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Applications of the Squarate Ester Cascade to the Expeditious Synthesis of Hypnophilin, Coriolin, and Ceratopicanol

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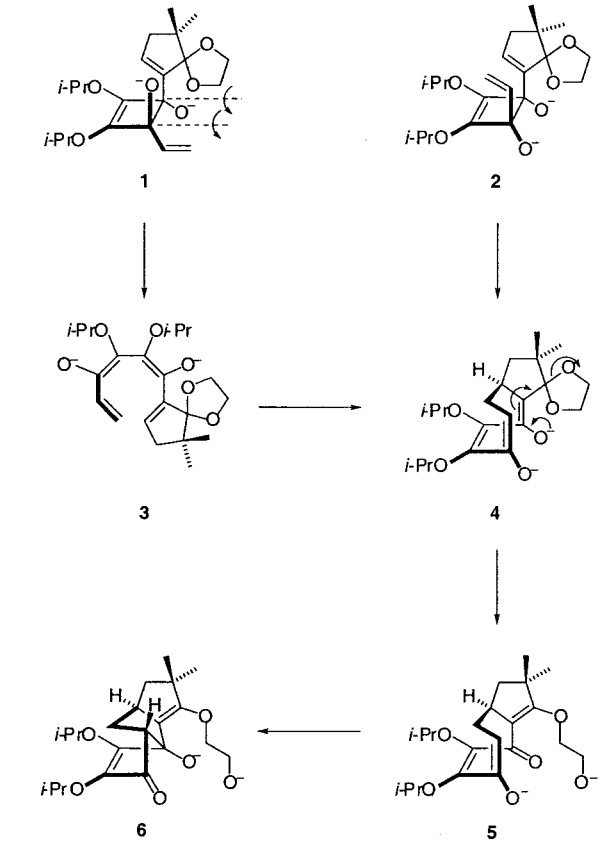
Abstract: The first applications of the squarate ester cascade to natural products synthesis have been realized. Only 10 laboratory steps mediate the conversion of diisopropyl squarate to (±)-hypnophilin (**8**). Key reactions include a combination of chlorination, reduction, dehydration, and oxidation maneuvers in the proper sequence. A penultimate precursor to **8** has previously been converted into coriolin (**9**), thereby allowing a formal synthesis of racemic **9** also to be claimed. A rather different strategy was employed to arrive at (±)-ceratopicanol (**10**). Of the seven steps involved, three consisted of the use of lithium in liquid ammonia. The three divergent synthetic objectives realized in these experiments involved (a) generation of an extended enolate anion and its regioselective *C*-methylation at the γ-carbon; (b) unprecedented reductive cleavage of a β-isopropoxy group in a 2,3-diisopropoxy-2-cyclopentenone setting; and (c) conventional conversion of an α-alkoxy ketone to the parent carbonyl system. Thus, the appreciable enhancement in structural complexity offered by the squarate cascade holds considerable potential for the concise synthesis of constitutionally intricate targets.

Cascade reaction sequences, those processes that take place via the sequential operation of several discrete chemical steps following initiation,[1] are inherently attractive for several reasons. For example, they often proceed with high levels of atom economy[2] and are generally accompanied by significant increases in structural complexity. Their practical importance is appreciably enhanced when the end product of the domino process[3] is amenable to synthetic modifications that deliver key target compounds in particularly concise fashion. A decade ago, the discovery was made in these laboratories that the sequential 1,2-addition of a pair of alkenyl anions (either the same or different) to a squarate ester sets into motion a sequence of mechanistic events exemplified in Scheme 1.[4] The second nucleophilic attack, which can proceed in an anti or syn manner to provide **1** and **2**, respectively, is subject to steric[5] or chelation control.[5,6] When **1** is formed, there follows a charge-driven

Scheme 1



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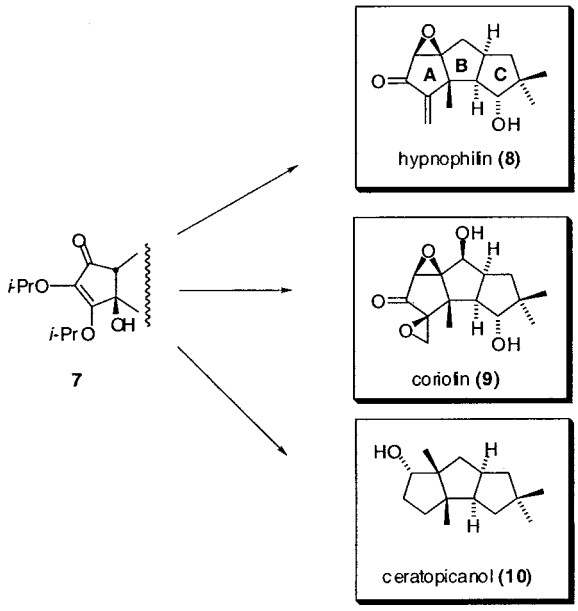
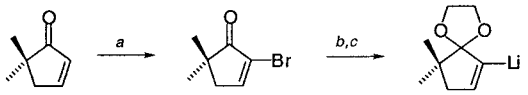
Scheme 2



conrotatory opening of the cyclobutene ring with generation of the coiled 1,3,5,7-octatetraene **3**. These intermediates are capable of rapid helical equilibration[6] and regioselective cyclization[4,5b] and have the ability to advance to product with asymmetric induction.[7] Arrival at **4** is realized somewhat more directly via a dianionic oxy-Cope rearrangement when cis addition as in **2** operates.[8] These mechanistic options can be distinguished when additional stereochemical markers are present.[9] The proper positioning of an acetal group as in **4** allows for the operation of an elimination reaction with the formation of **5**. This step guarantees that the subsequent transannular aldol ring closure is completely regiodirected and that a highly functionalized linear triquinane will be generated.[10]

In this report, we detail for the first time the manner in which select end products of these deep-seated cascade processes can be utilized for the expeditious synthesis of natural products.[11] These goals demand that the signature part structure **7**, invariably generated from diisopropyl squarate, be amenable to reductive, oxygenative, and alkylative modification (Scheme 2). Little information is currently available concerning the chemical alteration of this highly oxygenated cyclopentenone system.[12] Considerable progress has now been made to offset this deficiency. Thus, the sesquiterpene hypnophilin (**8**)[13,14] has been

Scheme 3



11

[a] Conditions: (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% br sm). (c) *tert*-Butyllithium, THF, −78 °C. (brsm = based on recovered starting material)

obtained via a 10-step sequence involving a combination of chlorination, reduction, dehydration, and oxidation maneuvers in the proper sequence. This degree of conciseness serves as the basis for a formal total synthesis of coriolin (**9**) as well.[15,16] An entirely different strategy has opened up a seven-step route to the fungal metabolite ceratopicanol (**10**).[17,18] The latter sequence is noteworthy in that three of the synthetic manipulations involve the use of lithium in liquid ammonia for accomplishing different synthetic objectives.

Results and Discussion

(±)-Hypnophilin and (±)-Coriolin. Central to the quest for hypnophilin (**8**) is the seminal recognition by Steglich and coworkers of its antitumor activity and ability to inhibit Gram-positive and Gram-negative bacteria as well as diverse fungi and yeasts.[13] In addition, this linearly fused triquinane embodies in its A ring an uncommon Michael acceptor arrangement that is presumably responsible for its biological activity. These considerations have prompted three successful syntheses of **8**. While the Little group made recourse to a 1,3-diyl trapping reaction as their key step,[14a] Curran deployed a tandem radical cyclization,[14b] and Weinges completed an enantioselective route by suitable structural modification of catalpol.[14c]

In 1969, the Umezawa group reported the isolation of coriolin (**9**) and defined its structure.[15] The more highly oxygenated perimeter of this tricyclopentanoid system and its reputed antitumor activity was sufficient cause for many investigators to undertake its total synthesis.[16] Since a key intermediate in the routes devised by the Danishefsky,[17] Ikegami,[18a] and Tatsuta groups[18b] intersects our own abbreviated scheme, the present undertaking also constitutes a stereocontrolled formal synthesis of coriolin (**9**).

Retrosynthetically, we envisioned the lithiated acetal **11** to be a properly delineated reactant. This building block was conveniently generated by bromination−dehydrobromination of the known 5,5-dimethyl-2-cyclopentenone,[19] standard acetalization, and halogen−metal exchange in the presence of *tert*-butyllithium, as outlined in Scheme 3.

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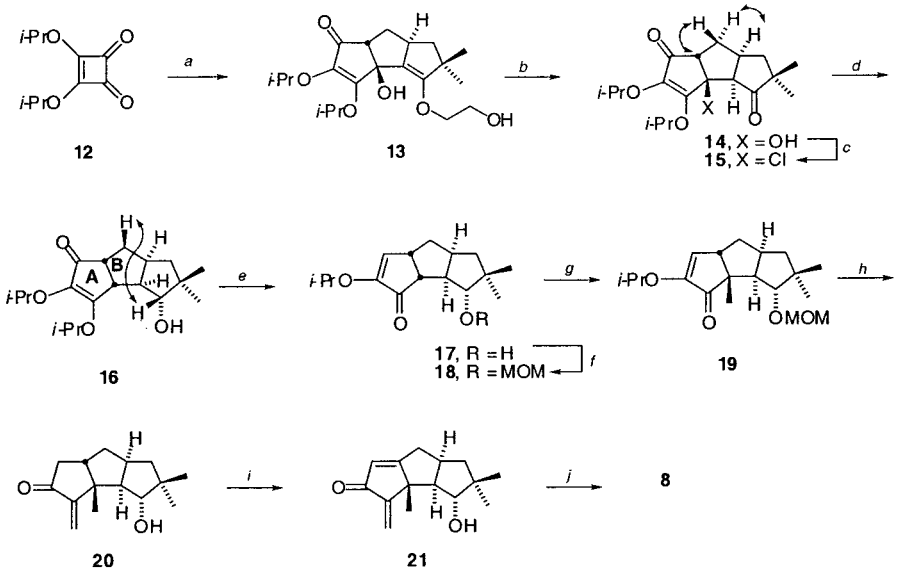
Scheme 4

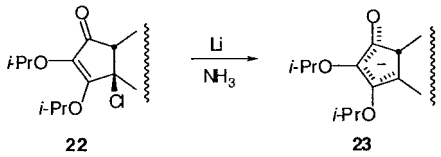


[a] Conditions: (a) **11**, THF, −78 °C, 5 min; CH_2=CHLi, 0 °C, 2 h; rt 16 h; degassed NH_4Cl solution; 36 h. (b) 10% H_2SO_4, overnight, rt (24% from **12**). (c) CH_3SO_2Cl, Et_3N, (DMAP), CH_2Cl_2, rt, overnight (72%). (d) Li, NH_3, THF, −78 °C, 1.5 h; Li benzoate, −78 °C (72%). (e) $LiAlH_4$, THF, −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) CH3Li, ether, 0 °C, 2 h; 30% H_2SO_4, THF, reflux 10 h (85%). (i) LDA, DMPU, THF; 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% br sm). (brsm = based on recovered starting material)

The addition of 2 equiv of **11** to diisopropyl squarate (**12**)[20] at −78 °C was followed by the introduction of excess vinyllithium (Scheme 4). Irrespective of the stereoselectivity adopted during the 1,2-addition of the second of these organometallic reagents, our expectation was that both pathways would eventuate in the formation of **4**. Spontaneous β-elimination within **4** to generate **5** is precedented in our earlier pilot studies[10] and was anticipated to advance via **5** into a fully regiocontrolled transannular aldol cyclization to give **6**. The cis, anti-fused tricycle **13**, which constitutes the doubly protonated form of **6**, was indeed isolated and purified chromatographically. However, convenience dictated that mild acid hydrolysis to deliver **14** be accomplished prior to workup. In this way, the diketone was isolated in 24% yield.

A comparable level of success was enjoyed during the subsequent conversion of **14** into chloride **15** (72%). Since the exposure to thionyl chloride and triethylamine proceeded with retention of configuration, an S_Ni process is likely operative.[12] Attempts to directly replace the Cl atom in **15** by a methyl group were next accorded attention, but to no avail. For example, no reaction was observed in the presence of trimethylaluminum under various conditions. In a similar vein, when the possible dehydrochlorination of **15** failed, the planned conjugate addition of several methylcopper reagents could not be evaluated.

These results led us to explore a more streamlined alternative protocol consisting of dissolving metal reduction with lithium liquid ammonia. Under these conditions, dechlorination *and* stereocontrolled reduction of the ring C ketone carbonyl occurred concurrently, without any deleterious consequences in the highly oxygenated A ring. The inertness exhibited by the latter subunit stems from transient conversion of the chlorinated enone typified by **22** into the extended enolate **23**. Although the direct methylation of **23** was entertained, *O*-alkylation of the saturated alkoxide was likely to be kinetically dominant, and this routing was therefore not pursued.



The cis, anti, cis intra-ring stereorelationship present in **15** and **16** was conveniently corroborated by NOESY studies, the implementation of which also confirmed the α-orientation of the hydroxyl group, as required of hypnophilin (see formulas).

Dehydrative 1,3-carbonyl transposition within **16** was now mandated, and success was realized by treatment with lithium aluminum hydride followed by workup with dilute aqueous acid. The choice of protecting group proved not to be crucial, and we therefore settled on generation of the MOM ether **18**. When methyl iodide was added to the lithium enolate of **18**, methylation was achieved with excellent regioselectivity (95% yield of **19**) and retention of the cis ring fusion (for the usual thermodynamic reasons).[21] At this juncture, treatment of **19** with methyllithium and subsequent heating with 30% sulfuric acid served to introduce the final carbon atom, effect dehydration, hydrolyze the enol ether, and bring about removal of the MOM group to furnish **20** (85%). This tactic set the stage for facile introduction of a second conjugated double bond, now necessarily endocyclic. This second site of unsaturation was generated by oxidation of the silyl enol ether of **20** with palladium acetate.[22] Arrival at hypnophilin (**8**) was now accomplished by

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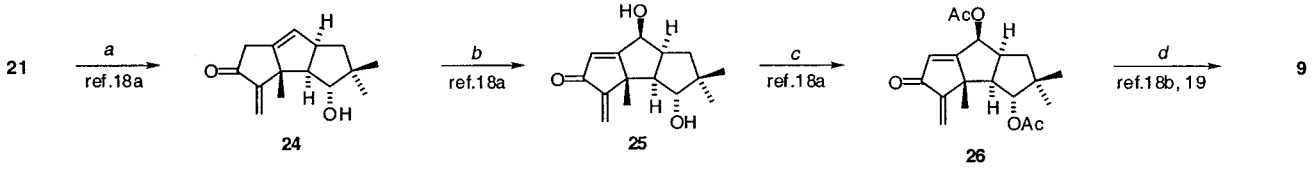
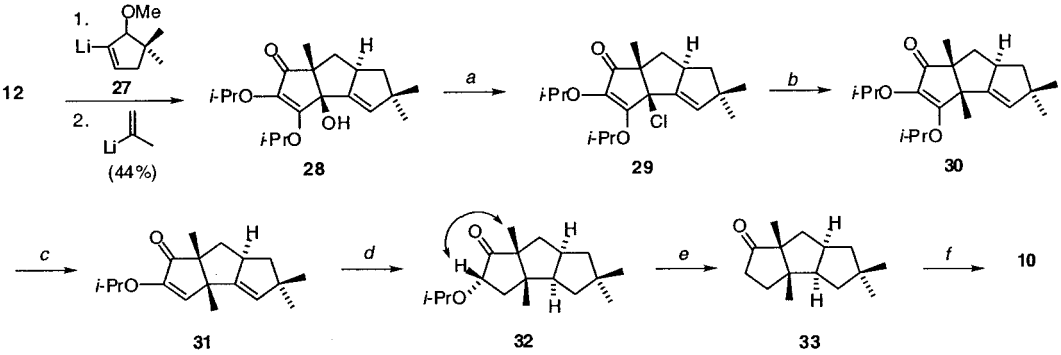
Scheme 5



[a] Conditions: (a) KO*t*-Bu, DME, −78 °C → rt; 10% aq HOAc. (b) MCPBA, CH_2Cl_2; DBU, C_6H_6 (48% from **21** brsm). (c) Ac_2O, DMAP, py (98%). (d) LiOH, THF; 30% H_2O_2 (12%).

Scheme 6



[a] Conditions: (a) CH_3SO_2Cl, DMAP, py (73%). (b) Li, NH_3; CH_3I, HMPA (74%). (c) Li, NH_3 (75%). (d) H_2, 5% Pd/C (91%). (e) Li, NH_3 (77%). (f) $NaBH_4$, MeOH (75%).

regioselective epoxidation through the agency of hydrogen peroxide and potassium carbonate. The spectral properties of synthetic **8** were identical in all respects to those of the natural product as supplied to us by Prof. D. Little and Dr. H. Schick.

As alluded to above, our abbreviated route to **21** also represents a formal total synthesis of (±)-coriolin (**9**) (Scheme 5). This key intermediate has previously been taken on to its β,γ-unsaturated isomer **24**, monoepoxidized, and subjected to β-elimination. For characterization purposes, Ikegami[18a] prepared the diacetate **26**, independent synthesis of which had been accomplished earlier by Tatsuta.[18b] The conversion of **26** into coriolin was then achieved conventionally.[18b,19]

(±)-Ceratopicanol. The discovery by Hanssen and Abraham of ceratopicanol (**10**) in agar cultures of the ascomycete *Ceratosystis piceae* proved noteworthy in that it constituted powerful indirect evidence for the biosynthetic origins of the entire class of those sesquiterpenoids associated with the humulene cascade.[23] This previous missing link features the five contiguous chiral centers, including two vicinal bridgehead quaternary carbons demanded of its origin from the protoilludyl cation. Three total syntheses of ceratopicanol have been reported.[24] These approaches have varied widely in their efficiency, the range of synthetic steps spanning from a low of 7 to a high of 21. In developing our own approach to **10**, we were intrigued by the likelihood of implementing a squarate-based strategy that would rival the shortest known route while developing new chemistry in support of this pathway. The details of this concise synthesis of ceratopicanol follow.

Arrival at the first tricyclic intermediate **28** was brought about by treating diisopropyl squarate (**12**) in turn with the cyclopentenyllithium **27** and 2-lithiopropene (Scheme 6). The first of these organometallics was available by alane reduction[25] of 2-bromo-5,5-dimethylcyclopentenone, subsequent *O*-methylation, and lithium−halogen exchange as before. The second nucleophile had its customary effect on heightening the overall yield of the cascade,[5b,8] in this case to the 44% level. The spontaneous loss of methanol that follows ring closure to the doubly enolic 1,3,5-cycloctatriene (see **4**) once again neatly sets a double bond into position. In this example, the unsaturated linkage is not additionally functionalized. The chloro ketone **29** was obtained using exactly the same chemistry as in the synthesis of **15**. Reduction of this compound with lithium in liquid ammonia afforded an extended enolate anion (see **23**) that underwent alkylation with methyl iodide only at the γ-position to furnish **30** (74% isolated). Despite our prior concerns over possible steric inhibition, this protocol proved to be an exceptionally direct means for introducing the second quaternary center.

When **30** was subjected to a second dissolving metal reduction, the result was efficient reductive cleavage of the β-isopropoxy substituent to give **31**. This transformation is recognized to diminish the level of oxygenation 50% of the way. To set the stage for removal of the second isopropoxy group, **31** was catalytically hydrogenated to furnish the tetrahydro derivative **32**, which proved well suited to a third reduction maneuver and generation of saturated ketone **33**. Borohydride reduction of **33** furnished racemic ceratopicanol (**10**), the ^1H and ^{13}C NMR spectra of which compared very well with the reported data.[23,24]

Summary

The demonstration that electrocyclic rearrangements of squarate ester derivatives are a valuable synthetic tool has been independently explored in extensive work carried out in the

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research groups headed by Liebeskind[26] and by Moore.[27] In the present variant, functionalized triquinane ring systems are generated from easily prepared starting materials in a single reaction, forming four new C−C bonds. Moreover, the cascade sequence furnishes the triquinane nucleus with sufficient functionality to allow for a myriad of further chemical transformations. The present study constitutes the first applications of this methodology to complex molecule synthesis. The squarate ester cascade is among those reactions that dramatically and efficiently change molecular topography. The efficient application of this reaction methodology to the total synthesis of hypnohilin and ceratopicanol as well as a formal synthesis of coriolin clearly demonstrates its potential for influencing a broad range of synthesis activities.

Acknowledgment. We gratefully acknowledge the generous financial support of the National Science Foundation, and thank Jian Liu for some early experiments.

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

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