Sensitivity of Substitution to the Extent of Self-Immolative Chirality Transfer during Reaction Cascades Originating from Squarate Esters

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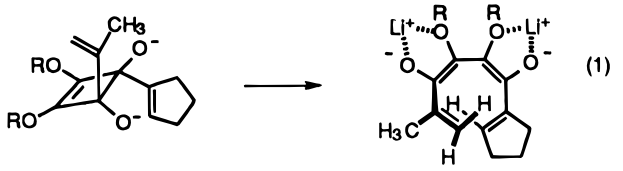
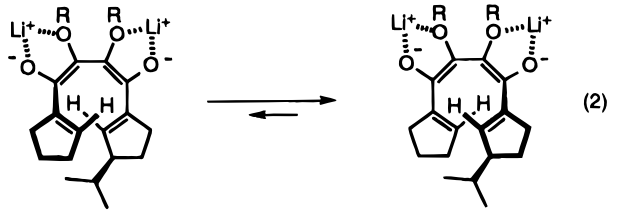
Reaction cascades induced by the addition to diisopropyl squarate of at least one cycloalkenyl anion possessing an oxygenated leaving group have been examined for the purpose of evaluating the level of chirality transferred to several new stereogenic centers as the original one is destroyed through β-elimination. A methoxy group alone necessarily resides too far from the bonding sites involved in conrotatory ring closure of the coiled octatetraene intermediate to have a large impact, viz. greater than 22% ee. The situation is considerably improved if a (*tert*-butyldimethylsilyl)oxy (OTBS) substituent is positioned nearer to this key helical biasing site. The relative rates of ring closure from the two helices of different pitch now become sufficiently different (>100:1) that mechanistic control by OTBS dominates completely. Finally, an example of overwhelming steric bias is detailed (see **30**), showing that electrocyclic control can also be achieved in this manner.

The squarate ester cascade is recognized to proceed by sequential passage through *three* dianionic intermediates. The initially formed *trans*-cyclobutene dialkoxides represented by **1** undergo relatively rapid conrotatory ring opening with a strong kinetic preference for positioning the oxido substituents outside as in **2** (eq 1).[1]



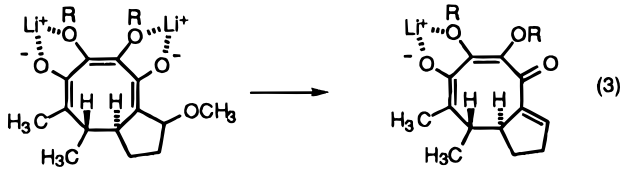
(1)

1 **2**



(2)

3 **4**



(3)

5 **6**

This substituent effect is in agreement with theoretical considerations[2] and does not appear to be amenable to modulation. The octatetraenes **2**, initially formed with preservation of the stereochemical information inherent in **1**, are sufficiently persistent in solution that equilibration with the diastereomeric helix can take place more rapidly than conrotatory ring closure (eq 2). As a consequence of this kinetic ordering, a substituent strategically positioned relative to the terminal carbons can direct the stereochemical course of cyclooctatriene formation.[3] In the illustrated example, **4** cyclizes more rapidly than **3** because significantly less nonbonded steric compression is encountered during the bonding process. Accordingly, the level and direction of stereoselection is subject to control.

The cyclooctatrienes so formed survive until an aqueous quench is brought about. In unsymmetrical cases, two protonation pathways are possible. Although the lesser substituted enolate carbon is often protonated more rapidly with resultant regiocontrolled transannular aldolization,[1] the direction of ring closure can be guaranteed by prior incorporation of a leaving group into one of the original alkenyllithium reactants.[4] As outlined in eq 3, β-elimination of methoxide ion in **5** leads to **6**, from which a single triquinane is generated.

Since **5** is an obligatory intermediate and the methoxy-substituted carbon is stereogenic, it is legitimate to inquire into what extent the chirality at this center might play a role on setting the configuration of the two methine carbons in **5** and, following the generation of **6**, the additional asymmetric atoms in the final product. These issues are examined herein.

Results

Simple Methoxy Substitution. The first goal was to prepare optically active 6-methoxy-1-lithiocyclohexene (**7**) and to coreact this species and 2-lithiopropene with diisopropyl squarate. Suitable optical enrichment in **7** was achieved by esterification of the racemic cyclohexenol with chloroacetyl chloride and enzymatic hydrolysis of this ester with lipase PS30 (Amano). These conditions delivered the (*R*)-(+)-alcohol (63% ee) and unhydrolyzed

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(1) Paquette, L. A.; Morwick, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 1230 and relevant references cited therein.

(2) (a) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099. (b) Thomas, B. E., IV; Evanseck, J. D.; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 4165. (c) Dolbier, W. R., Jr.; Koroniak, H.; Houk, K. N.; Sheu, C. *Acc. Chem. Res.* **1996**, *29*, 471.

(3) Paquette, L. A.; Hamme, A. T., II; Kuo, L. H.; Doyon, J.; Kueuzholz, R. *J. Am. Chem. Soc.* **1997**, *119*, 1242.

(4) (a) Paquette, L., A.; Doyon, J. *J. Am. Chem. Soc.* **1995**, *117*, 6799. (b) Paquette, L., A.; Doyon, J. *J. Org. Chem.* **1997**, *62*, 1723.

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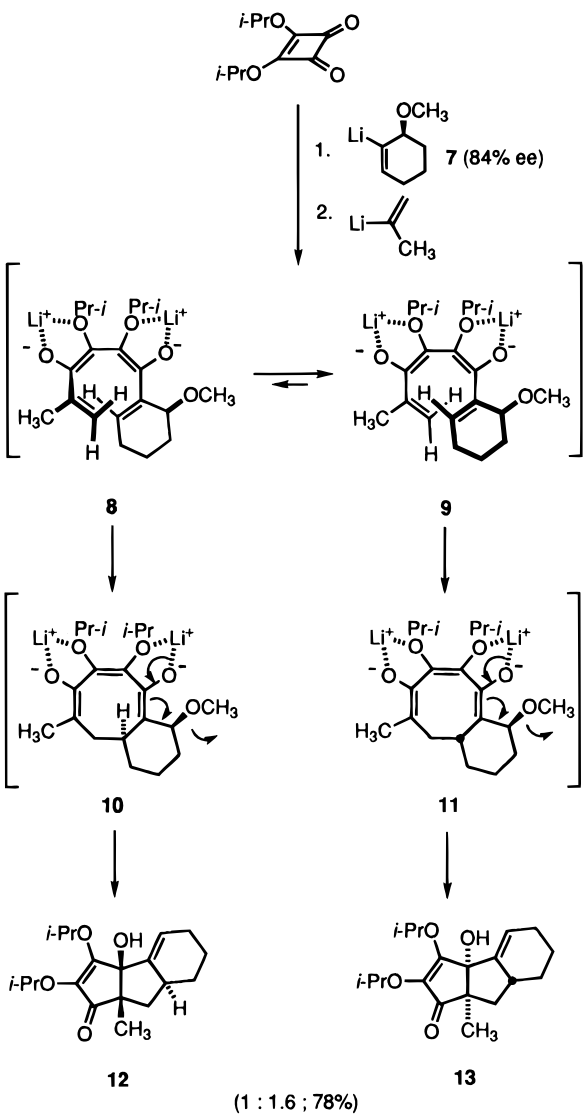
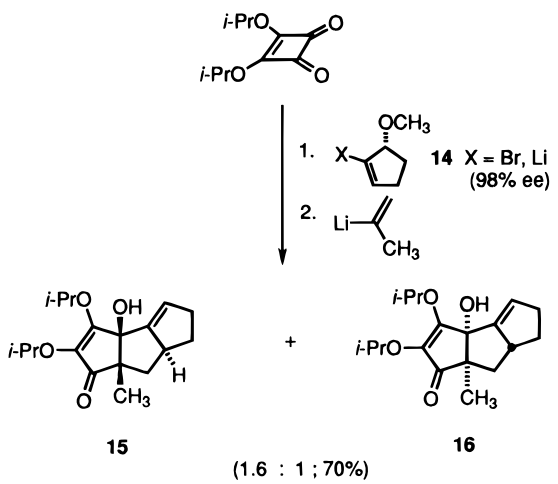
Scheme 1



(*S*)-(−)-chloroacetate (90% ee). The latter product was saponified, and the $[\alpha]_D$ of the resultant alcohol was compared to reported optical rotations[5,6] prior to O-methylation with sodium hydride and methyl iodide. Following implementation of the planned cascade reaction, the anticipated tricyclic product was isolated in 78% yield. The enantiomeric composition of this material varied to a minor degree from run to run and peaked at 22% ee (HPLC analysis on a Chiracel OD-H column). The predominating enantiomer was judged to be **13** on the strength of the specific rotation of the product, $[\alpha]^{22}_D$ −48.4°, which is opposite in direction to that exhibited by **15**, and its direct relationship to **19** of confirmed relative configuration (see below).

The partial racemization associated with the use of **7** in Scheme 1 is attributed to the rather distal relationship of the methoxy group to the olefinic carbon at the opposite end of the helix in **8** and **9**. We presume that helical equilibration operates[3] and that **9** cyclizes to **11** at a rate modestly accelerated over the competitive **8** → **10** transformation. Attention is called explicitly to the fact that the cyclization of **8** and **9** as orchestrated by the methoxy substituent sets a second stereogenic center prior to elimination of the first. Due to the intramolecular distances involved, the self-immolative chirality transfer in this example is only modest.

Scheme 2



(*R*)-(+)-2-Bromocyclopenten-5-ol[7] was obtained by enzymatic hydrolysis of the chloroacetate in the predescribed manner. Following O-methylation as before, the (*S*)-(+)-bromo ether **14** was conveniently obtained at the 98% ee level. Since **14** is of the opposite absolute configuration of **7**, its involvement in a parallel cascade process should deliver more **15** than **16** if any of the original stereogenicity is retained (Scheme 2). Indeed, execution of this experiment afforded the unsaturated triquinane, $[\alpha]_D$ +70.1°, in 70% yield. Chiral HPLC analysis of this sample showed the enantiomeric excess to reside again at the 22% level. Spectral comparison of **15/16** with the known racemic triquinane[4b] confirmed the gross structural assignment. Identification of **15** as the predominant enantiomer is based on its opposite sign of optical rotation relative to that of **13**.

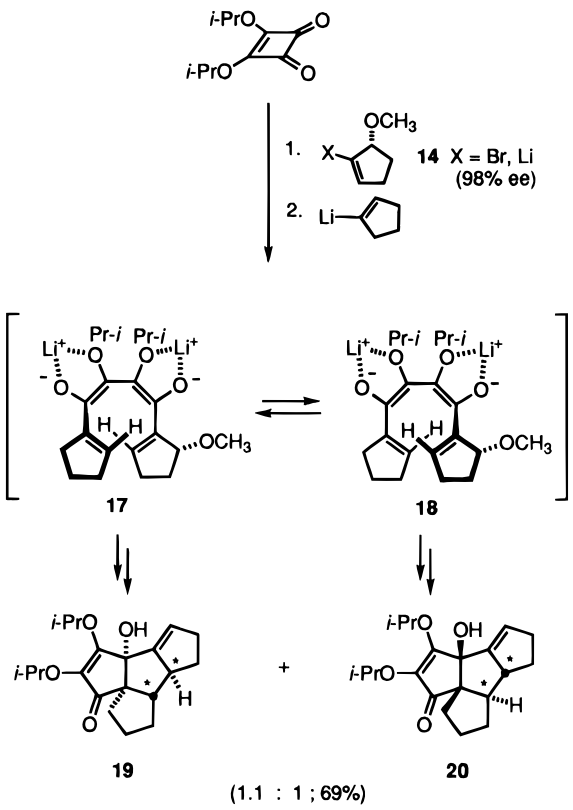
In both of the preceding examples, the extent of substitution within the 2-propenyllithium reagent is below the level necessary to confirm that the electrocyclization pathway was actually followed. Cis addition of this nucleophile and subsequent dianionic oxy-Cope rearrangement would deliver the identical end products. A major distinction does separate the two pathways, viz. *adoption of the [3.3] sigmatropic alternative does not allow for loss of optical purity!* Thus, although the results depicted in Schemes 1 and 2 reveal an inability to preserve enantioselectivity completely, they remain highly suggestive of the fact that the electrocyclic cascade is operative. The test case for attaining proper stereochemical proof involved the co-condensation of **14**-Li (98% ee) and cyclopentenyllithium with diisopropyl squarate (Scheme 3). The exclusive formation of **19/20** is fully consistent with the intervention of **17** and **18**. However, the enantiomeric excess was now found to reside at an all-time low of 5%. We have recognized for some time that cyclopentenyllithium is a particularly efficient reaction partner in squarate cascades. This efficiency could be a manifestation of accelerated cyclization of octatetraenes such as **17** and **18** that carry a cyclopentene ring at both of their termini. Should cyclization be sufficiently efficient to occur more rapidly than helical equilibration, then the distribution of **19** and **20** would be dictated

(5) Johnson, C. R.; Sakaguchi, H. *Synlett* **1992**, 813.

(6) (a) Corey, E. J.; Chen, C.-P.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5547. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

(7) Corey, E. J.; Srinivas Rao, K. *Tetrahedron Lett.* **1991**, *32*, 4623.

Scheme 3



entirely by the distribution of the diastereomeric monoadducts,[3] which in these cases closely parallel 1.1:1. Were **17** and **18** in mutual equilibrium, the reasonable expectation would be that steric constraints in **18** would contribute to a disfavoring of its conversion to **20** to an extent greater than that present in **8**. Since the proportion of **19** is not enhanced, this alternative suggestion has low credibility.

Recrystallization of the **19/20** mixture was met with preferential formation of crystals of the racemate.[10] Crystallographic analysis of material produced in this manner revealed the all-important fact that the hydrogen atoms at the two asterisked sites are trans-related as required by the electrocyclic mechanism (Figure 1).

Dual Substitution of a Cyclopentene Nucleophile. At this point, recourse to the more highly substituted cyclopentenyl bromide **24** (85% ee, chiral HPLC analysis) was resorted to since this system necessarily positions a bulky *tert*-butyldimethylsiloxy (OTBS) group immediately adjacent to a ring closure site in the octatetraene. The preparation of (−)-**24** was achieved by bromination-dehydrobromination of levorotatory enone **21**[8] followed by Luche reduction[9] (Scheme 4). The cis alcohol which predominated over the trans isomer by a factor of 4.7:1 was obtained pure following chromatography and O-methylated in the conventional fashion with sodium hydride and methyl iodide. Addition of the lithium derivative of **24** to an equimolar amount of diisopropyl squarate in THF at −78 °C followed by a modest excess

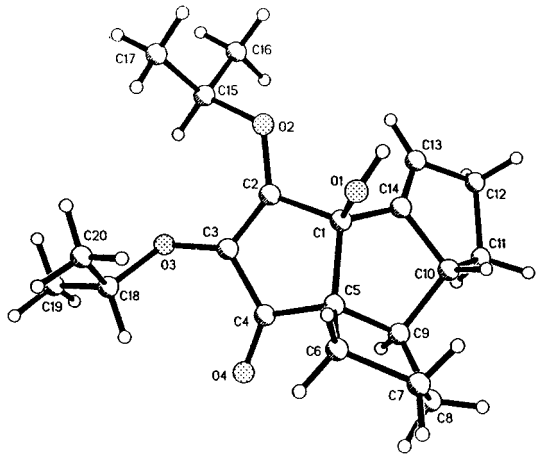
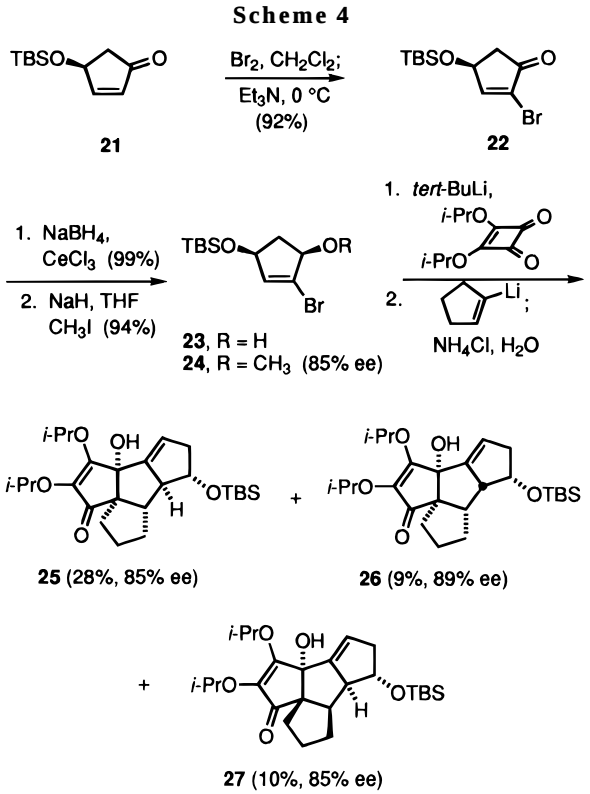


Figure 1. Computer-generated perspective drawing of the final x-ray model of **19/20**.

Scheme 4

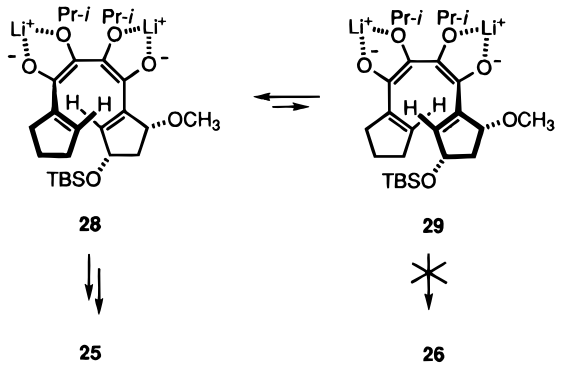


of cyclopentenyllithium resulted in the coformation of three isomeric tetraquinane products. These ketones could be separated with reasonable efficiency on silica gel, identified by a combination of NMR techniques (see Experimental Section), and confirmed to be of high optical purity by HPLC analysis on a Chiralpak AD column.

Particularly relevant is the realization that **25** arises from an electrocyclic cascade, while **26** and **27** are produced via a dianionic oxy-Cope sequence. Since full stereochemical transmission operates in the latter mechanistic context, it is expected that **26** and **27** be obtained at the same optical purity level as the starting bromide **24**. This is indeed the case. Especially revealing is the finding that **25** is also formed at the 85% ee level, thereby indicating that stereochemical integrity is being preserved during operation of the electrocyclic reaction channel as well. The exclusive formation of **25** denotes that while the conrotatory ring closure of tetraene **28** is

(8) Paquette, L. A.; Heidelbaugh, T. M. *Org. Synth.* **1996**, *73*, 44.
(9) (a) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (b) Luche, J.-L.; Rodriquez-Hahn, L.; Crabbé, P. *Chem. Commun.* **1978**, 601.
(10) The authors have deposited the atomic coordinates for the X-ray structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

Scheme 5

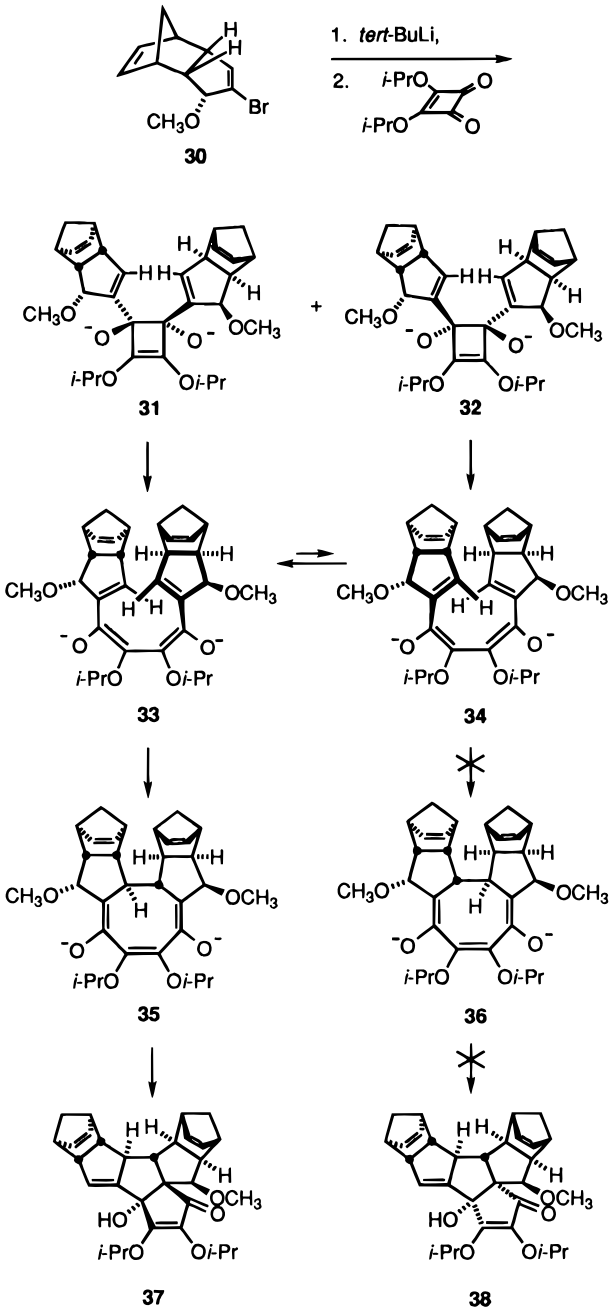


kinetically favorable, the analogous 8π process does not operate at a detectable level in **29** (Scheme 5). Evidently, the sterically demanding OTBS group forces this substituent away from the immediate vicinity of the bonding site so as to minimize its steric impact.

Heightened Steric Control. In the preceding examples, the biasing influence for selectivity in bond formation from one or the other pitch of equilibrating helical octatetraenes has come from a methoxy group alone or in combination with a (*tert*-butyldimethylsilyl)-oxy substituent. In an earlier investigation,[3] the norbornenyl component of bromide **30** was shown to exhibit overriding steric interference relative to smaller alkenyl reaction partners, such that bonding occurred only on its exo face. This kinetic preference should continue to be seen when 2 equiv of the lithium derivative of **30** is added to diisopropyl squarate. Thus, although 2-fold addition will likely result in the formation of near-equal amounts of diastereomers **31** and **32** and these dialkoxides are progenitors of **33** and **34**, respectively, the expectation is that **34** will be unable to progress to **36** because of excessive steric constraints (Scheme 6). Rather, **34** should equilibrate with **33**. Since this helix is arranged such that ring closure operates on the exo surface of the intra-ring π bond at both termini, conversion to **35** should not be structurally impeded. The C_2 symmetry of **35** allows for β-elimination of either methoxy group prior to transannular aldolization as in **37**, which should prove to be the only product as long as second-stage cis addition is an inoperative reaction channel.

Indeed, the reaction in question delivered a single polycyclic compound in 55% isolated yield. The high crystallinity of this product invited structural elucidation by X-ray crystallography.[10] As seen in Figure 2, the myriad of stereogenic centers resident in this structure, most notably the trans,trans arrangement of the three vicinal methine protons and the trans disposition of the OH and OCH_3 substituents, identify the product to be **37**. Consequently, in this instance it is the architectural nature of the nucleophile and not necessarily the stereochemistry of the methoxy-substituted carbon that controls the transfer of chirality into the product of the electrocyclic cascade.

Scheme 6



Conclusions

A central challenge associated with application of the squarate electrocyclic cascade in synthesis is that of fully appreciating those factors responsible for controlling the relative rates of 8π conrotatory ring closure of the 1,3,5,7-octatetraene intermediates. As noted previously, the stereochemical outcome of the multistep process is decided at this stage, the initial diastereoselection being lost because of the ability of these coiled intermediates to experience rapid helical equilbration. Another issue to contend with involves regiocontrol of the site of protonation in the cyclized dienolates (e.g., **5**), one solution to which is to position a leaving group properly vis-a-vis one of the reactive centers such that β-elimination is operational. In this way, transannular aldolization is limited to a single direction.

The present exploratory study provides informative insight into several determinants of stereocontrol at these pivotal stages of the cascade. In practice, the placement of a leaving group at the proper site in one of the alkenyl anions neces-sarily fixes its position rather distal from the bonding sites within the octatetraenes that develop. Intermediates **8**, **9**, **17**, and **18** concisely display this structural feature. In practice, this distal relationship cannot adequately meet the challenge of modulating the

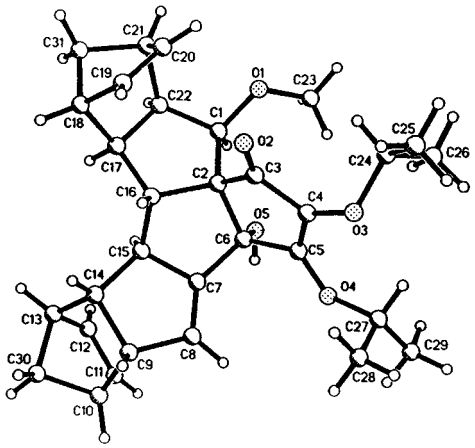


Figure 2. Computer-generated perspective drawing of the final x-ray model of **37**.

relative rates of cyclization such that one ring closure operates to the total exclusion of the other.

Two ways in which to resolve this problem have been satisfactorily explored. Maximization of the prospects for total stereocontrol can be achieved by positioning a second substituent closer to an octatetraene terminus or by introducing an overwhelming steric bias into a nucleophile. In the first instance exemplified by **28** and **29**, closure on the π-surface anti to the OTBS substituent is kinetically dominant. While it is true that a second stereogenic center is introduced to oversee the stereodirectionality of 8π electrocyclization, this second oxygenated center can prove serviceable in many synthetically utilitarian ways. The second tactic, reflected in helix **33**, is notably effective in curtailing any mechanistic leakage by way of its diastereomer **34**. The end result is that **37**, a product endowed with 13 stereogenic centers, is produced exclusively in a single laboratory operation.

Experimental Section

The general experimental protocols followed in this study parallel those described earlier in ref 1.

(*S*)-(−)-1-Bromo-6-methoxycyclohexene (7). A solution of racemic 1-bromocyclohexen-6-ol (23.8 g, 134 mmol) and triethylamine (28.5 g, 282 mmol) in dry CH_2Cl_2 (250 mL) was cooled to 0 °C and treated dropwise during 3 h with chloroacetyl chloride (30.4 g, 269 mmol). The dark reaction mixture was allowed to warm to room temperature and poured over 250 mL of an ice−water mixture. The product was extracted into CH_2Cl_2, and the combined organic extracts were dried and concentrated. Kugelrohr distillation of the residue under reduced pressure (100−140 °C, 10−20 Torr) afforded 33 g (96%) of the chloroacetate as a pale yellow liquid which was taken directly into the next step.

The chloroacetate was taken up in 600 mL of phosphate buffer (0.05 M, pH 7) and 200 mL of THF. Upon the addition of lipase PS30 (Amano, 2.0 g), a vigorous reaction was initiated. The pH of the reaction mixture was maintained at 6.8 by the continuous infusion of a 2 N NaOH solution via a syringe pump interfaced with a pH stat. When further reaction came to a near stop at approximately 65% reaction, the emulsion was filtered through a bed of Celite to remove the enzyme and extracted with four portions (200 mL each) of ether. The combined ethereal phases were dried and concentrated. Chromatography of the residue on silica gel (elution with 10−50% ethyl acetate in hexanes) gave 10 g (43%) of the (*R*)-(+)-alcohol, $[\alpha]^{21}_D$ +52° (*c* 1.40, $CHCl_3$) (63% ee), and 11 g (33%) of (*S*)-(−)-chloroacetate, $[\alpha]^{21}_D$ −93° (*c* 1.55, $CHCl_3$). The latter material was dissolved in methanol (100 mL) containing several KOH pellets, stirred for 1 h, concentrated under reduced pressure, dissolved in ether (200 mL), and washed with a saturated NH_4Cl solution (2 × 30 mL) and brine (2 × 30 mL) prior to drying and solvent evaporation. Chromatographic purification on silica gel (elution with 50% ethyl acetate in hexanes) gave the (*S*)-(−)-carbinol as a pale yellow oil, $[\alpha]^{21}_D$ −74° (*c* 1.47, $CHCl_3$) (90% ee).

To a cold (0 °C) suspension of sodium hydride (0.77 g, 32.2 mmol) in dry THF (50 mL) was added dropwise during 1 h a THF solution (10 mL) containing the above alcohol (3.8 g, 21.5 mmol) and methyl iodide (4.6 g, 32.2 mmol). The cooling bath was removed, and the reaction mixture was stirred overnight at 20 °C. An aqueous NH_4Cl solution (20 mL) was added carefully, and the mixture was extracted with ether. The combined organic extracts were washed with brine (2 × 10 mL), dried, and concentrated. The residue was purified by chromatography on silica gel (elution with 20% ethyl acetate in hexanes) to give the methoxy bromide as a pale yellow oil (4.1 g, 100%); IR (film, cm^{-1}) 1643, 1454, 1437, 1365, 1335, 1192, 1095, 1070, 995, 954; ^1H NMR (300 MHz, C_6D_6) δ 6.20 (dd, J = 5.0, 3.5 Hz, 1 H), 3.72 (dd, J = 4.0, 2.5 Hz, 1 H), 3.42 (s, 3 H), 2.20−1.85 (series of m, 4 H), 1.80−1.45 (series of m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 133.4, 122.6, 78.5, 57.3, 28.4, 27.7, 16.9; MS *m*/*z* (M^+) calcd 191.0155, obsd 191.0149; $[\alpha]^{22}_D$ −57.7° (*c* 1.21, $CHCl_3$).

Reaction Cascade Leading to 12 and 13. A solution of **7** (0.26 g, 1.36 mmol, 80% ee) in dry THF (7 mL) was treated dropwise at −78 °C with *tert*-butyllithium (1.6 mL of 1.7 M in pentane, 2.72 mmol), and the mixture was stirred at −78 °C for 1 h. Diisopropyl squarate (0.30 g, 1.51 mmol) dissolved in THF (8 mL) was introduced at −78 °C, and the mixture was stirred at −78 °C for another 2.5 h. Vinyllithium generated from 2-bromopropene (0.36 g, 2.97 mmol) in THF (15 mL) and *tert*-butyllithium (3.7 mL of 1.7 M in pentane, 6.29 mmol) at −78 °C for 1 h, was transferred in the cold via cannula into the above mixture, which was subsequently stirred at 22 °C for 17 h before being saturated with an NH_4Cl solution (10 mL) and extracted with ether (2 × 20 mL). The organic layers were combined, washed with water (20 mL) and brine (20 mL), dried, and concentrated to provide a brown oil. Purification of this material by flash chromatography on silica gel (elution with 20% ethyl acetate in hexanes) gave the diquinanes **12** and **13** as a white solid (0.33 g; 78%): $[\alpha]^{22}_D$ −84.9° (*c* 0.61, $CHCl_3$). The spectral data for this sample were identical to those reported for the racemic material.[4b]

(*R*)-(+)-1-Bromo-5-methoxycyclopentene (14). A solution of (*R*)-1-bromocyclopenten-5-ol (0.20 g, 1.24 mmol), $[\alpha]^{20}_D$ +28.4°)[7] was blanketed with N_2, cooled to 0 °C, and treated sequentially with methyl iodide (0.23 mL, 3.72 mmol) and sodium hydride (0.05 g, 2.48 mmol). The mixture was allowed to warm to room temperature when more sodium hydride was introduced until no alcohol remained (TLC analysis), quenched with saturated NH_4Cl solution, and extracted with ether. The combined organic phases were washed with brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with 10% ethyl acetate in petroleum ether) furnished **14** as a colorless oil (190 mg, 87%): IR (film, cm^{-1}) 1620, 1455, 1355, 1190, 1100; ^1H NMR (300 MHz, $CDCl_3$) δ 6.09−6.08 (m, 1 H), 4.38−4.33 (m, 1 H), 3.36 (s, 3 H), 2.47−2.30 (m, 1 H), 2.29-2.14 (m, 2 H), 1.96−1.85 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 135.5, 122.0, 87.2, 55.7, 30.5, 28.5; MS *m*/*z* (M^+) calcd 175.9837, obsd 175.9825; $[\alpha]^{25}_D$ +2.1° (*c* 1.0, $CHCl_3$).

Reaction Cascade Leading to 15 and 16. A cold (−78 °C) solution of **14** (0.28 g, 1.60 mmol) in dry THF (5 mL) was blanketed with argon, treated dropwise via cannula with 1.87 mL of 1.7 M *tert*-butyllithium, stirred at −78 °C for 1 h, and treated rapidly with 2-lithiopropene [from reaction of 2-bromopropene (0.28 mL, 3.19 mmol) with 3.8 mL of 1.7 M *tert*-butyllithium in dry THF (5 mL)]. The reaction mixture was stirred at −78 °C for 2 h, warmed to room temperature during 2 h, and quenched with saturated $NaHCO_3$ solution. After 30 min of stirring, the product was extracted into ether (3 × 30 mL) and processed in the predescribed manner to give 0.17 g (70%) of the triquinanes **15** and **16** as a white solid, $[\alpha]^{23}_D$ +70.1° (*c* 0.52, $CHCl_3$) or 22% ee. The spectral properties of this material were identical to those reported for the racemic material.[4b]

Cascade Reaction Leading to 19 and 20. A solution of cyclopentenyl iodide (0.21 g, 1.10 mmol) in dry THF (3 mL) was cooled to −78 °C and treated sequentially with *tert*-butyllithium (1.3 mL of 1.7 M in hexanes, 2.20 mmol) and diisopropyl squarate (198 mg, 1.00 mmol). After 1 h of agitation, (5-methoxycyclopentenyl)lithium [prepared in an identical manner from **14** (0.379 g, 2.14 mmol, $[\alpha]^{24}_D$ +2.0°)] was introduced and stirring was maintained at −78 °C for 4 h, at 0 °C for 10 h, and at 20 °C for 2 h. After an NH_4Cl quench, the products were extracted into ether (2 × 30 mL) and the combined organic layers were processed as before. Chromatography of the residue on silica gel (elution with 10% ethyl acetate in petroleum ether) gave 0.229 g (69%) of the tetraquinanes **19** and **20** as a white solid, $[\alpha]^{22}_D$ −3.3° (*c* 1.57, $CHCl_3$). After recrystallization from hexanes, racemic white crystals of mp 103−104 °C were obtained and subjected to X-ray crystallographic analysis: IR ($CHCl_3$, cm^{-1}) 1693, 1619; ^1H NMR (300 MHz, C_6D_6) δ 5.67 (dd, J = 4.7, 2.9 Hz, 1 H), 5.37−5.23 (m, 2 H), 2.95−2.91 (m, 1 H), 2.50−2.18 (m, 3 H), 1.95−1.78 (m, 5 H), 1.56−1.51 (m, 1 H), 1.27−1.19 (m, 2 H), 1.17−1.06 (m, 13 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 202.9, 165.1, 154.3, 129.7, 121.4, 75.9, 73.6, 72.2, 71.6, 57.7, 54.8, 37.1, 22.4, 32.2, 32.0, 27.8, 23.0, 22.9, 22.6, 22.4; MS *m*/*z* (M^+) calcd 332.1988, obsd 332.1990.

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.19; H, 8.61.

(4*S*)-(−)-2-Bromo-4-[(*tert*-butyldimethylsilyl)oxy]-2-cyclopentenone (22). Bromine (1.4 mL, 27.1 mmol) was added dropwise at 0 °C to a solution of (−)-**21** (5.32 g, 25.1 mmol) in CH_2Cl_2 (250 mL). After 30 min of stirring, triethylamine (5.2 mL, 37.4 mmol) was introduced and the reaction was allowed to proceed at 0 °C for 1 h. The reaction mixture was washed with water (100 mL) and brine (100 mL), dried, and concentrated. Purification of the residue by flash chromatography on silica gel (elution with 100:1 hexanes/ethyl acetate) provided **22** as a yellow oil (6.74 g, 92%): IR (film, cm^{-1}) 1733, 1592, 1259, 1089; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 2.5 Hz, 1 H), 4.92−4.88 (m, 1 H), 2.83 (dd, J = 18.3, 5.9 Hz, 1 H), 2.32 (dd, J = 18.3, 1.9 Hz, 1 H), 0.86 (s, 9 H), 0.09 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 198.0, 161.1, 127.5, 69.4, 43.6, 25.6, 17.9, −4.7; MS *m*/*z* (M^+) calcd 290.0289, obsd 290.0319; $[\alpha]^{22}_D$ −25.3° (*c* 0.69, $CHCl_3$).

Anal. Calcd for $C_{11}H_{19}BrO_2Si$: C, 45.51; H, 6.60. Found: C, 45.59; H, 6.58.

(1*R*,4*S*)-(−)-2-Bromo-4-[(*tert*-butyldimethylsilyl)oxy]-2-cyclopentenol (23). Sodium borohydride (1.29 g, 34.1 mmol) was added slowly at 0 °C to a solution of **22** (9.91 g, 34.1 mmol) and cerium(III) chloride heptahydrate (12.69 g, 34.1 mmol) in methanol (170 mL), and the mixture was stirred at this temperature for 1 h. Water (100 mL) was introduced, and the product was extracted into ether (2 × 200 mL). The combined organic layers were washed with water (200 mL) and brine (200 mL), dried, and concentrated. The residue was subjected to flash chromatography on silica gel (elution with 10:1 hexanes/ethyl acetate) to provide 9.87 g (99%) of a 4.7:1 mixture of cis and trans alcohols. Rechromatography using 20:1 hexanes/ethyl acetate gave pure **23** as a colorless oil: IR (film, cm^{-1}) 3379, 1620, 1360,1035; ^1H NMR (300 MHz, $CDCl_3$) δ 5.97 (m, 1 H), 4.58−4.53 (m, 1 H), 4.43−4.30 (m, 1 H), 2.83 (br 1 H), 2.74 (dt, J = 13.5, 7.2 Hz, 1 H), 1.67 (dt, J = 13.5, 4.8 Hz, 1 H), 0.84 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 136.3, 129.5, 76.5, 73.3, 43.5, 25.7, 18.0, −4.7; MS *m*/*z* (M^+) calcd 292.0534, obsd 292.0514; $[\alpha]^{22}_D$ −33.7° (*c* 0.66, $CHCl_3$).

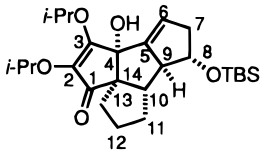
Anal. Calcd for $C_{11}H_{21}BrO_2$: C, 45.05; H, 7.22. Found: C, 45.14; H, 7.24.

(3*S*,5*R*)-(−)-1-Bromo-3-(*tert*-butyldimethylsiloxy)-5-methoxycyclopentene (24). A solution of **23** (1.11 g, 3.78 mmol) in dry THF (15 mL) was added dropwise at 0 °C to a magnetically stirred slurry of sodium hydride (0.23 g of 60% dispersion in mineral oil, 5.75 mmol) in the same solvent (10 mL). After 1 h at this temperature, methyl iodide (1.2 mL, 19.3 mmol) was introduced and stirring was maintained at room temperature for an additional 2 h. Water (10 mL) was added, and the product was extracted into ether (2 × 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried, and evaporated. Purification of the residue by flash chromatography on silica gel (elution with 100:1 hexanes/ethyl acetate) provided **24** as a faintly yellow liquid (1.09 g, 94%): IR (film, cm^{-1}) 1620, 1359, 1253, 1092; ^1H NMR (300 MHz, $CDCl_3$) δ 6.05 (m, 1 H), 4.60−4.55 (m, 1 H), 4.26−4.22 (m, 1 H), 3.55 (s, 3 H), 2.66 (dt, J = 13.5, 7.4 Hz, 1 H), 1.72 (dt, J = 13.5, 4.6 Hz, 1 H), 0.87 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 137.7, 126.6, 84.0, 73.1, 55.0, 39.8, 25.8, 18.1, −4.6; MS *m*/*z* (M^+) calcd 306.0620, obsd 306.0635; $[\alpha]^{22}_D$ −44.3° (*c* 0.95, $CHCl_3$).

Reaction Cascade Leading to 25−27. A cold (−78 °C), magnetically stirred solution of **24** (308 mg, 1.00 mmol) exhibiting $[\alpha]^{22}_D$ −39.3° (*c* 0.95, $CHCl_3$) (87% ee) in dry THF (4 mL) was treated dropwise with *tert*-butyllithium (1.18 mL of 1.7 M in pentane, 2.01 mmol) via syringe and stirred for 1 h. An equally cold solution of diisopropyl squarate (99 mg, 0.50 mmol) in dry THF (4 mL) was introduced via cannula. After 3 h at this temperature, a solution of 1-lithiocyclopentene [from 388 mg (2.00 mmol) of the iodide *tert*-butyllithium (2.4 mL of 1.7 M in pentane in dry THF (5 mL), 4.1 mmol] cooled to −78 °C was next added, and the reaction mixture was allowed to warm to room temperature and stirred overnight prior to being quenched with a deoxygenated saturated NH_4Cl solution (10 mL). The products were extracted into ether (3 × 40 mL), the combined organic layers were washed with brine, dried, and concentrated, and the residue was chromatographed on silica gel (elution with 9:1 petroleum ether/ethyl acetate) to give 65 mg (28%) of **25**, 20 mg (9%) of **26**, and 23 mg (10%) of **27**.

For **25**: colorless oil; IR (film, cm^{-1}) 3590, 1693, 1618, 1464, 1382, 1373, 1307; ^1H NMR (300 MHz, C_6D_6) δ 5.54 (dd, J = 2.9, 1.8 Hz, 1 H), 5.33 (heptet, J = 6.1 Hz, 1 H), 5.25 (heptet, J = 6.1 Hz, 1 H), 4.06 (dt, J = 7.7, 7.0 Hz, 1 H), 3.13−3.07 (m, 1 H), 2.54−2.31 (m, 4 H), 2.01−1.92 (m, 1 H), 1.87−1.65 (m, 4 H), 1.18−1.13 (m, 10 H), 1.06 (d, J = 6.1 Hz, 3 H), 0.93 (s, 9 H), 0.00 (s, 3 H), −0.02 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 202.9, 165.1, 151.9, 129.7, 119.3, 83.0, 76.2, 73.7, 72.1, 71.7, 64.6, 52.7, 45.7, 34.3, 32.4, 28.0, 26.0 (3 C), 23.1, 23.0, 22.7, 22.4, 18.1, −4.6, −4.7; MS *m*/*z* (M^+) calcd 462.2802, obsd 462.2805; $[\alpha]^{25}_D$ −37.6° (*c* 2.33, $CHCl_3$) (85% ee).

Anal. Calcd for $C_{26}H_{42}O_5Si$: C, 67.49; H, 9.15. Found: C, 67.31; H, 9.22.



Irradiate	Observe	%n.O.e.
H-8 (δ 4.06)	H-9	2.3
	H-10	15.4
H-9 (δ 3.10)	H-8	2.8

For **26**: colorless oil; IR (film, cm^{-1}) 3588, 1693, 1619, 1464, 1381, 1308, 1258; ^1H NMR (300 MHz, C_6D_6) δ 5.54 (t, J = 2.1 Hz, 1 H), 5.37 (heptet, J = 6.2 Hz, 2 H), 4.45−4.39 (m, 1 H), 3.01−2.93 (m, 1 H), 2.89−2.63 (m, 2 H), 2.29 (dt, J = 13.1, 3.1 Hz, 1 H), 2.19−1.92 (m, 4 H), 1.85−1.73 (m, 2 H), 1.54−1.38 (m, 1 H), 1.18−1.10 (m, 12 H), 0.89 (s, 9 H), −0.05 (s, 3 H), −0.06 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 202.3, 149.0, 133.8, 120.7, 78.0, 73.5, 72.0, 71.6, 69.8, 52.7, 49.6, 47.9, 30.0, 29.4, 27.8, 26.1 (3 C), 26.0, 22.8, 22.73, 22.68, 18.3, −4.9, −5.0; MS *m*/*z* (M^+) calcd 462.2802, obsd 462.2791; $[\alpha]^{25}_D$ −119.0° (*c* 2.02, $CHCl_3$) (89% ee).

Anal. Calcd for $C_{26}H_{42}O_5Si$: C, 67.49; H, 9.15. Found: C, 67.24; H, 9.13.

Same numbering as **25**

Irradiate	Observe	%n.O.e.
H-8 (δ 4.42)	H-9	16.4
H-9 (δ 2.97)	H-8	17.2
	H-10	9.3

For **27**: colorless oil; IR (film, cm^{-1}) 3590, 1695, 1618, 1464, 1381, 1309; ^1H NMR (300 MHz, C_6D_6) δ 5.52 (dd, J = 2.4, 1.8

Hz, 1 H), 5.29 (heptet, J = 6.2 Hz, 2 H), 4.41 (dt, J = 7.4, 5.2 Hz, 1 H), 3.20−3.14 (m, 1 H), 2.80−2.71 (m, 1 H), 2.64 (dt, J = 3.0, 2.3 Hz, 2 H), 2.13−2.06 (m, 3 H), 1.84−1.62 (m, 4 H), 1.18−1.02 (m, 12 H), 0.92 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 202.4, 164.6, 149.9, 133.4, 121.1, 77.5, 76.9, 73.6, 71.5, 70.2, 56.0, 49.3, 29.9, 29.2, 27.6, 26.0 (3 C), 22.7, 22.6, 22.5, 18.2, −4.56, −4.63; MS m/z (M^+) calcd 462.2802, obsd 462.2811; $[\alpha]^{25}_D$ +110.6° (c 0.94, $CHCl_3$) (85% ee).

Anal. Calcd for $C_{26}H_{42}O_5Si$: C, 67.49; H, 9.15. Found: C, 67.22; H, 9.71.

Same numbering as **25**

Irradiate	Observe	%n.O.e.
H-8 (δ 4.41)	H-9	3.9
	H-10	1.1
H-9 (δ 3.17)	H-8	2.7
	H-10	11.5
H-10 (δ 2.76)	H-8	1.1
	H-9	15.4

(3a*S*,4*R*,4a*R*,5*S*,8*R*,8a*R*,8b*S*,8c*S*,9d*S*,9*R*,12*S*,12a*R*,13b*R*)-4,4a,5,8,8a,8b,8c,8d,9,12,12a,13b-Dodecahydro-13b-hydroxy-1,2-diisopropoxy-4-methoxy-5,8:9,12-dimethano-3*H*-pentaleno[2,1-*a*:3,3a-*a*′]diinden-3-one (37). To a cold (−78 °C) solution of **30** (800 mg, 3.32 mmol) in dry THF (30 mL) was added *tert*-butyllithium (4.00 mL of 1.7 M in pentane, 6.80 mmol). After 3 h at −78 °C, a solution of diisopropyl squarate (328 mg, 1.66 mmol) in dry THF (20 mL) was introduced dropwise during 10 min at −78 °C, and the yellow solution was stirred for 18 h at room temperature while the color turned to orange. After the solution was quenched with saturated NH_4Cl solution (30 mL) and stirred for an additional hour, the layers were separated and the aqueous phase was extracted twice with ether. The combined organic solutons were washed twice with brine, dried, and evaporated. Purification of the residue by chromatography on silica gel (elution with 10% ethyl acetate in hexanes) afforded 917 mg (55%) of **37** as colorless crystals, mp 199−200 °C (from hexanes): IR ($CHCl_3$, cm^{-1}) 3590, 1705, 1631, 1378, 1304, 1106; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24 (dd, J = 5.4, 3.0 Hz, 1 H), 6.12 (dd, J = 5.4, 3.0 Hz, 1 H), 6.07−5.99 (m, 2 H), 5.25 (heptet, J = 6.1 Hz, 1 H), 5.17 (t, J = 2.5 Hz, 1 H), 4.73 (heptet, J = 6.2 Hz, 1 H), 4.40 (d, J = 9.0 Hz, 1 H), 3.27 (s, 3 H), 3.25−3.17 (m, 2 H), 2.94−2.89 (m, 3 H), 2.67−2.59 (m, 2 H), 2.57−2.50 (m, 1 H), 2.43−2.36 (m, 1 H), 2.28 (s, 1 H), 1.92 (dd, J = 8.4, 3.6 Hz, 1 H), 1.54 (dt, J = 8.1, 1.8 Hz, 1 H), 1.45−1.40 (m, 1 H), 1.35−1.25 (m, 8 H), 1.21 (d, J = 6.2 Hz, 3 H), 1.11 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 196.4, 159.7, 155.6, 137.4, 135.5, 134.2, 132.9, 130.8, 122.4, 83.2, 79.0, 76.7, 73.5, 71.4, 61.3, 59.0, 58.6, 56.1, 55.8, 52.1, 51.6, 51.3, 50.7, 47.0, 45.9, 45.7, 44.4, 23.2, 22.9, 21.5; MS m/z (M^+) calcd 490.2719, obsd 490.2718.

Anal. Calcd for $C_{31}H_{38}O_5$: C, 75.89; H, 7.81. Found: C, 75.72; H, 7.63.

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