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Three-Component Coupling via the Squarate Ester Cascade as a Concise Route to the Bioactive Triquinane Sesquiterpene Hypnophilin

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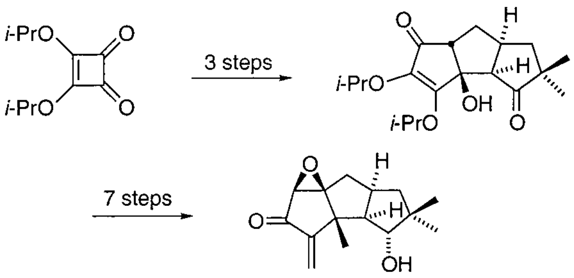
ABSTRACT



A squarate ester cascade is used to provide in one step, via the coupling of three reactants, a highly oxygenated linear triquinane product. The latter is transformed in nine steps into hypnophilin. The access route involves a combination of chlorination, reduction, dehydration, and oxidation maneuvers in the proper sequence.

In 1993, the discovery was made that 2-fold addition of alkenyl anions (either the same or different) to a squarate ester initiates a cascade of mechanistic events that eventuates in the formation of highly functionalized polyquinanes.[1] While cis addition triggers a sigmatropic rearrangement sequence dominated by a dianionic oxy-Cope rearrangement,[2,3] trans adducts undergo charge-driven bond reorganization via an electrocyclic reaction channel.[4] The stereochemical features of the structurally related end products, where distinctive, reveal their specific mode of generation.[5] In the intervening years, these unusual, deep-seated chemical transformations have been screened for their overall scope,[6] capacity to accommodate heteroatom incorporation,[7] and ability to respond to asymmetric induction.[8] Among the more notable findings to emerge from these studies are the remarkable capabilities of dienolates housed in 1,3,5,7-octatetraenyl networks to experience rapid helical equilibration[9] and regioselective cyclization.[2b,3] Herein we describe the first application of this chemistry to targeted natural products synthesis.

The challenge was to transform diisopropyl squarate (**1**)[10] into hypnophilin (**12**) in as few steps as possible. The isolation and characterization of this linearly fused triquinane

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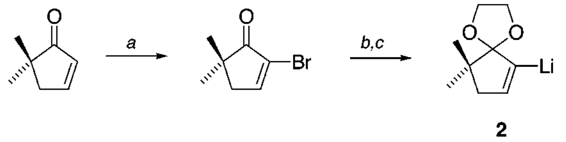
attracted early attention as a consequence of its reputed antibacterial and antitumor properties.[11] Three syntheses of **12** have since been disclosed from laboratories headed by Little,[12] Curran,[13] and Weinges.[14] Application of the 1,3-diyl trapping reaction and a tandem radical cyclization featured prominently in the first two routes. The third approach was enantioselective and consisted of a rather lengthy sequence involving suitable structural modification of commercially available catalpol.

The first step in the present undertaking was the sequential addition of the lithiated cyclopentenyl acetal **2** and vinyllithium to **1**. The organometallic nucleophile **2** was readily available by conventional bromination−dehydrobromination of 5,5-dimethyl-2-cyclopentenone[15] followed by acetalization and exposure to *tert*-butyllithium for the purpose of halogen−metal exchange (Scheme 1). The choice of **2** was predicated on our expectation that arrival at intermediate **D** would materialize from either of the originating diastereomeric bisadducts **A** or **B** (Scheme 2). The proper incorporation of an acetal as in **D**, previously shown to be capable of controlling the directionality of subsequent ring closures,[16] was expected to guarantee conversion to **E** as a prelude to transannular aldolization as in **F**. This species is recognized to be the dialkoxide of the cis, anti-fused tricycle **3**. At the experimental level, **3** can be isolated by flash chromatography on silica gel. Most often, however, rapid assembly of the linearly fused triquinane core in this fashion was directly followed by acidic hydrolysis of the enol ether functionality to give **4** in 24% overall yield (Scheme 3). Since seven distinctively unique chemical steps operate sequentially while progressing from **1** to **4**, the average yield for each step is 80%.

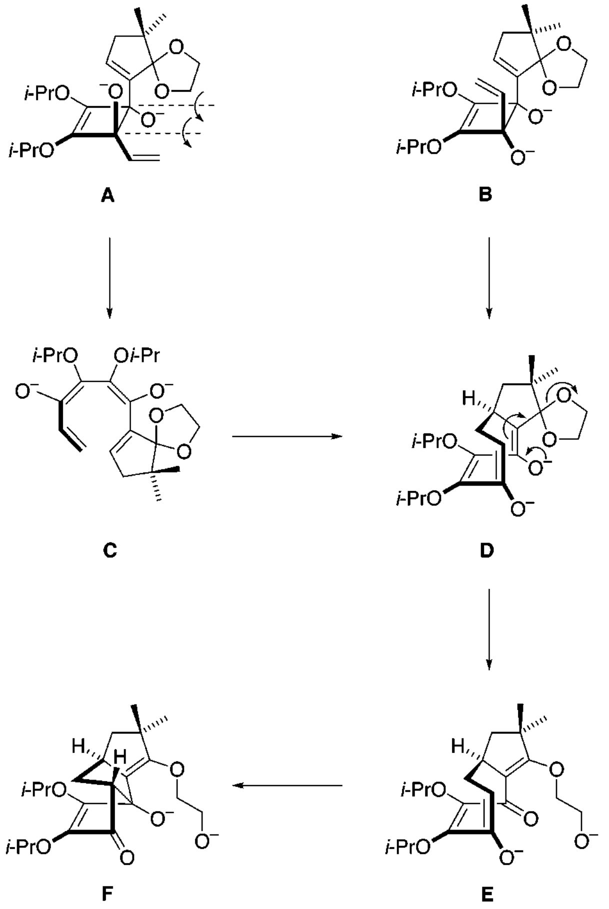
Scheme 1[a]



[a] (a) Br_2, CH_2Cl_2, 0 °C, 40 min; Et_3N, 20 °C, 3 h (77%). (b) Ethylene glycol, Dowex 50X4-400, C_6H_6, reflux 3 days (80% brsm). (c) *tert*-Butyllithium, THF, −78 °C (brsm = based on recovered starting material).

The hydroxyl group in **4** was next converted into the chloride functionality in **5** with retention of configuration by exposure to methanesulfonyl chloride and triethylamine in CH_2Cl_2 containing a small amount of DMAP.[17] Several attempts to replace the chlorine atom in **5** by the necessary angular methyl group failed. For example, the direct treatment of **5** with trimethylaluminum led to no reaction. Similarly, the prior dehydrochlorination of **5** did not provide a feasible forum for the subsequent conjugate addition of various methylcopper reagents.

Scheme 2



A convenient and efficient alternative to these protocols began in the form of an initial dissolving metal reduction with lithium in liquid ammonia. Concurrent dechlorination and reduction of the ketone carbonyl was seen without any deleterious consequences in the highly oxygenated A-ring. As in the case of **4**, NOESY studies were implemented for the purpose of establishing relative stereochemistry (see formulas). For **6**, the evidence was clear that the configuration of the hydroxyl group was that required of the target. Continued success was enjoyed with the lithium aluminum hydride reduction of **6**. Workup with dilute acid eventuated in dehydrative 1,3-carbonyl transposition and the formation of **7** (76%). Once protection of the hydroxyl substituent as its MOM ether had been achieved, it proved an easy matter to introduce the α-methyl group regiospecifically by conventional condensation of the enolate anion of **8** with methyl

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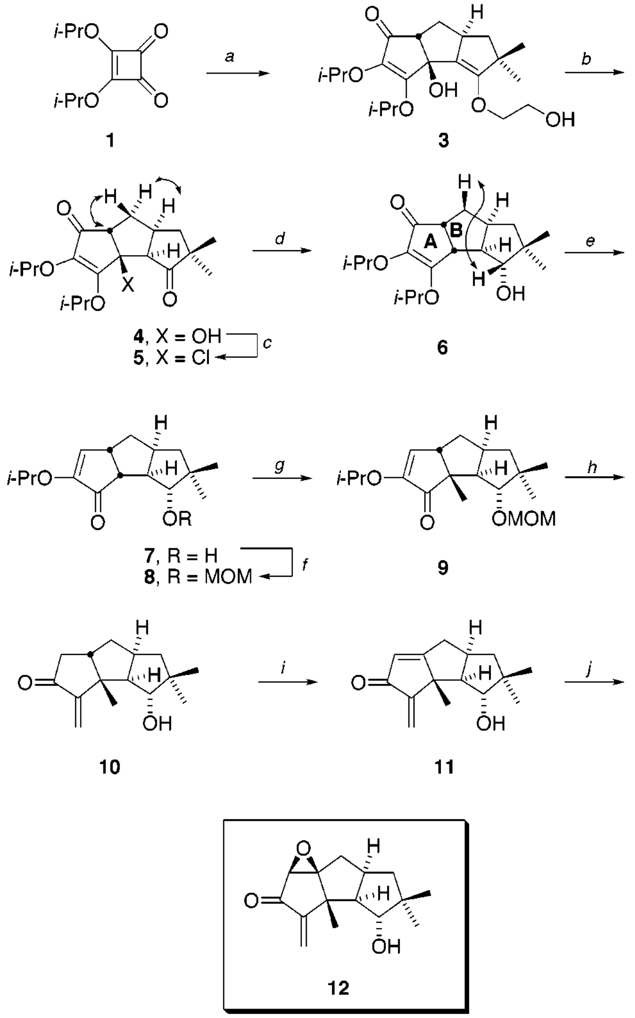
Scheme 3[a]



[a] (a) **2**, THF, −78 °C, 5 min; $CH_2{=}CHLi$; 0 °C, 2 h; rt, 16 h; degassed NH_4Cl solution; 36 h. (b) 10% H_2SO_4, overnight, rt (24% from **1**). (c) CH_3SO_2Cl, Et_3N, (DMAP), CH_2Cl_2, rt, overnight (72%). (d) Li, NH_3, THF, −78 °C, 1.5 h; Li benzoate, −78 °C (72%). (e) $LiAlH_4$, THF, −10 °C, 5 min; 1 N HCl (76%). (f) CH_3OCH_2Cl, (*i*-Pr)$_2$NEt, CH_2Cl_2, rt, overnight (quant). (g) LDA, HMPA, THF, CH_3I, rt, overnight (95%). (h) CH_3Li, ether, 0 °C, 2 h; 30% H_2SO_4, THF, reflux, 10 h (85%). (i) LDA, THF, DMPU; TMSCl; Pd(OAc)$_2$, CH_3CN, rt, overnight (60%). (j) K_2CO_3, 30% H_2O_2, H_2O, CH_2Cl_2, rt, 3 h (80% brsm) (brsm = based on recovered starting material).

iodide (95%). The critical retention of the cis ring juncture in **9** was adopted as a direct result of the usual kinetic and thermodynamic factors associated with bicyclo[3.3.0]octyl systems.[18]

The final carbon was introduced by addition of methyllithium to **9**. Subsequent treatment with 30% sulfuric acid in THF provided the ideal conditions for concurrent dehydration in the exocyclic direction, hydrolysis of the enol ether functionality, and deprotection of the MOM group. This tactic afforded **10** with an efficiency of 85% and set the stage for incorporation of a second double bond, now necessarily endocyclic. The introduction of this second site of unsaturation was accomplished by oxidation of the silyl enol ether of **10** with palladium acetate.[19] Reaction of **11** with hydrogen peroxide in the presence of potassium carbonate resulted in regioselective epoxidation to generate hypnophilin (**12**), the spectral properties of which were identical in all respects to those of the natural product (^{1}H and ^{13}C NMR, IR, MS).

In summary, the present investigation has demonstrated the feasibility of a direct 10-step route from a squarate ester to a representative functionalized triquinane natural product. This inaugural study is expected to chart possible directions for accessing other polyquinane molecules of interest. Progress toward this goal is currently underway.[20]

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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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(20) All compounds are considered to be of >97% purity based upon NMR and TLC analyses.