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Concise Total Syntheses of the Bioactive Mesotricyclic Diterpenoids Jatrophatrione and Citlalitrione

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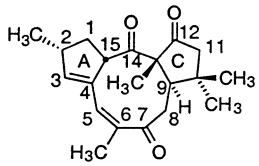
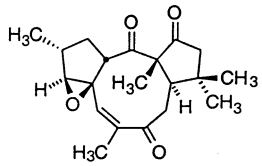
Abstract: The highly functionalized [5.9.5] tricyclic framework resident in jatrophatrione (**1**) and citlalitrione (**2**) has been synthesized. The route begins with the tandem anionic oxy-Cope rearrangement/methylation/transannular ene cyclization of **21** and subsequent introduction of a conjugated enone double bond. Hydroxyl-directed 1,4-reduction of this functionality in **25** with $LiAlH_4$/CuI/hexamethylphosphoramide/tetrahydrofuran sets the stage for the implementation of a Grob fragmentation and expedited generation of **27**. Stereocontrolled intramolecular hydrosilylation allows for the subsequent introduction of a cyclic carbonate as in **53**. This intermediate undergoes remarkably efficient, fully regiocontrolled Treibs reaction to generate **54**, with this maneuver serving as a pivotal step for making **1** available five steps later. Treatment of **1** with *m*-chloroperbenzoic acid leads to **2**, with attack occurring preferentially on a α-face of the double bond more remote to the carbonyl.

In 1976, Torrance et al.[1] disclosed the isolation from *Jatropha microrhiza* of an architecturally novel diterpenoid, which they called jatrophatrione (**1**). In the same account, the University of Arizona team revealed that this tumor-inhibitory agent was particularly active toward the P-388 (3PS) lymphocytic leukemia test system. The structural features of jatrophatrione, secured by a combination of spectroscopic and X-ray crystallographic techniques, are such that the dienone chromophore is substantially twisted and consequently devoid of significant through-conjugation. As a result, the mechanism of action suggested for **1** involves a retrograde Michael reaction that unmasks a highly electrophilic C8−C9 enone double bond set to capture protein-bound sulfhydryl groups covalently.[2]

More than a decade later, extraction of the roots of "tlapelex patli," the Aztec term for *Jatropha dioica*, obtained in northeastern Mexico led to the isolation of citlalitrione (**2**).[3] This plant source is widely recognized by the natives to have beneficial effects in the treatment of skin cancer. The closely related structural features of **1** and **2**, which include an unprecedented [5.9.5] tricyclic core, and their therapeutic properties hold particular fascination. As part of our program dealing with the de novo construction of anti-cancer agents, we have pursued and accomplished total syntheses of **1**[4] and **2**. We are unaware of equivalent successful ventures involving these unusual compounds.



1



2

Previous papers from this laboratory have described an approach that focused on the initial acquisition of 9-epijatrophatrione (**3**).[5] The intent behind this decision was to provide a forum for the potential isomerization of this more strained (ca. 6.5 kcal/mol) isomer into **1** via **4** and **5** (Scheme 1). Should ring opening in **3** prove feasible and **4** be capable of interconversion with **5** in advance of cyclization to give **1**, much of the conjecture surrounding the biological mechanism of action would be substantiated. The advanced polycyclic intermediates that were reached in the course of the earlier investigation were instrumental in providing insight concerning how jatrophatrione and citlalitrione might be concisely approached.

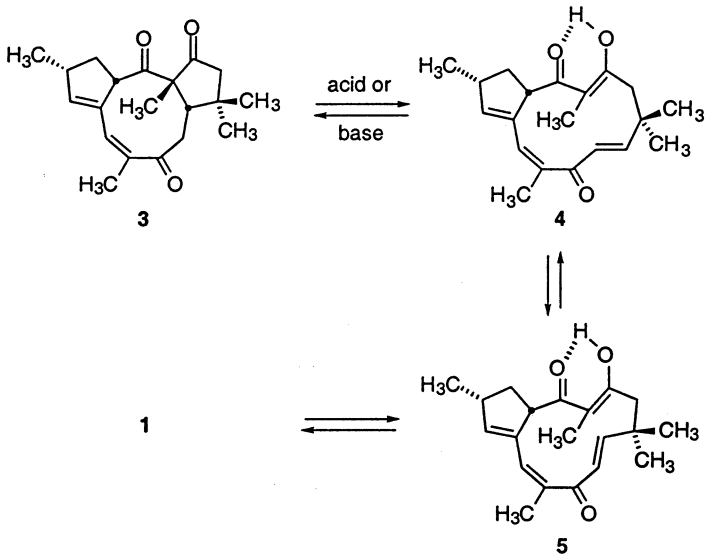
Retrosynthetic Analysis and Strategy

The synthetic plan called for the initial construction of the building blocks **D** and **E** in Scheme 2. The carbinol resulting from 1,2-addition of the cerate reagent derived from **E** to the exo surface of **D** defines a substrate that was expected to be

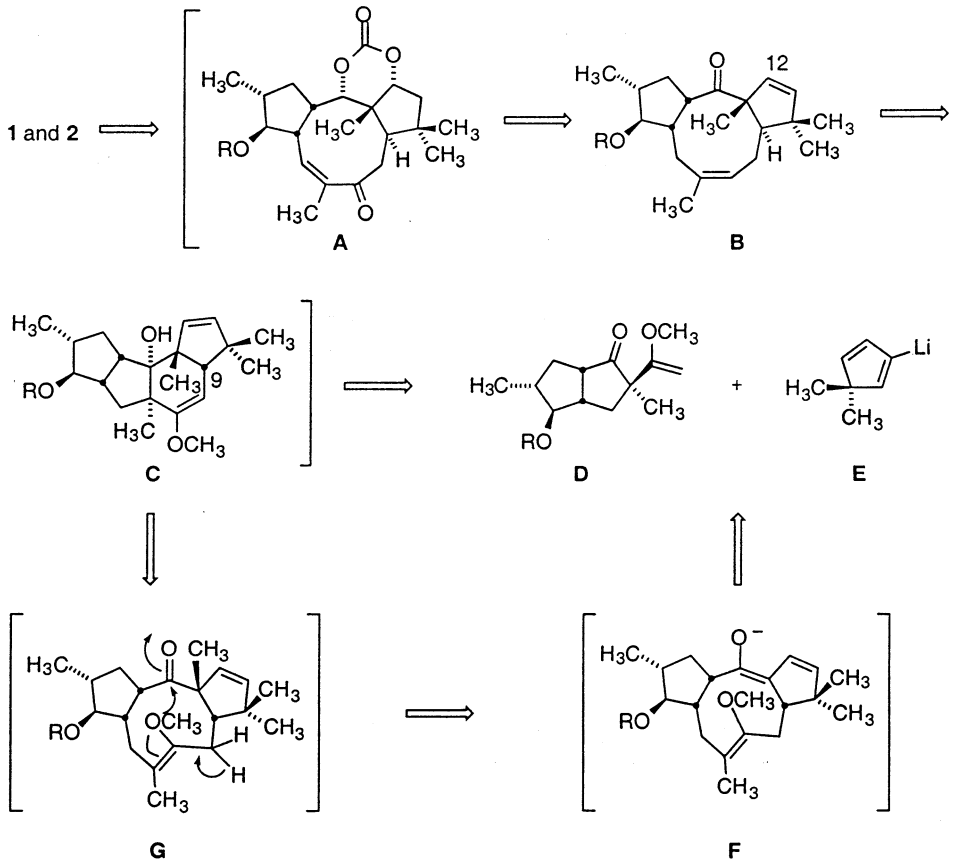
(1) Torrance, S. J.; Wiedhopf, R. M.; Cole, J. R.; Arora, S. K.; Bates, R. B.; Beavers, W. A.; Cutler, R. S. *J. Org. Chem.* **1976**, *41*, 1855.
(2) (a) Kupchan, S. M.; Sigel, C. W.; Matz, M. J.; Saenz Renauld, J. A.; Haltiwanger, R. C.; Bryan, R. F.; *J. Am. Chem. Soc.* **1970**, *92*, 4476. (b) Haltiwanger, R. C.; Bryan, R. F. *J. Chem. Soc. B* **1971**, 1598. (c) Kupchan, S. M.; Sigel, C. W.; Matz, M. J.; Gilmore, C. J.; Bryan, R. F. *J. Am. Chem. Soc.* **1976**, *98*, 2295.
(3) Villarreal, A. M.; Dominguez, X. A.; Williams, H. J.; Scott, A. I.; Reibenspies, J. *J. Nat. Prod.* **1988**, *51*, 749.
(4) For a preliminary communication delineating our concise approach to jatrophatrione, consult Paquette, L. A.; Yang, J.; Long, Y. O. *J. Am. Chem. Soc.* **2002**, *124*, 6542.
(5) (a) Paquette, L. A.; Nakatani, S.; Zydowski, T. M.; Edmondson, S. D.; Sun, L.-Q.; Skerlj, R. *J. Org. Chem.* **1999**, *64*, 3244. (b) Paquette, L. A.; Edmondson, S. D.; Monck, N.; Rogers, R. D. *J. Org. Chem.* **1999**, *64*, 3255.

10.1021/ja021177r CCC: $25.00

Scheme 1



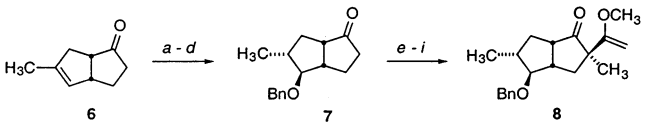
Scheme 2



responsive to [3.3] oxyanionic sigmatropy. The operation of this ring expansion allows for generation of the highly reactive enolate anion **F**. The latter intermediate was expected to experience stereocontrolled α-methylation from the convex surface, thereby setting the stage for an anticipated transannular ene reaction as illustrated in **G**. Moving further along the retrosynthetic path, there was made clearly apparent the need to invert the configuration at C9 in **C** as the mesocyclic[7] nature of the central ring was reestablished. The first tactic was to be addressed by hydroxyl-directed reduction of a derived enone, the second by utilization of a Grob fragmentation.[8] The generation of **B** in this fashion was to be followed by reduction to the α-alcohol and regiocontrolled oxygenation at C12 by intramolecular hydrosilylation.[9] In this way, dehydration to

(6) The feasibility of attaining stereocontrol by rotation around the σ bonds flanking an olefinic linkage has been previously demonstrated by us in a tricyclic precursor to taxusin: (a) Paquette, L. A.; Zhao, M. *J. Am. Chem. Soc.* **1993**, *115*, 354. (b) Paquette, L. A.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5203.
(7) See footnote 4 in Leonard, N. J.; Milligan, T. W.; Brown, T. L. *J. Am. Chem. Soc.* **1960**, *82*, 4075.
(8) Review: Becker, K. B.; Grob, C. A. *Chem. Double-Bonded Funct. Groups* **1977**, *2*, 653−723.
(9) Magnus, P. D.; Nobbs, M. S. *Synth. Commun.* **1980**, *10*, 273.

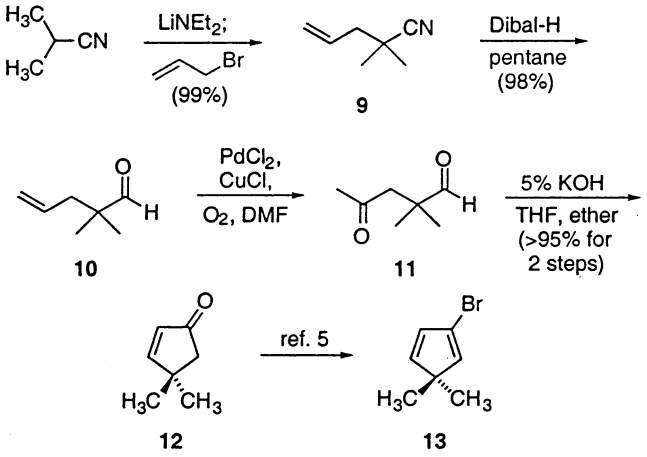
Scheme 3 [a]



6 7 8

[a] (a) $(CH_3O)_3CH$, CH_3OH, TsOH (88%). (b) BH_3·THF; H_2O_2, NaOH (81%). (c) KH, BnBr, Bu_4NI (95%). (d) TsOH, acetone, H_2O (98%). (e) LDA, CH_3I, THF, HMPA (75%). (f) Me_3SiCl, Et_3N (90%). (g) AcCl, $ZnCl_2$ (60%). (h) $(CH_3O)_3CH$, CH_3OH, TsOH (71%). (i) 450 °C, 0.4 Torr, quartz chips (95%).

Scheme 4



9 10 11 12 13

introduce the C3−C4 double bond would precede unmasking of the sensitive 1,3-dicarbonyl functionality.

This retrosynthetic plan can most conveniently be divided into three subsequences: the construction of a diquinane of type **D**; the structural reorganization and other key factors associated with formation of the tricyclic framework defined in **B**; and proper introduction of the remaining functional groups.

Synthesis of the Diquinane Subunit

A means for the construction of a structural analogue of **8** has been described in a preceding paper.[5] Only the significant changes involved in the chemical modification of **6** will therefore be stressed (Scheme 3). Presently, the carbonyl group in **6** was protected as the dimethyl acetal in order to take advantage of efficiency greater than that associated with 1,3-dioxolane production. Following conventional hydroboration, the β-hydroxyl group was transformed into the benzyl ether. This tactic ultimately proved well suited to the eventual return to an unmasked OH at this site. As expected, the benzyloxy substituent proved resistant to the Lewis acid-catalyzed acetylation of the intermediate silyl enol ether and to the flash vacuum pyrolysis conditions required to achieve the thermal extrusion of methanol. The efficiency with which **8** was isolated (95%) is noteworthy.

Construction of the Tricyclic Nucleus

The strategy derived from the retrosynthetic analysis presented earlier required the availability of 1-bromo-3,3-dimethylcyclopenta-1,3-diene (**13**), the precursor to which is 4,4-dimethyl-2-cyclopentenone (**12**, Scheme 4). This ketone has traditionally been prepared by the Magnus method,[9] the steps in which have long been realized to be capricious and labor-intensive. The significantly more convenient route summarized in Scheme 4 was therefore implemented here. This sequence of reactions is not scale-limited and offers excellent throughput. The correct number of carbon atoms is set at the outset by C-allylation of the isobutyronitrile anion, as generated with lithium diethylamide.[10] The Dibal-H reduction[11] that immediately follows gave aldehyde **10**, which proved to be an excellent substrate for Wacker oxidation as earlier recognized.[9]

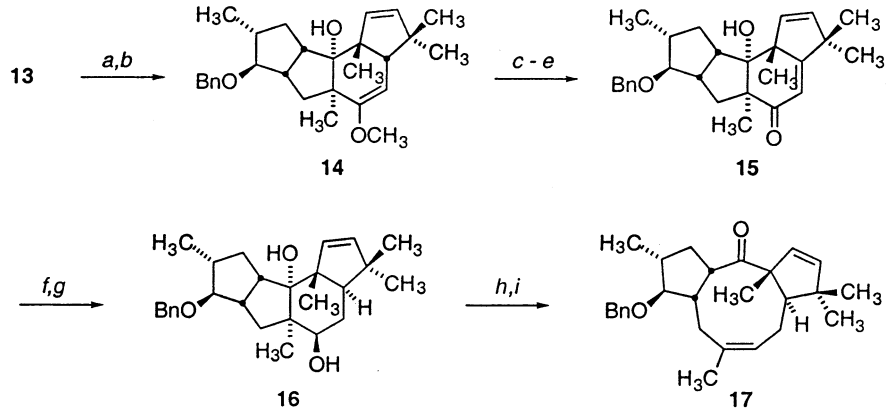
It was now time to couple **8** and **13**, and use was made of dried cerium trichloride[12] to curtail the ready enolizability of the ketone component (Scheme 5). The generation of this adduct will be recognized to establish the cisoid relationship of the enol ether and cyclopentadiene double bonds necessary for successful oxy-Cope rearrangement. In light of considerable precedent,[13] advancement to ring-expanded product was expected to proceed via a chairlike transition state to set the configuration of the cyclononadienyl olefinic centers as in **F** (Scheme 2). Methylation of this strained enolate anion generates a species of type **G**, the structural distortion in which orients the carbonyl oxygen in close proximity to an allylic hydrogen atom across the ring. The ensuing transannular hydrogen atom transfer with ring closure to furnish **14** is thereby facilitated.

With the availability of **14**, we were in a position to investigate an efficacious means for effecting epimerization at C9. Treatment with *N*-bromosuccininide (NBS) in aqueous tetrahydrofuran (THF) resulted in the concurrent generation of an α-bromo ketone moiety and a bromo oxetane ring.[5] This intermediate was then carried through the stage where heating with lithium bromide and lithium carbonate in dimethylformamide (DMF)[14] gave rise to the α,β-unsaturated ketone. Since the deployment of reducing conditions was about to begin, it became first necessary to remove the remaining bromine atom. The optimum conditions for the conversion to **15** involved stirring with powdered zinc in methanol.

With arrival at **15** came opportunities to screen various protocols that are offered by hydroxyl-directed hydrogenation.[15] As expected from the classical work of Henbest and Wilson,[16] exposure of **15** to buffered peracetic acid resulted in the stereoselective formation of α-epoxide **18** (Scheme 6). To further enrich the number of substrates available for study, **18** was subjected to Luche reduction,[17] from which only the isomer with a second α-hydroxyl group was obtained. The slow rate of this process served to highlight the heightened steric congestion prevailing in **18**. The stereochemical assignment to **19** was founded on an 8.7% nuclear Overhauser enhancement (NOE) at H7 when H15 was irradiated. Our rather extensive efforts to accomplish proper saturation of the C8−C9 double bond in both **18** and **19** were singularly unsuccessful. We shall therefore restrict our comments to a few more notable observations. Thus, hydrogenation of **19** over Crabtree's catalyst[15d] at

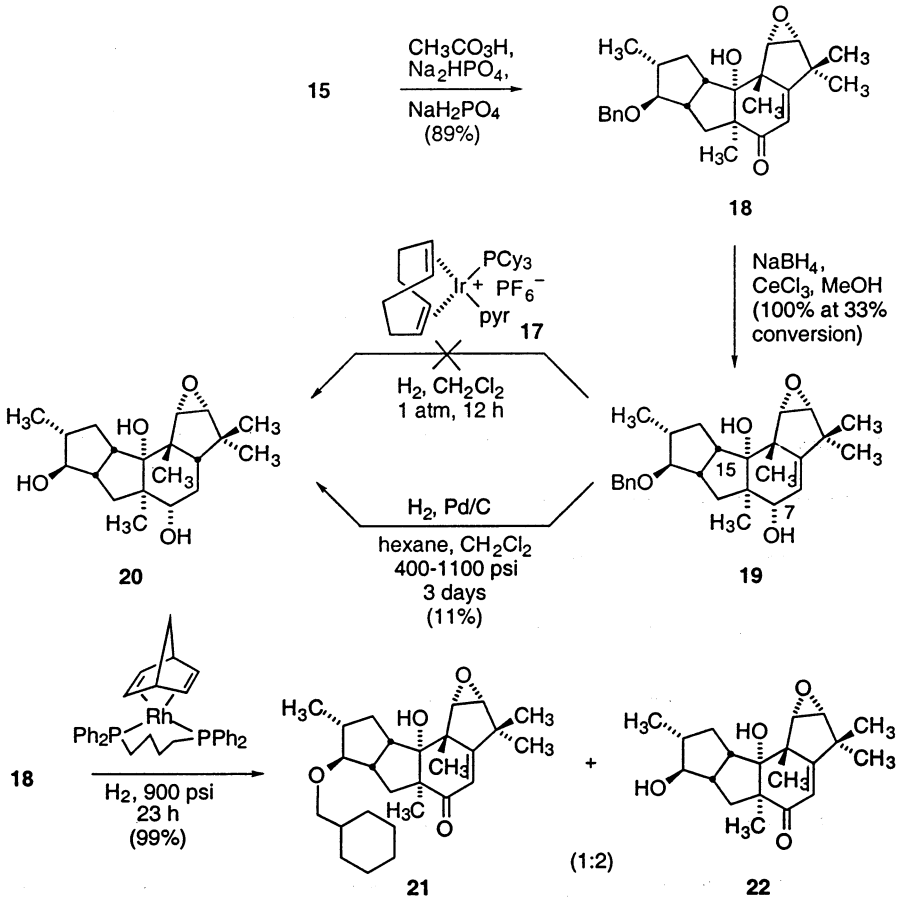
(10) Julia, S.; Julia, M.; Linstrumelle, G. *Bull. Soc. Chim. Fr*. **1966**, 3499.
(11) Marshall, J. A.; Andersen, N. H.; Schlicher, J. W. *J. Org. Chem*. **1970**, *35*, 858.
(12) Paquette, L. A. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley and Sons: Chichester, U.K., 1995; p 1031.
(13) Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971. (b) Paquette, L. A. *Angew. Chem., Int. Ed. Engl*. **1990**, *29*, 609.
(14) For lead references, see Wang, X.; Paquette, L. A. *Tetrahedron Lett*. **1993**, *34*, 4579.
(15) (a) Thompson, H. W.; McPherson, E. *J. Am. Chem. Soc.* **1974**, *96*, 6232. (b) Brown, J. M.; Naik, R. G. *J. Chem. Soc., Chem. Commun*. **1982**, 348. (c) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc*. **1983**, *105*, 1072. (d) Crabtree, R. H.; Davis, M. W. *J. Org. Chem*. **1986**, *51*, 2655. (e) Paquette, L. A.; Peng, X.; Bondar, D. *Org. Lett*. **2002**, *4*, 937.
(16) Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc*. **1957**, 1958.
(17) (a) Luche, J.-L. *J. Am. Chem. Soc*. **1978**, *100*, 2226. (b) Luche, J.-L.; Rodriguez-Hahn, L.; Crabbé, P. *J. Chem. Soc., Chem. Commun*. **1978**, 601.

Scheme 5 [a]



[a] (a) *t*-BuLi; $CeCl_3$, **8** (80%). (b) KO*t*-Bu, 18-cr-6; CH_3I (70%). (c) NBS, THF, H_2O (92%). (d) LiBr, Li_2CO_3, DMF, Δ (81%). (e) Zn, MeOH (83%). (f) $LiAlH_4$, CuI, HMPA. (g) $LiAlH_4$, ether (88%). (h) MsCl, $(i\text{-Pr})_2NEt$ (98%). (i) KO*t*Bu, *t*-BuOH (87%).

Scheme 6



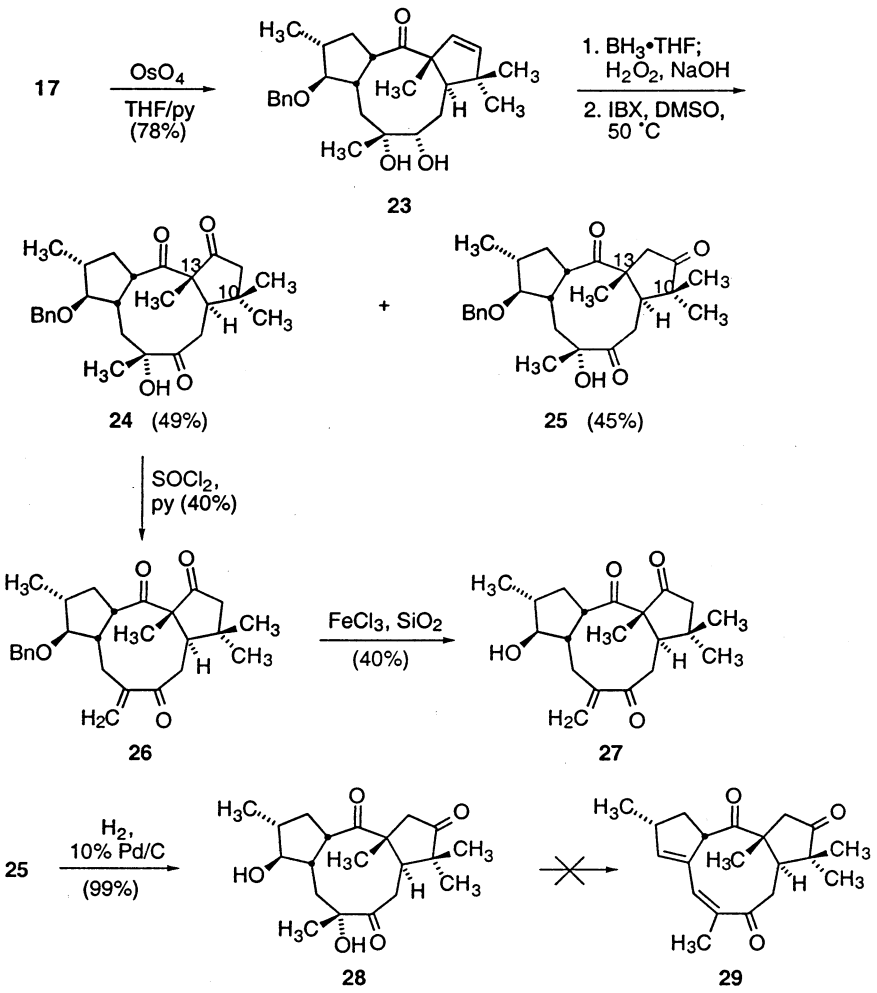
elevated pressures gave rise to ill-defined multicomponent reaction mixtures. At lower pressures, no reaction was seen. Palladium on carbon (5%) afforded similar results. When reduction was allowed to proceed at 400−1100 psi for 3 days, there could be isolated 11% of the unwanted diastereomer **20**. When similar attempts were made to saturate **18** by means of catalysis involving $[Rh(NBD)(DIPHOS\text{-}4)]BF_4$,[18] reduction of the phenyl group as in **21** and hydrogenolysis as in **22** were uniquely observed (ratio 1:2).

The demise of this strategy prompted our return to an examination of the conjugate reduction of **15**. In particular, we were attracted to a brief report by Saegusa and co-workers[19] in which the ability of CuI to promote the efficient 1,4-reduction of enones by $LiAlH_4$ in the presence of hexamethylphosphoramide (HMPA) as cosolvent was touted. In our hands, these conditions proved to be more useful than we had hoped. The major product (77%) was the dihydro ketone in which hydride delivery had occurred predominantly syn to the hydroxyl. The stereoselectivity was greater than 14:1. Diol **22** was also produced (12%). When we recognized this outcome, the initially formed mixture was routinely reduced with $LiAlH_4$ to convert all of the product to **16** (88% isolated, Scheme 5),[20] the

(18) (a) Corey, E. J.; Engler, T. A. *Tetrahedron Lett.* **1984**, *25*, 149 (b) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866.

(19) Tsuda, T.; Fujii, T.; Kawasaki, K.; Saegusa, T. *J. Chem. Soc., Chem. Commun.* **1980**, 1013.

Scheme 7



stereochemical features of which were corroborated by 2D NMR spectroscopic techniques and direct comparison with the 9β epimer, which was already available to us.

Tricyclic ketone **17** was subsequently synthesized by formation of the monomesylate of **16** and exposure of this intermediate to potassium *tert*-butoxide in *tert*-butyl alcohol at room temperature for 1 h. The efficiency of this two-step sequence (85%) was matched by the welcome appearance of the cyclononenone carbonyl absorption at 1677 cm^{-1}.[21]

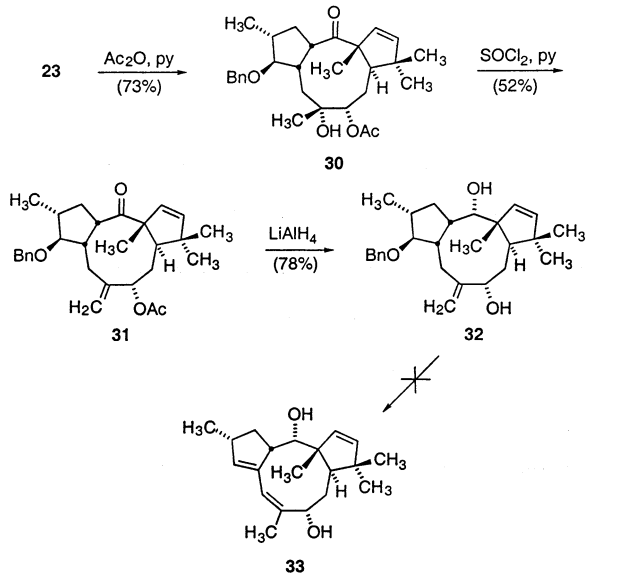
Exploratory Functionalization Studies

In our first experiments involving **17**, we were concerned with establishing the dienone functionality along the leading edge (C3−C7). Accordingly, this intermediate was allowed to react with osmium tetraoxide and pyridine in THF (Scheme 7). Even under stoichiometric conditions, dihydroxylation proceeded slowly and stereoselectively. Significantly, only the C6−C7 double bond was attacked to furnish **23** (78% based on recovered **17**), and no tendency was exhibited by this product for transannular hemiketalization. The subsequent hydroboration of **23** was followed by *o*-iodoxybenzoic acid (IBX) oxidation.[22] This two-step sequence afforded triketones **24** and **25** in approximately equal amounts. The separation of these regioisomers was easily accomplished by chromatography on silica gel, and their structural assignments could be made with confidence by comparative analysis of chemical shifts and 2D NMR analysis. For example, C13 in **24** is flanked by two carbonyl groups and is consequently shifted more downfield (65.5 ppm) than its counterpart in **25** (54.3 ppm). Similarly, C10 in **24** (38.1 ppm) is more upfield than that in **25** (48.7 ppm).

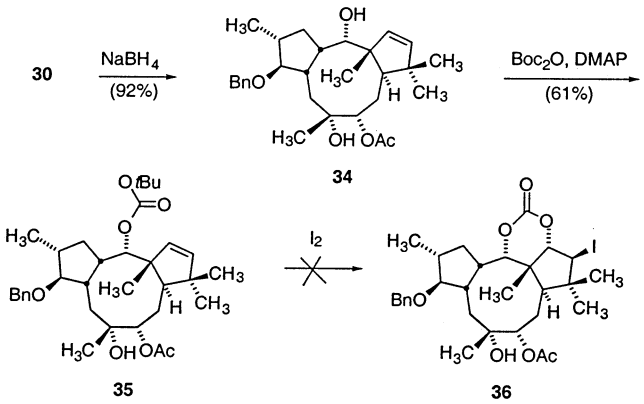
The dehydration of **24** became our next goal. After a series of experiments showed this to be an erratic transformation, we settled on the use of thionyl chloride in pyridine for this purpose. Only the exocyclic olefin isomer **26** could be characterized. Careful examination of the literature suggested that exposure of **26** to silica gel on which 10% $FeCl_3$ had been previously adsorbed might provide the activation required for internal migration of the double bond with subsequent elimination of benzyl alcohol.[23] If successful, these relatively mild conditions would introduce the targeted dienone moiety in rather efficient fashion. This optimism was dashed, however, when it was determined that this solid-phase reagent only brought about unprecedented debenzylation without dehydration as in **27**. We note here our inability to generate the xanthate of **27** as a direct result of the general sensitivity of this class of triketones to basic reagents.

(20) In contrast, the direct reduction of **25** with $LiAlH_4$ in the absence of CuI and HMPA afforded **26** in only 11% yield.
(21) Paquette, L. A.; Pegg, N. A.; Toops, D.; Maynard, G. D.; Rogers, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 277.
(22) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019.
(23) Keinan, E.; Mazur, Y. *J. Org. Chem.* **1978**, *43*, 1020.

Scheme 8



Scheme 9



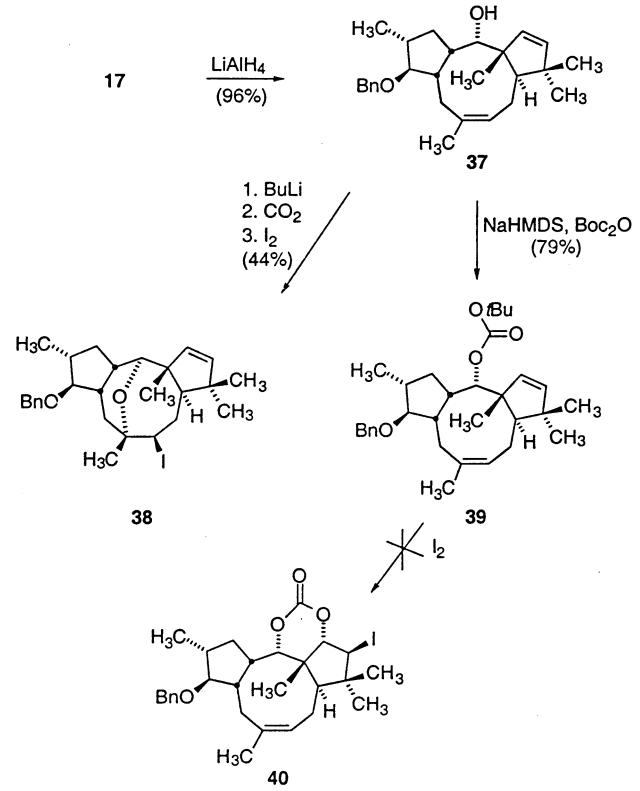
To validate these observations, **25** was subjected to hydrogenolysis, and the resulting **28** was subjected to a series of dehydration experiments. Under no circumstances was evidence for conversion to **29** uncovered.

Inasmuch as **23** could be monoacetylated to give **30** (Scheme 8), we were led to scrutinize as well its response to attempted dehydration. Like **24**, an exclusive tendency to position the newly formed double bond external to the nine-membered ring as in **31** was seen. In light of these developments, it was not surprising to find that conditions for transforming **32** into **33** were not found despite a considerable expenditure of effort. Most notable among these studies was our discovery that the highly touted KAPA reagent[24] had no effect on **32**.

Operating on the belief that a change in conformational topology would be contributory to more facile dehydration, we were attracted to the iodocyclization of the homoallylic *tert*-butyl carbonate **35** (Scheme 9). Were the conversion to **36** to be realizable, a significant ensemble of dihedral angle alterations would be set in place relative to the state of affairs resident in **35** and its congeners. To this end, diol **34** was readily formed by sodium borohydride reduction of **30** and lent itself conveniently to conversion to **35**. The real issue that lay before us, the cyclization of **35** in the presence of iodine, could, however, not be implemented under a variety of conditions.[25]

In light of the preceding observations, our attention was redirected to intermediates having the cyclononene double bond

Scheme 10



in its original interior position. This alternative plan, outlined in Scheme 10, was initiated by the reduction of ketone **17** to alcohol **37** with lithium aluminum hydride. The conversion of **37** to the homoallylic carbonate was accomplished by bubbling CO_2 into a THF solution of the corresponding lithium alkoxide as originally described by Cardillo et al.[26] On the basis of earlier work by the Bologna group, the treatment of this intermediate with iodine was expected to result in cyclofunctionalization of the cyclopentene ring and regioselective formation of an iodocarbonate structurally related to **36**. This process did not materialize, iodo ether **38** being formed instead in modest yield.

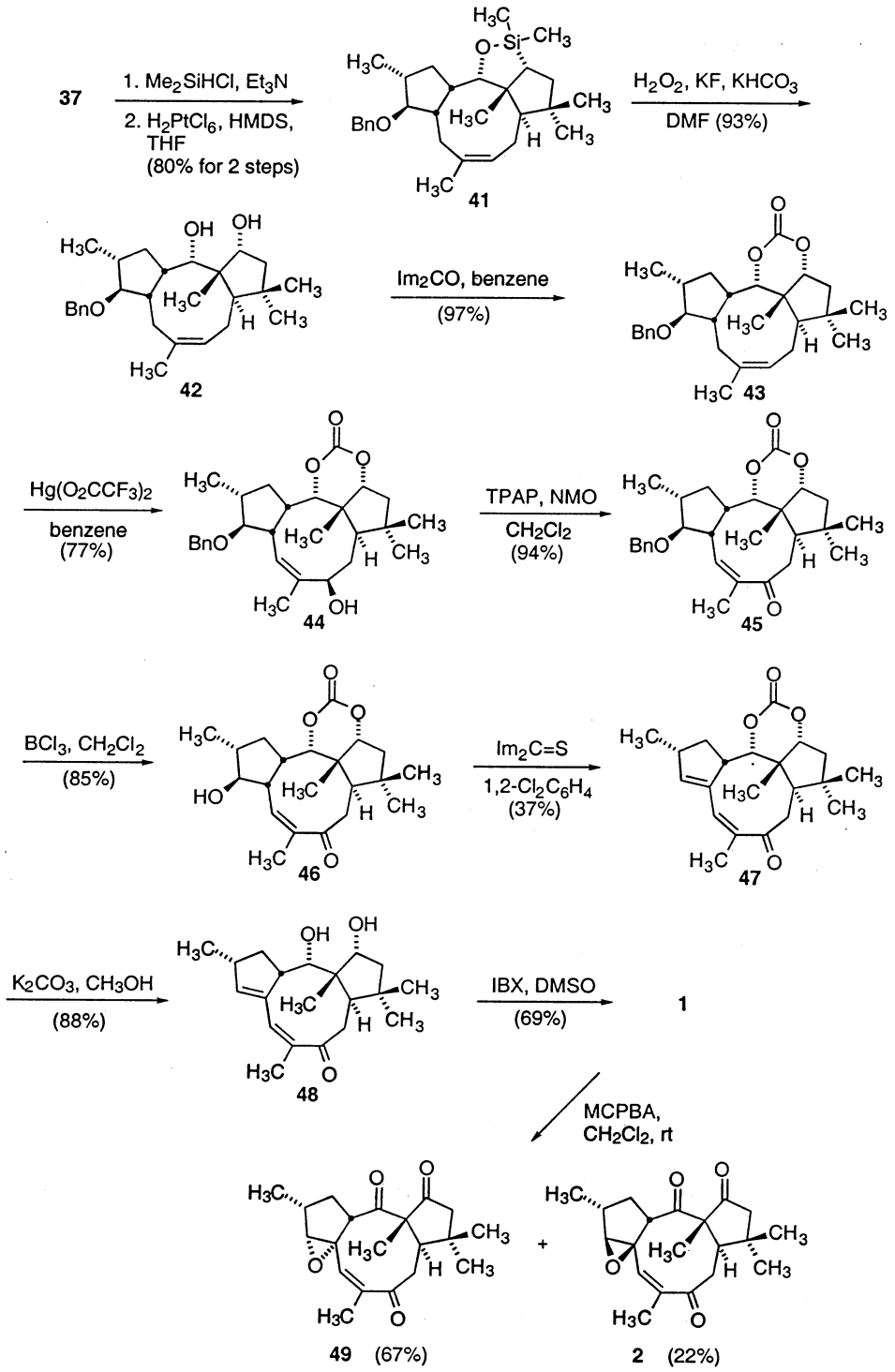
Although halo etherifications have been known for some time,[27] we are unaware of any prior example that proceeds with initial decarboxylation of a lithium carbonate. The disincentive of these systems for entering into carbonate formation across C12 and C14 was further reinforced by our inability to bring about the conversion of **39** into **40**.

The End Game Protocol

With identification of the problematic step discussed above, we moved to consider the possibility of implementing intramolecular hydrosilylation technology for ultimately bonding an oxygen atom cleanly to C12. This tactic is not predicated on the initial generation of a halonium ion in a highly congested environment and proceeds instead by platinum-catalyzed internal capture of a silyl hydride.[28] At the experimental level, the

(24) (a) Brown, C. A. *Synthesis* **1978**, 754. (b) Abrams, S. R.; Shaw, A. C. *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. VIII, p 146.
(25) (a) Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013. (b) Duan, J. J.-W.; Smith, A. B., III *J. Org. Chem.* **1993**, *58*, 3703.
(26) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Chem. Soc., Chem. Commun.* **1981**, 465.
(27) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3B, Chapt. 6.

Scheme 11



generation of **41** from **37** proved to be a spectacularly successful and efficient step (Scheme 11). We envisioned that the carbon−silicon bond formed in this manner would be preserved until rather late into the synthesis, and some effort was expended in this direction because of the economy of chemical steps that it offered. However, this oxidative cleavage could not be deferred because of the conditions necessarily implemented during installation of the dienone sector. Therefore, the oxidation of **41** with potassium fluoride and hydrogen peroxide was merged with subsequent heating of diol **42** with carbonyldiimidazole[29] to arrive at cyclic carbonate **43**. The oxidative step proceeded very slowly under the conventional conditions that prescribe the co-use of potassium bicarbonate in aqueous THF.[30] However, when alternative recourse was made to DMF as the reaction medium,[31] the reaction time was shortened to 8 h and a 97% yield of **42** was consistently realized.

The task of elaborating the functionality present in the carbon atoms defined by C3−C7 now had to be addressed. When

(28) (a) Tamao, K.; Nakajima, T.; Sumiya, R.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6090. (b) Tamao, K.; Tanaka, T.; Nakajima, T.; Sumiya, R.; Arai, H.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 3377.
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(30) Review: Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599.

possible solutions based on regiodirected epoxide ring cleavages or on conventional allylic oxidation schemes proved to no avail, it was made clear that this challenge had to be resolved in a different manner. In 1948, Treibs briefly described his observations involving the allylic acetoxylation of olefins upon heating with mercuric acetate in acetic acid.[32] This process has been adopted only infrequently since that time,[33−35] seemingly because the conditions have generally come to be regarded as somewhat too forcing. At the mechanistic level, the mercuric reagent presumably attacks the π bond to generate a mercurinium ion, the rearrangement of which to an allylic organomercurial sets the stage for solvolysis with formation of Hg(0) and one or both epimeric allylic acetates.[33,36] On this basis, it was anticipated that heating **43** with mercuric trifluoroacetate in benzene followed by stirring with aqueous sodium bicarbonate might possibly lead stereoselectively to **44** in a simple *one-pot* operation. Indeed, these conditions led smoothly to the formation of **44** in an isolated yield of 77%. We attribute the remarkably good regioselectivity of this transformation to the unsymmetrical nature of the putative mercurinium ion, whose biased "open character" places a modicum of positive charge on the methyl-substituted carbon (C6) and induces more facile deprotonation at C5 as allylic mercurial character develops.[37] No allylic alcohol having an exocyclic double bond was noted, a feature that hints at the possible operation of thermodynamic control.

With the preparation of **44** accomplished, oxidation with tetra-*n*-propylammonium perruthenate (TPAP)[38] was undertaken to give **45**, the benzyloxy group in which was cleaved with boron trichloride in CH_2Cl_2.[39] The last major hurdle, the regiodirected dehydration of **46**, now had to be addressed. Two considerations held central importance as we assessed this step. First, a syn elimination of the C3 hydroxyl was mandated in either of the two regiochemical options. Also, pilot studies carried out on less advanced analogues of **46** revealed a strong kinetic preference for avoidance of the site of ring fusion. Since these model systems lacked the C5−C6 double bond, our working proposition was that the enone segment might well induce a higher level of acidification at H4 relative to H2 despite the nonplanarity of this chromophore.

We initially engaged **46** in xanthate formation, only to discover that this hydroxy ketone is sensitive to basic reagents. Its vinylogous aldol character is likely responsible for this behavior. In contrast, the targeted dehydration could be brought about without event simply by heating **46** with thiocarbonyldiimidazole in 1,2-dichlorobenzene.[40] This tactic lent itself to the formation of a two-component product mixture, chromatographic separation of which furnished in 37% yield the target dienone **47** and 10% of the $\Delta^{2,3}$-regioisomer.

We could now undertake hydrolysis of the cyclic carbonate ring. With K_2CO_3 in methanol at room temperature, the conversion of **47** to **48** was complete in 3 h (88%). This reaction time is significantly longer than the 5 min required to perform the quantitative saponification of **44** under identical conditions.[41] This kinetic inequality can be traced to a more elevated level of ring strain in **44**. The 2-fold oxidation of **48** to jatrophatrione (**1**) was mediated by IBX in dimethyl sulfoxide (DMSO).[22] The synthetic material produced in this manner exhibited a 500 MHz ^{1}H NMR spectrum fully consistent with that of the natural sample recorded earlier at lower field strength.[42] However, the ^{13}C NMR data originally reported differs from our measurements made at 100 and 125 MHz in a systematic way ($\rho = 0.998$). As detailed elsewhere,[43] a minor complication associated with the dwell clock in their Fourier transform spectrometer of those involved in the isolation of **1** is likely responsible for this phenomenon.

Notwithstanding, we can confidently assert that the total synthesis of racemic jatrophatrione has indeed been accomplished since the treatment of **1** prepared as detailed above with *m*-chloroperbenzoic acid in CH_2Cl_2 at room temperature leads unmistakably to citlalitrione (**2**, 22%) alongside a greater proportion of the unnatural α-epoxide **49** (67%). In this instance, the ^{1}H and ^{13}C NMR spectra of synthetic **2** were identical to those registered for the natural sample, whose structural features had previously been secured by means of X-ray crystallography.

Summary

The first total syntheses of two representative [5.9.5] tricyclic diterpenoids have been accomplished. The several noteworthy facets of this venture include an anionic oxy-Cope rearrangement that conveniently sets in place a tetracyclic structural framework (viz., **14**) capable of ready chemical modification. With arrival at **17** only seven steps later, it becomes possible to hydroxylate C12 and C14 via intramolecular hydrosilylation and to protect this pair of α-OHs as a cyclic carbonate. Application of the Treibs reaction to **43** constituted a particularly productive step, with the resulting allylic alcohol **44** serving as a reliable platform for regiocontrolled dehydration as defined by **46** → **47**. Finally, the 1,3-diketone segment is introduced to deliver jatrophatrione (**1**), subsequent peracid oxidation of which gives (±)-citlalitrione (**2**). The length of the linear sequence from the point of convergence is 20 steps. We anticipate that the successful route to **1** and **2** detailed herein will significantly facilitate the rational synthesis of other diterpenoids of this class.

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Supporting Information Available: Complete experimental procedures and spectral data for all previously unreported compounds described herein, including copies of the ^{1}H NMR spectra of synthetic jatrophatrione as well as natural and synthetic citlalitrione (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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