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Competitive Stereochemical Control Operative during Conrotatory Electrocyclization of Helically Equilibrating Diquinanyl-Substituted 1,3,5,7-Octatetraenyl Bisenolates

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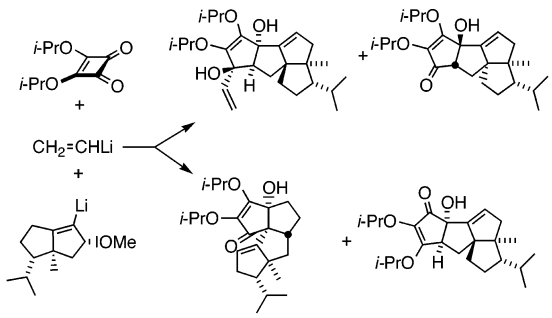

Activation of the squarate ester cascade by adding the lithiated bicyclo[3.3.0]octene **20** and vinyllithium sequentially to **1** results in the isolation of the four tetracyclic products **21**−**24**. The structures of the topographically complex products were deduced by 2D NMR spectroscopy and X-ray diffraction studies. The mechanistic insights gained by these findings are discussed. The product distribution is telltale evidence for predominant 1,2-addition of the second alkenyl anion. Product stereochemistry is in turn diagnostic of the preferred mode of conrotatory ring closure operating within equilibrating helical intermediates of opposite pitch. A competing pathway for the elimination of methanol in these highly functionalized intermediates has been observed for the first time.

Polyquinanes are widely recognized to be important structural components of numerous naturally occurring substances.[1] In addition, this compound class continues to serve as valued synthetic intermediates[2] and useful mechanistic probes.[3] As an extension of our early work directed toward definition of the scope of the squarate ester cascade,[4] we undertook a study designed to construct in record few steps a select group of sesquiterpenes.[5] Ironically, arrival at hypnophilin, coriolin, and ceratopicanol was achieved without the involvement of chiral building blocks. As a consequence, the factors controlling the operation of several competing steps in the overall series of transformations could not be determined. In the present paper, we describe our more recent observations involving the fate of conformationally equilibrating 1,3,5,7-octatetraenyl bisenolates with regard to their preferred mode of conrotatory cyclization and other chemical transformations. The existence of this class of elusive doubly charged helical intermediates came to light during several prior investigations.[6] Since then, their chemistry has been little studied. Presently, we have capitalized on the squarate ester cascade to access these topologically fascinating dianions.

Background

Treatment of diisopropyl squarate (**1**) with 1 equiv of an enantiopure cyclic alkenyllithium reactant such as **2**

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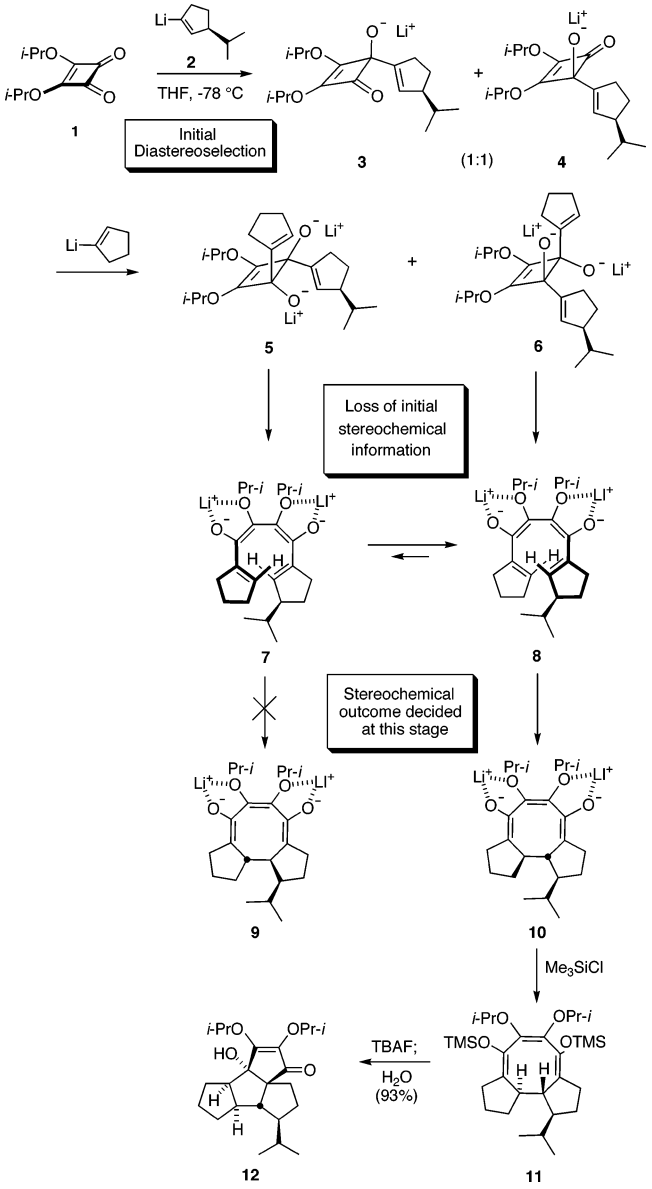
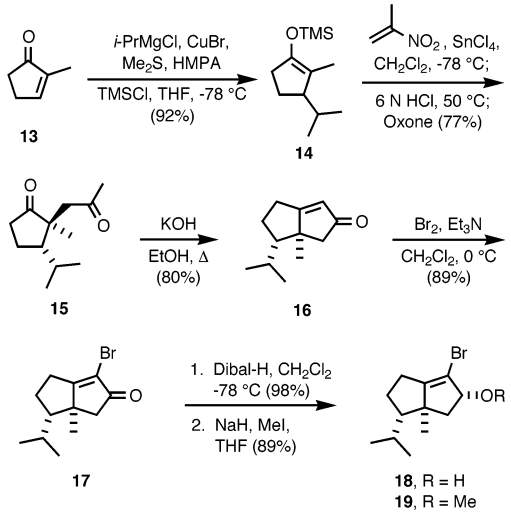
SCHEME 1



gives rise efficiently to a 1:1 mixture of diastereomers **3** and **4** (Scheme 1). The absence of definable diastereoselection at this stage was anticipated because the nucleophilic addition occurs at one of two adjacent carbonyl sites residing on a planar platform. This eventuality holds little synthetic advantage. However, subsequent exposure of the **3/4** mixture to cyclopentenyllithium and then to chlorotrimethylsilane furnished **11** as the only characterizable product in 64% yield. Because product stereochemistry is not decided in step 1, the conrotatory ring opening of **5** and **6** must be a prelude to the generation of **7** and **8**, which are able to interconvert at low temperature. Beyond this, the isopropyl substituent present in **2** must control the absolute stereogenecity of the two newly formed chiral centers in **11**. This end result is achieved because the presence of the isopropyl group on the interior of helix **7** sufficiently impedes the rate of ring closure to **9** that the **7** → **8** → **10** →**11** reaction channel dominates kinetically. Upon hydrolysis, **11** is transformed in high yield into **12**, presumably as the result of more rapid protonation at the less sterically hindered carbanion center in the dienolate intermediate. The prospects of adopting one-pot conversions of the **1** → **12** type in synthesis are consequently quite promising, in contrast to the earlier supposition.

SCHEME 2



Results

In line with the mechanistic principles delineated above, recourse to a more sterically bulky diquinane nucleophile came to be regarded as a potentially useful diagnostic for several reasons. Its deployment in place of **2** could induce operation of enhanced levels of 1,4-addition of the second nucleophile. The latter mode of attack has occasionally been observed,[7] but its serviceability has not been pursued. Furthermore, rather unique modes of ring fusion to the bicyclo[3.3.0]octane building block could ultimately come into play. We know of no examples where competitive generation of isomeric templates of this type has been examined. Added motivation for the pursuit of this line of investigation came from its latent potential for the expedient construction of naturally occurring tetraquinane diterpenes such as the crinipellins.

The requisite alkenyl bromide was obtained from 2-methylcyclopentenone, which was prepared from the inexpensive saturated ketone by reaction with sulfuryl chloride in carbon tetrachloride.[8] Conjugate addition of diisopropylcuprate to **13** followed by direct reaction with chlorotrimethylsilane provided the enol ether **14**[9] (Scheme 2). The Michael addition of **14** to 2-nitropropene[10] was followed by hydrolysis of the resulting intermediate in 6 N HCl and treatment with Oxone.[11] This last maneuver converted the byproduct oxime into the ketone and made possible the isolation of **15** in 77% yield. The subsequent

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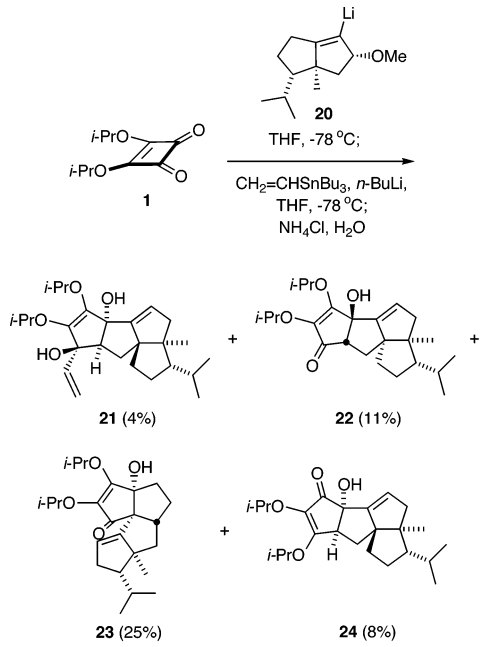
SCHEME 3



cyclization of **15** with KOH in 95% ethanol generated **16** and set the stage for conventional α-bromination. Reduction of **17** with diisobutylaluminum hydride provided only the α-alcohol, *O*-methylation of which generated **19**. The role of the methoxyl substituent was to serve as a leaving group and thereby direct in irreversible fashion the course of the post-equilibration transannular aldol reactions.[12] The proper positioning of an alkoxy group relative to a developing enolate anion is known to be particularly useful for controlling whether a linear or angular polyquinane end product is formed.[13]

In a key experiment, 1 equiv of the lithium reagent **20**, prepared by subjecting **19** to halogen−metal exchange, was added to **1** at −78 °C. Simultaneously, an excess of vinyllithium was generated by transmetalation of tributylvinylstannane[14] and subsequently transferred via cannula to the cold reaction mixture after 30 min. These conditions led to the isolation of four chromatographically separable products ultimately identified as **21** (4%), **22** (11%), **23** (25%), and **24** (8%) (Scheme 3). NOESY experiments were initially instrumental in defining the global three-dimensional structural features and stereochemistry of tetraquinanes **22**−**24**. As demonstrated in Figure 1, **22** exhibits three significant nOe interactions involving H-2*β* with H-3, H-2α with H-14*β*, and H-2α with H-13*β* (see A). In the case of **23**, an equal number of diagnostic nOe interactions reveal the close proximity of H-6*β* to H-8, H-7α to H-9α, and H-22 to the methyl group at C-18 (see B). For **24**, the key signals are associated with H-2α/H-3 and correlations of the methyl group at C-18 with H-2α and H-10α (see C).

Further corroboration of these structural assignments was gained through chemical transformations and crystallographic analysis. Thus, treatment of **24** with *p*-

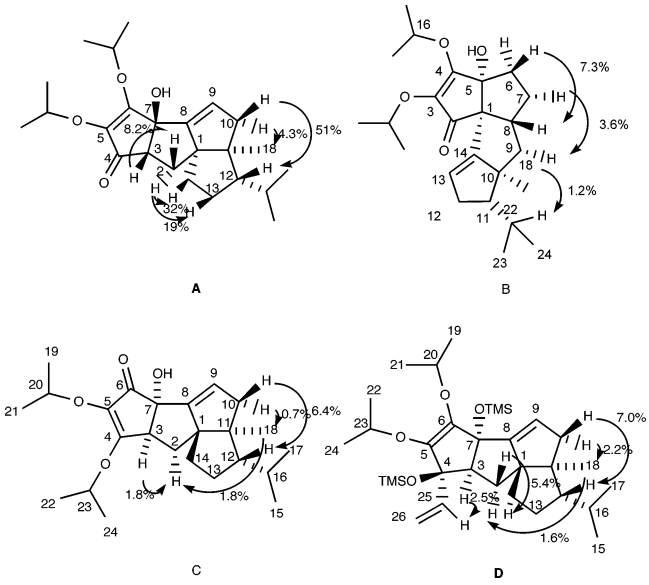
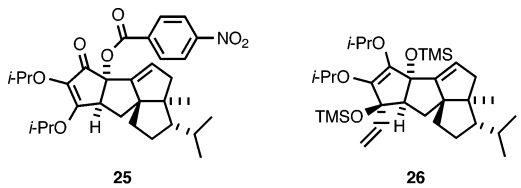


FIGURE 1. nOe data for **22**−**24**.

nitrobenzoyl chloride afforded ester **25** as pale yellow crystals from ether-dichloromethane that were well suited to X-ray diffraction. The relative stereochemistry of α-ketol **24** has been unequivocally defined by crystallographic means.



In light of the fact that **21** was co-polar with some unknown impurities, it could not easily be obtained in a pure state. To remedy this situation, crude **21** was converted to **26** (58%) by reaction with chlorotrimethylsilane and hexamethyldisilazane in pyridine.[15] Chromatography and subsequent desilylation afforded pure **21**, which proved to be highly unstable in $CDCl_3$ solution. Like its tetracyclic counterparts, the silylated ether **26** was characterized by three telltale nOe interactions. These are defined in (D) (Figure 1).

Because major product **23** could not be induced to provide high-quality crystals by recrystallization from a wide selection of solvent systems, it was chemically modified by a three-step sequence that involved stepwise *O*-silylation with *tert*-butyldimethylsilyl triflate, allylic oxidation with the chromium oxide-3,5-dimethylpyrazole complex,[16] and exposure to tetrabutylammonium fluoride (Scheme 4). Recrystallization of **29** from isopropyl alcohol afforded white crystals suitable for crystallographic analysis. These results show that **23** is a regioisomer and not a stereoisomer of **24**, its structural framework differing distinctively from that present in all three other accompanying tetracyclic products.

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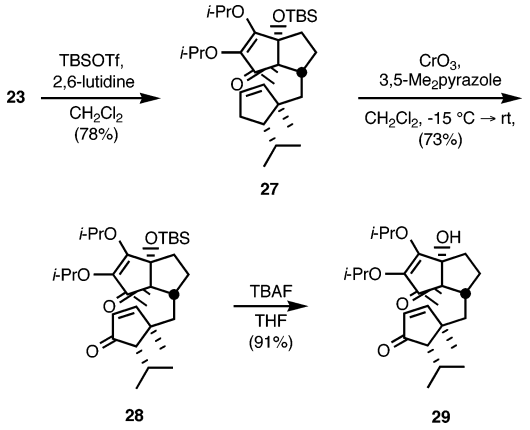
SCHEME 4

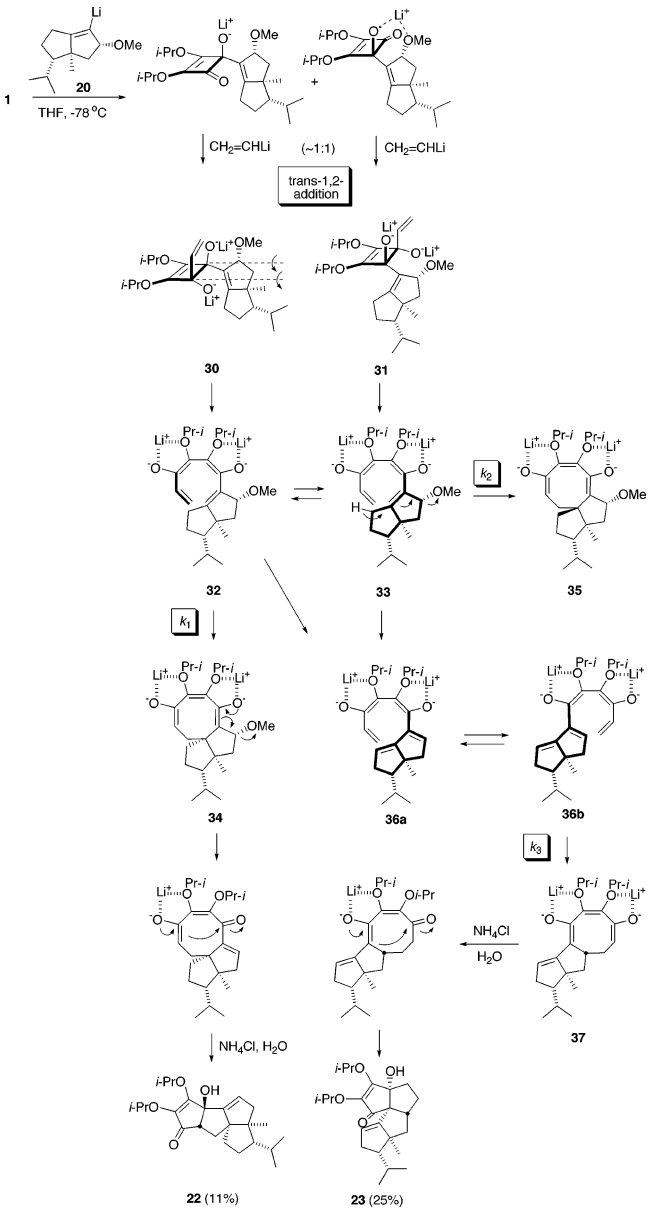


Discussion

The customarily dominant reaction pathway begins with trans 1,2-addition of the two alkenyllithium reagents to the squarate ester. When such an event materializes in the present setting, approximately equal amounts of diastereomers **30** and **31** are expected to be generated (Scheme 5). The lack of diastereoselectivity holds importance, as the subsequent conrotatory ring opening within **30** and **31** can only deliver 1,3,5,7-octatetraenyl bisenolates **32** and **33** in the same relative proportion. If helical equilibration between this pair of conformers is amenable to operation on a rapid time scale as observed for **7** and **8**, then subsequent slower advance to **34** and **35** will be dependent on the relative magnitudes of k_1 and k_2. These steps transform in irreversible fashion the differing angles of pitch resident in **32** and **33** into an additional stereocenter. For **34** and **35**, the stereogenicity distinction involves a quaternary carbon. The eight-membered ring is fused to a *trans*-bicyclo[3.3.0]-octene in **34**. The alternative cis configuration is present in **35**. Subsequent β-elimination and transannular aldolization within **34** eventually results in the establishment of two additional chiral centers in the product **22**. Because no companion tetracyclic isomer derivable in like fashion from **35** was isolated, it is reasonable to conclude that the alternative elimination of methanol leading to **36** is kinetically preferred.[17] The pentaenyl intermediate **36**, which is in principle also accessible from **32**, evidently prefers to undergo ring closure via conformer **36b** to generate **37** and ultimately **23**. No prior example of a change such as this in the timing of the alkoxide elimination step has previously been observed.

If the initial stage of the squarate cascade involves a 1,4-addition, the series of steps that is thereby triggered eventuates in the formation of an α-ketol polycyclic product. This signature structural feature materializes as a result of the comparable operation of ensuing steps as outlined in Scheme 6. Under these circumstances, the formation of near equal amounts of **38** and **39** will be followed by conversion to the advanced octatetraenyl intermediates **40** and **41**. This eventuality, when coupled with the potential for facile helical equilibration, causes k_4 and k_5 to be the controlling factors for product

SCHEME 5

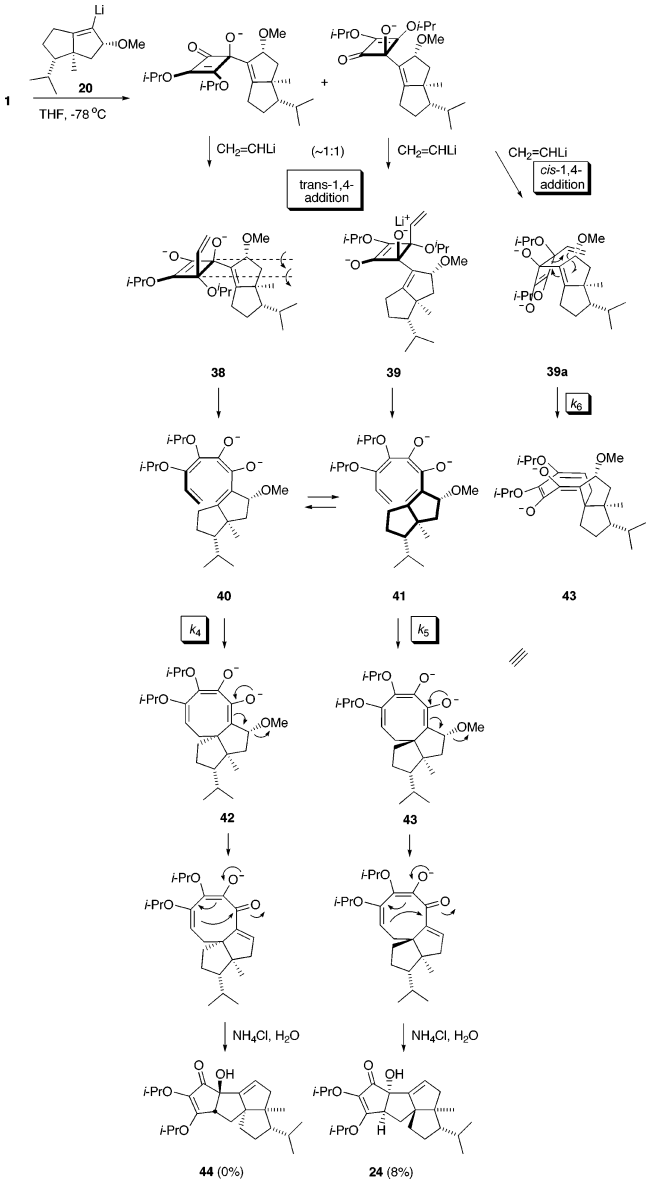


distribution. Because **44** was not formed, the pathway involving the generation of a trans-fused bicyclo[3.3.0]-octene would appear to dominate matters substantially and perhaps exclusively. We note that the alternative possibility exists that neither k_4 nor k_5 are competitive and that **24** originates instead via a routing involving a second-stage cis 1,4-addition. The transient formation of **39a** in this manner opens the door for the subsequent operation of an anionic oxy-Cope process via the boatlike structure **39a**. The rate of this [3.3] sigmatropic rearrangement (k_6, Scheme 6) could plausibly be the most accelerated of the entire subset.

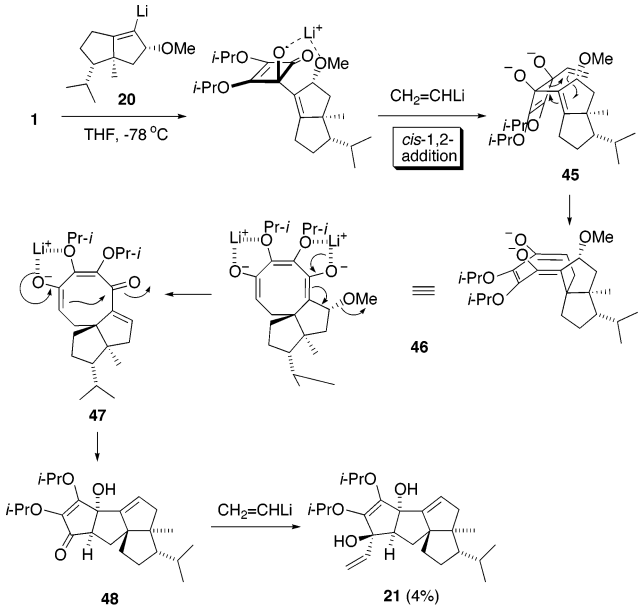
The conversion of **48** to **21** is an obvious artifact, being the result of a side reaction in which the excess vinyllithium is consumed (Scheme 7). The structural features resident in **48** are the consequence of an initial cis 1,2-addition to generate **45**, whose dianionic oxy-Cope rearrangement leads via **46** to **47** and ultimately the tetraquinane ketone **48**.

(17) It is possible that the loss of methanol in this fashion operates at one or more steps prior to this conrotatory cyclization. This distinction forms the subject of continuing investigation.

SCHEME 6



SCHEME 7



Summary

Sequential addition of the lithiated bicyclo[3.3.0]octene **20** and vinyllithium to diisopropyl squarate (**1**) provides an unrivaled opportunity for delineating select mechanistic aspects of the ensuing reaction cascade. On the basis of the product distribution, the conclusion can be reached that 1,2-addition of the second nucleophile operates more readily than 1,4-addition by a factor in excess of 5:1. Additionally, the telltale stereochemical features provide sufficient information to deduce that the conrotatory electrocyclization of **32** occurs more rapidly than that involving the helical conformer of opposite pitch, viz., **33**. This kinetic preference is seemingly controlled by the proximal isopropyl substituent, with covalent carbon−carbon bond formation materializing preferably on the face of the pπ-terminus opposite to that on which this alkyl group resides. This steric bias eventuates in the predominant generation of tetracyclic system characterized by a trans-fused diquinane subunit as seen in the predominant product **22**. The tandem occurrence of cis 1,4-addition and [3.3] sigmatropic change is limited in its operation, again a likely consequence of nonbonded steric compression. Once again, the squarate ester cascade is shown to be among those reactions that are capable of bringing about dramatic changes in molecular topography in a single laboratory operation. The discovery of yet another pathway involving the ejection of methanol (as lithium methoxide) in advance of conrotatory octatetraene electrocyclization as operative in the formation of **23** further expands the synthetic utility of this remarkable multistep process.

Experimental Section

(2*S,3*S**)-3-Isopropyl-2-methyl-2-(2-oxopropyl)cyclopentanone (15).** To a solution of 2-nitropropene (9.22 g, 105.9 mmol) in CH_2Cl_2 (200 mL) was added dropwise tin tetrachloride (74 mL, 1 M in CH_2Cl_2, 74 mmol) at −78 °C during 15 min. A solution of **14**[18] (15.0 g, 70.6 mmol) in CH_2Cl_2 (150 mL) was introduced via cannula over 30 min, and the mixture was stirred at −78 °C for 3 h, treated with 10% HCl (100 mL), heated to reflux overnight, cooled to rt, and carefully treated with Oxone (86.8 g, 141.2 mmol) during 1 h. The resultant mixture was heated to reflux for 3 h, cooled to rt, and extracted with Et_2O. The organic phase was washed with water, saturated $NaHCO_3$ solution, and brine, dried, and evaporated. The residue was purified by flash chromatography on silica gel (elution with ether−petroleum ether 1:4) to afford **15** (10.6 g, 77%) as a colorless oil; IR (neat, cm^{-1}) 1738, 1713; ^1H NMR (300 MHz, $CDCl_3$) δ 2.93 (d, J = 18.7 Hz, 1H), 2.86 (d, J = 18.7 Hz, 1H), 2.52 (ddd, J = 18.7, 12.5, 9.4 Hz, 1H), 2.28 (dd, J = 18.7, 8.4 Hz, 1H), 2.12 (ddd, J = 9.4, 6.4, 1.0 Hz, 1H), 2.03 (s, 3H), 1.93 (ddd, J = 17.8, 9.8, 6.4 Hz, 1H), 1.62−1.49 (m, 1H), 1.36 (ddd, J = 24.4, 12.5, 8.4 Hz, 1H), 0.92 (t, J = 6.4 Hz, 6H), 0.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 223.5 (s), 206.6 (s), 51.8 (t), 49.0 (s), 48.5 (d), 36.6 (t), 30.2 (q), 29.6 (d), 24.9 (t), 22.5 (q), 21.8 (q), 17.4 (q); HRMS (EI) *m/z* (M^+) calcd for $C_{12}H_{20}O_2$ 196.1463, obsd 196.1492.

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(3a*S,4*S**)-3a,4,5,6-Tetrahydro-4-isopropyl-3a-methylpentalen-2(1*H*)-one (16).** To a refluxing solution of potassium hydroxide (13.7 g, 244 mmol) in 95% ethanol (600 mL) was added a solution of **15** (16.0 g, 81.5 mmol) in the same medium (200 mL) via cannula during 1 h. After an additional 2 h of heating, the mixture was cooled to rt, treated with 5% HCl (143 mL), and extracted with ether−CH_2Cl_2 (2:1). The organic phase was washed with saturated $NaHCO_3$ solution, water, and brine, dried, and evaporated. The residue was purified by flash chromatography on silica gel (elution with ether−petroleum ether 1:4) to afford **16** (11.66 g, 80%) as a colorless oil; IR (neat, cm^{-1}) 1709, 1629; ^1H NMR (300 MHz, $CDCl_3$) δ 5.70 (t, J = 1.1 Hz, 1H), 2.70−2.46 (m, 2H), 2.28 (s, 2H), 2.15−2.04 (m, 1H), 1.78−1.63 (m, 1H), 1.57−1.48 (m, 1H), 1.21 (dt, J = 10.7, 8.0 Hz, 1H), 0.99 (s, 3H), 0.89 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 210.7 (s), 195.9 (s), 123.0 (d), 54.7 (d), 52.5 (t), 51.9 (s), 30.2 (d), 29.5 (t), 24.8 (t), 21.7 (q), 21.6 (q), 19.6 (q); HRMS (EI) *m/z* (M^+) calcd for $C_{12}H_{18}O$ 178.1358, obsd 178.1352.

(3a*S,4*S**)-1-Bromo-3a,4,5,6-tetrahydro-4-isopropyl-3a-methylpentalen-2(1*H*)-one (17).** A solution of **16** (7.73 g, 43.4 mmol) in CH_2Cl_2 (300 mL) was treated with bromine (2.22 mL, 43.4 mmol) in CH_2Cl_2 (130 mL) via cannula over 30 min at 0 °C. The mixture was stirred at 0 °C for 30 min, triethylamine (9.06 mL, 65 mmol) in CH_2Cl_2 (100 mL) was added dropwise in the cold, and stirring was maintained at 0 °C for 2 h prior to dilution with H_2O and extraction with ethyl acetate. The organic phase was washed with saturated $NaHCO_3$ solution and brine, dried, and evaporated. The residue was purified by flash chromatography on silica gel (elution with hexanes−ethyl acetate 10:1) to give **17** (9.83 g, 89%) as a pale yellow solid, mp 88−89 °C; IR (neat, cm^{-1}) 1723, 1642; ^1H NMR (300 MHz, $CDCl_3$) δ 2.48−2.25 (m, 2H), 2.23 (d, J = 7.5 Hz, 1H), 2.16 (d, J = 7.5 MH, 1H), 1.99−1.88 (m, 1H), 1.65−1.50 (m, 1H), 1.43−1.32 (m, 1H), 1.08 (dt, J = 10.5, 8.0 Hz, 1H), 0.84 (s, 3H), 0.69 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 201.2 (s), 190.7 (s), 115.4 (s), 54.8 (d), 51.4 (s), 50.6 (t), 30.1 (d), 28.8 (t), 25.2 (t), 21.6 (q), 21.5 (q), 19.6 (q); HRMS (EI) *m/z* (M^+) calcd for $C_{12}H_{17}BrO$ 256.0462, obsd 256.0456.

(2*R,3a*S**,4*S**)-1-Bromo-2,3,3a,4,5,6-hexahydro-4-isopropyl-3a-methylpentalen-2-ol (18).** To a solution of **17** (8.33 g, 32.4 mmol) in CH_2Cl_2 (325 mL) was added a solution of Dibal-H (1.0 M in hexane, 48.6 mL, 48.6 mmol) under N_2 at −78 °C. The mixture was stirred at −78 °C for 1 h, quenched with 10% sodium potassium tartarate solution (150 mL), stirred until the two phases were clear, and extracted with ethyl acetate. The combined organic phases were washed with H_2O and brine, dried, and evaporated, and the residue was purified by flash chromatography on silica gel (elution with hexanes−ethyl acetate, 12:1) to afford **18** (8.24 g, 98%) as a white solid, mp 61.5−62 °C; IR (neat, cm^{-1}) 3334, 1682; ^1H NMR (300 MHz, $CDCl_3$) δ 5.07−5.01 (m, 1H), 2.39 (dd, J = 12.6, 6.4 Hz, 1H), 2.20−2.03 (m, 4H), 1.68 (dd, J = 12.6, 7.4 Hz, 1H), 1.69−1.56 (m, 1H), 1.49−1.40 (m, 1H), 1.25 (dt, J = 10.8, 7.0 Hz, 1H), 0.94 (s, 3H), 0.87 (d, J = 6.3 Hz, 3H), 0.85 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 157.3 (s), 113.6 (s), 81.3 (d), 57.2 (d), 54.6 (s), 50.4 (t), 30.1 (t), 29.9 (d), 22.3 (t), 21.8 (q), 21.5 (q), 18.3 (q); HRMS (EI) *m/z* (M^+) calcd for $C_{12}H_{19}BrO$ 258.0619, obsd 258.0622.

(1*S,5*R**,6a*S**)-4-Bromo-1,2,3,5,6,6a-hexahydro-1-isopropyl-5-methoxy-6a-methylpentalene (19).** A slurry of sodium hydride (60% suspension in mineral oil, 2.85 g, 71.2 mmol) in THF (300 mL) was cooled to 0 °C, and a solution of **18** (14.2 g, 54.8 mmol) in THF (200 mL) was added dropwise via cannula over 15 min. Stirring at 0 °C was continued for 30 min followed by cannulation of a solution of methyl iodide (8.87 mL, 142.5 mmol) in THF (60 mL). The reaction mixture was stirred at 0 °C for 1 h and at rt for 2 h, quenched with methanol (30 mL) and saturated NH_4Cl solution (30 mL), and extracted with ethyl acetate. The combined extracts were washed with brine, dried, and evaporated. The residue was purified by flash chromatography on silica gel (elution with hexanes−ethyl acetate 30:1) to afford **19** (13.31 g, 89%) as a colorless oil; IR (neat, cm^{-1}) 1725; ^1H NMR (300 MHz, $CDCl_3$) δ 4.73−4.68 (m, 1H), 3.38 (s, 3H), 2.29 (dd, J = 12.4, 6.2 Hz, 1H), 2.21−2.02 (m, 3H), 1.70 (dd, J = 12.4, 7.3 Hz, 1H), 1.65−1.57 (m, 1H), 1.50−1.42 (m, 1H), 1.28−1.18 (m, 1H), 0.92 (s, 3H), 0.86 (t, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 158.4 (s), 111.1 (s), 90.0 (d), 57.2 (d), 56.4 (q), 54.6 (s), 47.6 (t), 30.20 (t), 30.17 (d), 22.4 (t), 21.9 (q), 21.7 (q), 18.6 (q); HRMS (EI) *m/ z* (M^+) calcd for $C_{13}H_{21}BrO$ 272.0775, obsd 272.0768.

Tetraquinane Generation via the Squarate Ester Cascade. A solution of bromide **19** (7.29 g, 26.7 mmol) in 210 mL of dry THF was treated with *tert*-butyllithium (34.55 mL, 1.7 M in pentane, 58.71 mmol) and stirred at −78 °C under N_2 for 30 min. A precooled (−78 °C) solution of diisopropyl squarate (4.41 g, 22.23 mmol) in THF (120 mL) was added via cannula in one portion, and stirring was maintained at −78 °C for 30 min. At the same time, vinyltributylstannane (22.6 g, 71.16 mmol) was dissolved in THF (150 mL) and treated with *n*-butyllithium (41.9 mL, 1.6 M in hexane, 66.6 mmol) at −78 °C under N_2. The vinyllithium solution was stirred at −78 °C for 30 min and cannulated into the reaction mixture, which was stirred at −78 °C for 6 h, at 0 °C for 3 h, and at rt for 16 h prior to cooling to 0 °C and dilution with deoxygenated NH_4Cl solution (160 mL). After additional stirring at rt for 48 h and extraction with ethyl acetate, the combined organic phases were washed with H_2O and brine, dried, and evaporated. The residue was purified by flash chromatography on silica gel (elution with hexanes−ethyl acetate 10:1 to 4:1) to afford **23** (2.147 g, 25%), **21** (352 mg, 4%), **24** (654 mg, 8%), and **22** (984 mg, 11%).

For **21**: IR (neat, cm^{-1}) 3456, 1687, 1633, 1610; ^1H NMR (300 MHz, $CDCl_3$) δ 6.02 (dd, J = 17.2, 10.4 Hz, 1H), 5.33 (dd, J = 2.9, 1.8 Hz, 1H), 5.26 (dd, J = 17.2, 1.2 Hz, 1H), 5.03 (dd, J = 10.4, 1.2 Hz, 1H), 4.85 (heptet, J = 6.1 Hz, 1H), 4.74 (heptet, J = 6.1 Hz, 1H), 2.63 (dd, J = 17.0, 1.8 Hz, 1H), 2.41 (dd, J = 7.6, 6.3 Hz, 1H), 2.23 (dd, J = 17.0, 2.9 Hz, 1H), 2.15 (s, 1H, OH), 1.94−1.87 (m, 2H), 1.77 (dd, J = 7.6, 1.2 Hz, 1H), 1.74−1.66 (m, 1H), 1.59−1.51 (m, 2H), 1.35−1.11 (m, 3H), 1.24 (d, J = 6.1 Hz, 3H), 1.22 (d, J = 6.1 Hz, 3H), 1.21 (d, J = 6.1 Hz, 3H), 1.19 (d, J = 6.1 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.90 (s, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 157.3 (s), 145.9 (d), 138.9 (s), 132.8 (s), 117.2 (d), 111.1 (t), 84.2 (s), 77.5 (s), 71.6 (d), 71.3 (d), 67.9 (s), 59.7 (d), 59.5 (d), 54.0 (t), 53.8 (s), 40.1 (t), 30.3 (t), 30.0 (t), 28.5 (d), 25.3 (q), 23.2 (q), 23.1 (q), 22.8 (q), 22.7 (q), 22.0 (q), 20.0 (q); HRMS (ES) *m/z* ($M + Na)^+$ calcd for $C_{26}H_{40}NaO_4$ 439.2818, obsd 439.2799.

For **22**: IR (neat, cm^{-1}) 3401, 1695, 1612; ^1H NMR (300 MHz, $CDCl_3$) δ 5.62 (dd, J = 3.2, 1.7 Hz, 1H), 5.38 (heptet, J = 6.1 Hz, 1H), 4.90 (heptet, J = 6.1 Hz, 1H), 2.79 (dd, J = 9.8, 0.7 Hz, 1H), 2.64 (dd, J = 17.2, 1.7 Hz, 1H), 2.24 (dd, J = 17.2, 3.2 Hz, 1H), 1.89 (dd, J = 12.4, 9.8 Hz, 1H), 1.71−1.62 (m, 1H), 1.65 (d, J = 12.3 Hz, 1H), 1.58−1.51 (m, 2H), 1.42−1.15 (m, 3H), 1.38 (d, J = 6.1 Hz, 3H), 1.31 (d, J = 6.1 Hz, 3H), 1.24 (t, J = 6.1 Hz, 6H), 0.91 (d, J = 6.6 Hz, 3H), 0.90 (s, 3H), 0.85 (d, J = 6.6 Hz, 3H); ^1H NMR (500 MHz, C_6D_6) δ 5.54 (s, 1H), 5.51 (heptet, J = 6.1 Hz, 1H), 5.40 (heptet, J = 6.1 Hz, 1H), 2.96 (d, J = 9.2 Hz, 1H), 2.60 (d, J = 7.1 Hz, 1H), 2.19 (dd, J = 7.1, 3.1 Hz, 1H), 1.96 (d, J = 12.2 Hz, 1H), 1.93 (dd, J = 12.2, 9.2 Hz, 1H), 1.76−1.73 (m, 1H), 1.67−1.60 (m, 1H), 1.59−1.51 (m, 1H), 1.47−1.41 (m, 1H), 1.36−1.25 (m, 1H), 1.33 (d, J = 6.1 Hz, 3H), 1.31 (d, J = 6.1 Hz, 3H), 1.30 (d, J = 6.1 Hz, 3H), 1.29 (d, J = 6.1 Hz, 3H), 1.21−1.09 (m, 1H), 0.92 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 199.8 (s), 165.8 (s), 153.8 (s), 134.2 (s), 120.7 (d), 77.4 (s), 73.2 (d), 71.7 (d), 69.2 (s), 59.3 (d), 59.2 (d), 53.7 (s), 53.4 (t), 40.1 (t), 34.6 (t), 30.6 (t), 28.4 (d), 23.0 (q), 22.6 (q), 22.55 (q), 22.47 (q), 21.9 (q), 19.4 (q); HRMS (ES) *m/z* ($M + Na)^+$ calcd for $C_{24}H_{36}NaO_4$ 411.2505, obsd 411.2492.

For **23**: IR (neat, cm^{-1}) 3414, 1696, 1657, 1614; ^1H NMR (500 MHz, $CDCl_3$) δ 5.42 (dd, J = 3.8, 1.5 Hz, 1H), 5.36 (heptet,

J = 6.1 Hz, 1H), 4.92 (heptet, J = 6.1 Hz, 1H), 2.95−2.91 (m, 1H), 2.52 (ddd, J = 15.5, 6.6, 3.8 Hz, 1H), 2.34 (ddd, J = 15.5, 10.0, 1.5 Hz, 1H), 2.12 (dt, J = 13.4, 7.2 Hz, 1H), 2.02−1.96 (m, 2H), 1.92 (s, 1H, OH), 1.82 (q, J = 7.0 Hz, 2H), 1.75−1.69 (m, 2H), 1.44 (dd, J = 13.4, 3.2 Hz, 1H), 1.37 (d, J = 6.1 Hz, 3H), 1.34 (d, J = 6.1 Hz, 3H), 1.27 (d, J = 6.1 Hz, 3H), 1.25 (d, J = 6.1 Hz, 3H), 1.14 (s, 3H), 0.88 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) ppm 200.3 (s), 167.8 (s), 158.4 (s), 131.3 (s), 124.9 (d), 83.2 (s), 73.9 (d), 72.1 (d), 68.2 (s), 63.9 (d), 57.2 (s), 52.9 (d), 44.7 (t), 39.8 (t), 36.5 (t), 32.4 (t), 28.3 (d), 22.71 (q), 22.69 (q), 22.63 (q), 22.3 (q), 21.8 (q), 21.7 (q), 18.7 (q); HRMS (ES) m/z $(M + Na)^+$ calcd for $C_{24}H_{36}NaO_4$ 411.2505, obsd 411.2495.

For **24**: IR (neat, cm^{-1}) 3402, 1697, 1600; ^{1}H NMR (500 MHz, C_6D_6) δ 5.72 (t, J = 1.3 Hz, 1H), 5.44 (heptet, J = 6.1 Hz, 1H), 5.32 (heptet, J = 6.1 Hz, 1H), 3.29 (d, J = 8.9 Hz, 1H), 2.62 (dd, J = 7.0, 1.3 Hz, 1H), 2.24 (dd, J = 7.0, 1.3 Hz, 1H), 1.91 (dd, J = 12.5, 8.9 Hz, 1H), 1.71−1.67 (m, 3H), 1.68 (d, J = 12.5 Hz, 1H), 1.55−1.50 (m, 1H), 1.46−1.39 (m, 1H), 1.29 (t, J = 6.1 Hz, 6H), 1.22 (d, J = 6.1 Hz, 6H), 1.20−1.16 (m, 1H), 0.94 (d, J = 6.5 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H), 0.89 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) ppm 198.2 (s), 170.4 (s), 153.6 (s), 131.8 (s), 121.2 (d), 78.9 (s), 73.6 (d), 71.4 (d), 68.6 (s), 58.5 (d), 54.5 (s), 54.2 (t), 53.4 (d), 40.8 (t), 34.0 (t), 30.4 (t), 28.4 (d), 24.1 (q, 2C), 22.95 (q, 2C), 22.90 (q), 21.6 (q), 19.5 (q); HRMS (ES) m/z $(M + Na)^+$ calcd for $C_{24}H_{36}NaO_4$ 411.2505, obsd 411.2500.

***p*-Nitrobenzoate 25.** To a solution of **24** (11.7 mg, 0.031 mmol) and DMAP (3.7 mg, 0.031 mmol) in CH_2Cl_2 (1 mL) were added triethylamine (33 μL, 0.24 mmol) and 4-nitrobenzoyl chloride (28 mg, 0.15 mmol) under N_2. After being stirred at rt for 20 h, the mixture was extracted with ethyl acetate. The organic phase was washed with 5% HCl, 1 N NaOH, $NaHCO_3$ solution, and brine, then dried and evaporated. The residue was purified by flash chromatography on silica gel (elution with hexanes−ethyl acetate 12:1) to afford **25** (8.0 mg, 51%) as yellow crystals, mp 122−123 °C; IR (neat, cm^{-1}) 1731, 1705, 1655, 1609; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 8.8 Hz, 2H), 8.20 (d, J = 8.8 Hz, 2H), 5.80 (s, 1H), 5.35 (heptet, J = 6.1 Hz, 1H), 5.04 (heptet, J = 6.1 Hz, 1H), 3.55 (d, J = 8.4 Hz, 1H), 2.69 (d, J = 17.2 Hz, 1H), 2.33 (d, J = 17.2, 3.4 Hz, 1H), 1.95 (dd, J = 12.4, 8.4 Hz, 1H), 1.76 (dd, J = 9.5, 4.6 Hz, 1H), 1.69 (d, J = 12.4 Hz, 1H), 1.62−1.54 (m, 2H), 1.50 (dd, J = 10.2, 4.5 Hz, 1H), 1.45−1.25 (m, 2H), 1.39 (d, J = 6.1 Hz, 3H), 1.34 (d, J = 6.1 Hz, 3H), 1.29 (d, J = 6.1 Hz, 3H), 1.25 (d, J = 6.1 Hz, 3H), 0.97 (s, 3H), 0.92 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 193.0 (s), 169.6 (s), 150.6 (s), 148.2 (s), 135.4 (s), 132.8 (s), 131.0 (d, 4C), 123.5 (d), 123.4 (s), 84.3 (s), 74.4 (d), 72.2 (d), 67.5 (s), 58.2 (d), 55.4 (s), 54.6 (t), 51.3 (d), 41.0 (t), 33.7 (t), 30.3 (t), 28.3 (d), 23.2 (q), 23.1 (q), 23.0 (q, 2C), 22.6 (q), 21.5 (q), 20.0 (q); HRMS (ES) m/z $(M + Na)^+$ calcd for $C_{31}H_{39}NNaO_7$ 560.2618, obsd 560.2607.

Silyl Ether 26. Indirect Purification of 21. To a solution of **21** (156 mg, 0.401 mmol) in pyridine (2 mL) were added dropwise hexamethyldisilazane (0.85 mL, 4.01 mmol) and chlorotrimethylsilane (0.254 mL, 2.0 mmol) under N_2 at 0 °C. After being stirred at rt for 4 h, the mixture was extracted with ethyl acetate, and the organic phase was washed with H_2O and brine, dried, and evaporated. The residue was purified by flash chromatography on silica gel (elution with hexanes−ethyl acetate 30:1) to give **26** (130 mg, 58%); IR (neat, cm^{-1}) 1685, 1636; ^{1}H NMR (500 MHz, C_6D_6) δ 6.19 (dd, J = 16.8, 10.5 Hz, 1H), 5.47 (dd, J = 16.8, 1.5 Hz, 1H), 5.37 (dd, J = 2.9, 1.6 Hz, 1H), 5.19 (heptet, J = 6.1 Hz, 1H), 5.11 (dd, J = 10.5, 1.5 Hz, 1H), 4.99 (heptet, J = 6.1 Hz, 1H), 2.73 (dd, J = 8.5, 1.6 Hz, 1H), 2.69 (dd, J = 13.2, 1.6 Hz, 1H), 2.33−2.28 (m, 1H), 2.26 (dd, J = 16.8, 2.9 Hz, 1H), 2.08 (dd, J = 13.2, 1.6 Hz, 1H), 1.87−1.71 (m, 2H), 1.66−1.58 (m, 1H), 1.55−1.53 (m, 1H), 1.43−1.24 (m, 2H), 1.37 (d, J = 6.1 Hz, 3H), 1.35 (d, J = 6.1 Hz, 3H), 1.27 (d, J = 6.1 Hz, 3H), 1.25 (d, J = 6.1 Hz, 3H), 0.98 (s, 3H), 0.96 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 6.5 Hz, 3H), 0.40 (s, 9H), 0.23 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) ppm 158.1 (s), 145.6 (d), 138.7 (s), 133.0 (s), 117.2 (d), 112.5 (t), 86.4 (s), 82.1 (s), 70.9 (d), 70.7 (d), 67.9 (s), 60.3 (d), 59.7 (d), 54.5 (t), 53.7 (s), 39.9 (t), 30.6 (t), 30.3 (t), 28.5 (d), 23.4 (q), 23.2 (q), 23.1 (q), 23.0 (q), 22.5 (q), 21.7 (q), 20.1 (q), 2.7 (q, 3C), 2.2 (q, 3C); HRMS (ES) m/z $(M + Na)^+$ calcd for $C_{32}H_{56}NaO_4Si_2$ 583.3609, obsd 583.3595.

To a solution of **26** (77 mg, 0.14 mmol) in THF (3 mL) was added TBAF (1.0 M in THF, 1.4 mL, 1.4 mmol), and the reaction mixture was stirred for 2 h, diluted with water, and extracted with ethyl acetate. The combined extracts were washed with brine, dried, and evaporated, and the residue was chromatographed on silica gel (elution with ethyl acetate−petroleum ether 1:6) to give pure **21** (52.6 mg, 91%).

Silylation of 23. A solution of **23** (121.3 mg, 0.312 mmol) in CH_2Cl_2 (3 mL) was treated sequentially with 2,6-lutidine (0.29 mL, 2.5 mmol) and *tert*-butyldimethylsilyl triflate (0.215 mL, 0.936 mmol) at 0 °C under N_2. After being stirred at rt for 48 h, the mixture was diluted with H_2O and extracted with ethyl acetate. The organic phase was washed with saturated $NaHCO_3$ solution and brine, then dried and evaporated. The residue was purified by flash chromatography on silica gel (elution with hexanes−ethyl acetate 20:1) to give **27** (121 mg, 78%); IR (neat, cm^{-1}) 1705, 1657, 1629; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.35 (heptet, J = 6.1 Hz, 1H), 5.24 (dd, J = 3.8, 1.5 Hz, 1H), 4.95 (heptet, J = 6.1 Hz, 1H), 2.73−2.67 (m, 1H), 2.46 (ddd, J = 17.0, 6.1, 1.5 Hz, 1H), 2.24 (dd, J = 17.0, 5.7 Hz, 1H), 2.18−1.95 (m, 3H), 1.74−1.67 (m, 2H), 1.63−1.57 (m, 2H), 1.40 (d, J = 6.1 Hz, 3H), 1.38−1.28 (m, 1H), 1.26 (d, J = 6.1 Hz, 3H), 1.22 (d, J = 6.1 Hz, 3H), 1.21 (d, J = 6.1 Hz, 3H), 1.07 (s, 3H), 0.84 (d, J = 6.4 Hz, 3H), 0.83 (d, J = 6.0 Hz, 3H), 0.81 (s, 9H), 0.11 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 201.9 (s), 166.0 (s), 157.0 (s), 132.6 (s), 123.6 (d), 86.8 (s), 73.8 (d), 72.1 (d), 68.3 (s), 63.9 (d), 56.7 (s), 57.3 (d), 45.9 (t), 39.5 (t), 35.6 (t), 30.7 (t), 28.4 (d), 25.9 (q, 3C), 22.8 (q, 2C), 22.6 (q), 22.4 (q), 21.9 (q), 21.7 (q), 18.9 (s), 18.5 (q), −2.3 (q), −2.7 (q); HRMS (ES) m/z $(M + Na)^+$ calcd for $C_{30}H_{50}NaO_4Si$ 525.3370, obsd 525.3355.

Oxidation of 27. A suspension of chromium trioxide (481 mg, 4.81 mmol) in CH_2Cl_2 (2 mL) was cooled to −15 °C, and 3,5-dimethylpyrazole (462 mg, 4.81 mmol) was added under N_2. After 15 min of stirring at −15 °C, a solution of **27** (121 mg, 0.24 mmol) in CH_2Cl_2 (10 mL) was added via cannula under N_2. Stirring was continued at −15 °C for 3 h and at rt for 20 h prior to quenching with 1 N NaOH solution (25 mL) and extraction with ethyl acetate. The organic phase was washed in turn with 1 N NaOH solution, 5% HCl, saturated $NaHCO_3$ solution, and brine, then dried and evaporated. The residue was purified by flash chromatography on silica gel (elution with hexanes−ethyl acetate 20:1) to give **28** (91.6 mg, 73%); IR (neat, cm^{-1}) 1707, 1638, 1620; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66 (s, 1H), 5.39 (heptet, J = 6.1 Hz, 1H), 4.91 (heptet, J = 6.1 Hz, 1H), 2.72−2.70 (m, 1H), 2.26−2.02 (m, 4H), 1.99−1.89 (m, 1H), 1.79 (q, J = 6.8 Hz, 2H), 1.62 (dd, J = 13.8, 2.9 Hz, 1H), 1.40 (d, J = 6.1 Hz, 3H), 1.28 (d, J = 6.1 Hz, 3H), 1.23 (s, 3H), 1.21 (t, J = 6.1 Hz, 6H), 0.90 (d, J = 6.3 Hz, 3H), 0.76 (d, J = 6.3 Hz, 3H), 0.75 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 209.8 (s), 198.9 (s) 186.3 (s), 166.7 (s), 132.0 (s), 127.1 (d), 88.0 (s), 74.5 (d), 72.4 (d), 72.2 (d), 70.3 (s), 55.8 (s), 50.9 (d), 44.2 (t), 36.4 (t), 31.4 (t), 25.9 (q, 3C), 25.8 (d), 25.7 (q), 22.7 (q, 3C), 22.6 (q), 22.3 (q), 20.8 (q), 18.5 (s), −2.4 (q), −2.6 (q); HRMS (ES) m/z $(M + Na)^+$ calcd for $C_{30}H_{48}NaO_5Si$ 539.1377, obsd 539.3159.

Desilylation of 28. To a solution of **28** (27 mg, 0.052 mmol) in THF (2 mL) was added TBAF (1.0 M in THF, 0.26 mL, 0.26 mmol), and the reaction mixture was stirred for 1.5 h, diluted with water, and extracted with ethyl acetate. The combined extracts were washed with brine, dried, and evaporated to leave a residue that was chromatographed on silica gel (elution with ethyl acetate−petroleum ether 1:6) to give **29** (19.2 mg, 91%) as colorless crystals, mp 138−139 °C; IR (neat, cm^{-1}) 3394, 1779, 1697, 1613; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (s,

1H), 5.39 (heptet, J = 6.1 Hz, 1H), 4.91 (heptet, J = 6.1 Hz, 1H), 2.91−2.82 (m, 1H), 2.23−2.03 (m, 4H), 1.99−1.87 (m, 3H), 1.68 (dd, J = 13.6, 3.2 Hz, 1H), 1.35 (t, J = 6.1 Hz, 6H), 1.38−1.21 (m, 1H), 1.25 (d, J = 6.4 Hz, 3H), 1.23 (s, 3H), 1.22 (d, J = 6.1 Hz, 6H), 0.93 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 209.9 (s), 198.4 (s), 186.6 (s), 167.7 (s), 131.0 (s), 126.1 (d), 85.0 (s), 74.5 (d), 72.6 (d), 72.5 (d), 69.5 (s), 56.0 (s), 50.6 (d), 43.4 (t), 37.2 (t), 32.2 (t), 25.6 (d), 25.0 (q), 22.75 (q), 22.70 (q), 22.6 (q), 22.3 (q), 22.2 (q), 20.8 (q); HRMS (EI) m/z (M^+) calcd for $C_{24}H_{34}O_5$ 402.2401, obsd 402.2404.

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Supporting Information Available: Details of the X-ray crystallographic analyses of **25** and **29** in addition to high field ^{1}H and ^{13}C NMR spectra for all compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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