, the enantiomeric representations of 6-10 are also involved.



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 neopentylic 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 sp²-hybridized carbon was a matter of consideration. Two such processes include attempted Wolff–Kishner and LiAlH₄/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/NH₃ can be identified at various stages of the synthesis, this routing making possible an economic eightstep sequence to arrive at **1** from **4**.

Acknowledgment. Financial support was provided by the National Science Foundation whom we thank.

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.

OL020208K

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