Tetrahedron 67 (2011) 10129–10146

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Synthesis of (±)- and (+)-perovskone☆

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ARTICLE INFO

*Article history:*
Received 23 July 2011
Received in revised form 15 September 2011
Accepted 16 September 2011
Available online 22 September 2011

*Keywords:*
Perovskone
Cyclialkylation
Friedel–Crafts alkylation
Cascade reaction
Pd–π–allyl chemistry and one-pot reaction

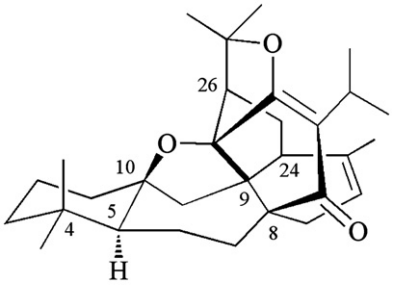
ABSTRACT

A biomimetic synthesis of the triterpene (±)-perovskone was achieved featuring a remarkable polycyclization process in which three rings, four bonds, and five stereocenters were created in a single operation in 82% yield. This convergent synthesis required 16 steps, starting from vanillin, and proceeded in 9% overall yield. A second route to prepare optically active quinone **2** took 15 steps in 36% overall yield and featured a palladium-catalyzed reductive allylic transposition to establish the C-5 chirality stereospecifically. Quinone (−)-**2** was converted to (+)-perovskone (**1**) via a polycyclization cascade, which created four rings, five bonds, and six stereocenters in a single operation in 50% yield.



## 1. Introduction

*Perovskia abrotanoides*, a member of the plant family Lamiaceae,[1] is a highly branched shrub found in Afghanistan, Baluchistan, and in the Northwest Frontier provinces of Pakistan. This plant is used locally in the Baluchistan area as a cooling medicine[2] and as a remedy for typhoid fever.[3,4]



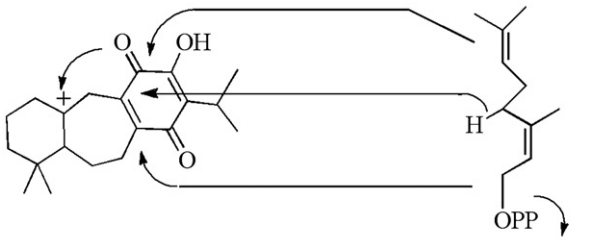

perovskone (**1**)

**Fig. 1.** Structure of perovskone.

In 1992 Ahmad and co-workers isolated the triterpene perovskone (**1**) from *P. abrotanoides*, *Karel syn. P. artemisioides* Boiss (Labiatae) (Fig. 1).[5] Perovskone contains a complex array of seven fused and bridged rings as well as seven asymmetric centers, thus posing a formidable challenge to total synthesis. Here we describe in detail our syntheses of (±)- and (+)-perovskone in which four of the seven rings and six of the seven stereocenters are established in a one-pot process.[6,7]

## 2. Results and discussion

The biosynthesis of perovskone, as proposed by Ahmad and co-workers, involves the addition of geranyl pyrophosphate to an icetexone precursor (Fig. 2).[8] This prompted us to mimic nature by using a Diels–Alder addition[9] of (*E*)-β-ocimene (**3**) to *p*-quinone **2**




an icetexone precursor

geranyl pyrophosphate

**Fig. 2.** Two conformations of quinone **2**.

☆ This article is part of a special issue honoring the many scientific contributions of Professor Gilbert Stork and in celebration of his 90th birthday.

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† Taken in part from the M.S. thesis of Jonathan E. Britton, University of Georgia (2002).

‡ Taken in part from the Ph.D. dissertation of Yang Li, University of Georgia (2006).

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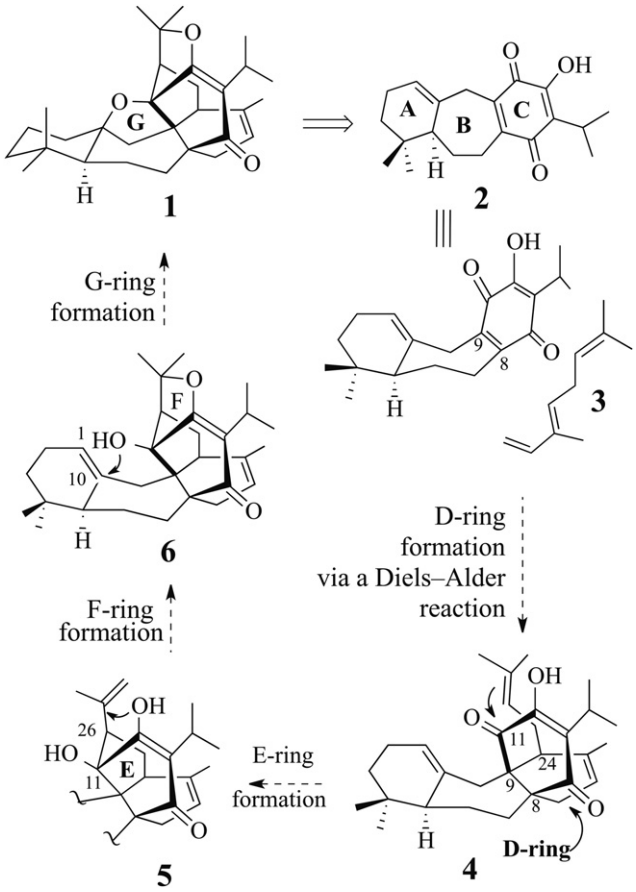
doi:10.1016/j.tet.2011.09.072

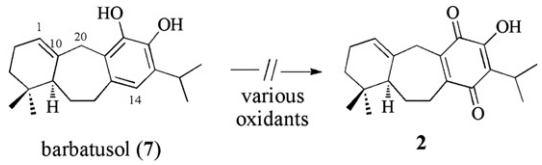
to assemble the critical D-ring (Scheme 1). Inspection of Drieding molecular models suggested that a diene would add to the α-face of dienophile **2**, creating the correct relative configurations at C-8, C-9, and C-24. In addition, the use of ocimene as the diene component




**Scheme 1.**

would subsequently permit ocimene the formation of the C-11,C-26 bond and the final carbocyclic ring (i.e., *E*) by an intramolecular Prins reaction involving the C-11 ketone of cycloadduct **4**. The acid-catalyzed formation of the heterocyclic F- and G-rings completes our perovskone retrosynthetic analysis (i.e., **4**→**5**→**6**→**1**).

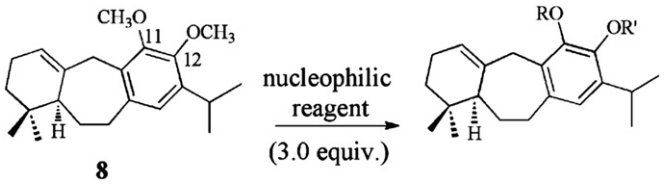
Recognition that the oxidation of barbatusol (**7**), for which we had already developed an eight-step synthesis,[10] would directly afford *p*-quinone **2** greatly influenced our synthetic strategy (Scheme 2). Unfortunately, the oxidation of barbatusol gave an unstable *o*-quinone.[11] Attempts to convert barbatusol methyl ether (**8**) to quinone **2** produced enones corresponding to oxidation at either C-20 or at C-1 arising from an allylic rearrangement.




**Scheme 2.**

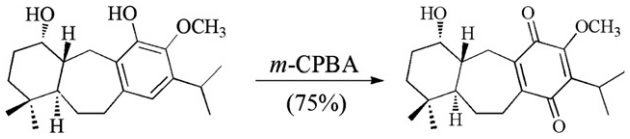
We were hopeful that selectively deprotecting the C-11 methoxy group of **8** would permit the oxidation of C-14 under mild conditions (Table 1). Traditional acidic demethylation conditions moved the C-1,C-10 double bond into conjugation,[11b] so the nucleophilic

**Table 1**
Regioselective demethylation using bulky alkylthiolates




| Nucleophilic reagent | Reaction temperature (°C) | Chemical yield (%) | Product(s) |
|---|---|---|---|
| NaS-Et | 150 | 65 | R=R′=H (**1**) |
| NaS-Et | 50 | 86 | R=H; R′=$CH_3$ (**9a**) R=$CH_3$; R=H (**9b**) **9a**/**9b**=3:2 |
| NaS-*i*-Pr | 65 | 75 | **9a**/**9b**=3:2 |
| NaS-*t*-Pr | 50 | 52 | **9a**/**9b**=2:1 |
| L-Selectride | 90 | 92 | **9a** only |

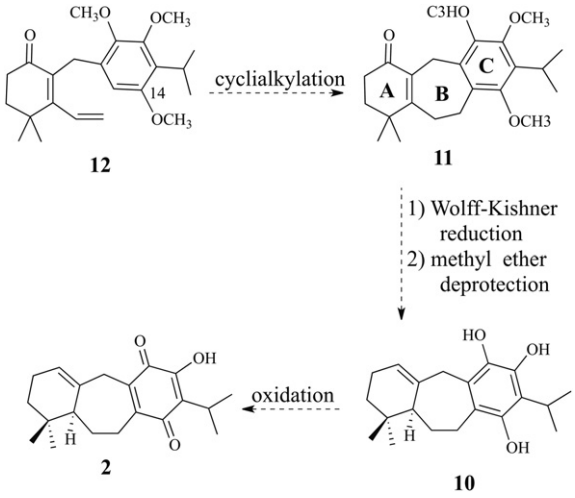
conditions developed by Feutrill and Mirrington[12] were examined. Complete demethylation of **8** was achieved upon treatment with excess sodium ethylthiolate in DMF at 150 °C. We speculated that either lower reaction temperatures or the use of bulky alkylthiolates might result in the selective deprotection of the more sterically accessible C-11 methoxy group; however, only modest selectivity was observed at temperatures between 50 °C and 60 °C with the sodium alkylthiolates studied (Table 1). In 1994, we reported that L-Selectride efficiently deprotects aryl methyl ethers and often exhibits a profound steric bias.[13] Indeed, treatment of **8** with L-Selectride gave only phenol **9a** in 92% yield. Unfortunately, the oxidation of **9a** to a *p*-quinone using mild oxidants like Fremy's salt,[14a] Rapoport's conditions (AgO and nitric acid),[14b] or HgO[14c] failed. Strong oxidants, such as $H_2O_2$,[14d] *m*-CPBA or $CrO_3$,[14e] oxidized the C-1,C-10 double bond instead. Extensive work established that a *p*-quinone could be prepared from a barbatusol-derived precursor if the phenol was the only oxidizable functional group present (Scheme 3).




**Scheme 3.**

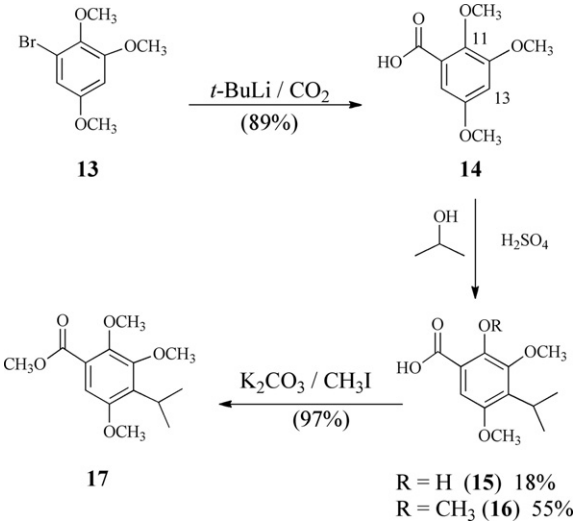
These observations led us to prepare hydroquinone **10**, which should oxidize under mild conditions without compromising the C-1,C-10 double bond (Scheme 4). Execution of this revised strategy required the synthesis of dienone **12** possessing an additional methoxy group at C-14.

Our synthesis of dienone **12** began with 1-bromo-2,3,5-trimethoxybenzene (**13**), which is available from vanillin in three steps in 63% overall yield.[15] Treatment of **13** with *tert*-butyllithium, followed by quenching the resultant carbanion with gaseous carbon dioxide, gave benzoic acid **14** in 89% yield (Scheme 5). An acid-catalyzed Friedel–Crafts alkylation using 2-propanol introduced the required isopropyl unit at C-13. Some cleavage of the C-11 methoxy group also occurred under these acidic conditions. Instead of isolating phenolic acid **15**, the crude mixture of benzoic acids **15** and **16** was treated with an excess of $K_2CO_3$ and iodomethane[16] and the resulting mixture was refluxed for 12 h. These conditions achieved the esterification of the benzoic acid and the reprotection of the C-11 hydroxyl group in nearly quantitative yield.



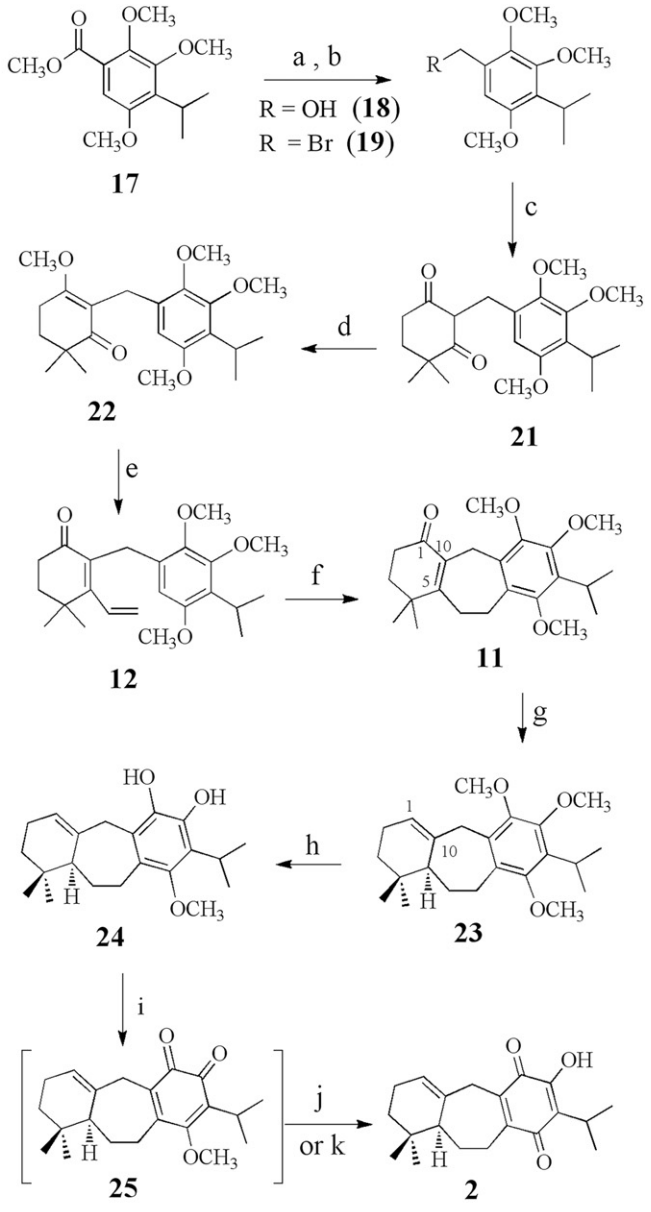

**Scheme 4.**

Ester **17** was converted into quinone **2** via the nine transformations shown in Scheme 6. The reduction of **17** and the conversion of benzylic alcohol **18** to benzylic bromide **19** were straightforward. Alkylation of 4,4-dimethyl-1,3-cyclohexanedione (**20**) with **19** furnished the *mono*-alkylated dione **21** in 68% yield.[17] Repeating this alkylation with recovered bromide provided additional dione **21** for a combined yield of 89%. Treatment of dione **21** with sodium hydride in DMF and dimethyl sulfate generated enol ether **22** in 99% yield. 1,2-Addition of vinylmagnesium bromide to **22**, followed by mild acid hydrolysis, produced the key cyclization precursor **12**. This Grignard reaction required activation of the cyclohexenone carbonyl group by cerium chloride[18] to suppress 1,4-addition and to overcome the steric influence of the *gem*-dimethyl group. The cyclialkylation[19] of **12** was accomplished in 96% yield using $TiCl_4$ as catalyst.[20]




**Scheme 5.**

Four transformations were needed to convert enone **11** into quinone **2**. The first step was a modified Wolff–Kishner reduction of **11** that both reduced the C-1 carbonyl group and caused the C-5,C-10 double bond to migrate to the C-1,C-10 position (cf. **23**).[21] Next, demethylation of two of the ether units was achieved in 75% yield using sodium ethylthiolate. Catechol **24** resisted all attempts at further deprotection. At first this seemed to be a setback.




**Reagents and Yields:** (a) LAH, 98%; (b) $PBr_3$, 92%; (c) 20% $K_2CO_3$, KI, 4,4-dimethylcyclohexane-1,3-dione (**20**), 68%; (d) NaH, $(CH_3O)_2SO_2$, 99%; (e) *(i)* $CeCl_3$, vinylmagnesium bromide; *(ii)* $H_3O^+$, 95%; (f) $TiCl_4$, 96%; (g) $TsNHNH_2$; $NaCNBH_3$, $H_3O^+$, 64%; (h) NaSEt, 90 °C, 86%; (i) $NH_4Ce(NO_3)_6$, (99%); (j) NaOH, 98%; (k) $H_3O^+$, 99%.

**Scheme 6.**

Fortunately, we realized that oxidation of catechol **24** would produce *o*-quinone **25**, in which the C-14 methoxy group can be regarded as part of a vinylogous ester. Hydrolysis of **25** with either base or acid would therefore produce the deprotected *o*-quinone, which could rearrange to a *p*-quinone.[22] Treatment of **24** with ammonium cerium(IV) nitrate[23] gave *o*-benzoquinone **25** in situ; addition of either sodium hydroxide or aqueous sulfuric acid to the oxidation reaction mixture produced *p*-benzoquinone **2** in excellent yield.[24]

Quinones are excellent dienophiles[25,26] and we were confident that quinone **2** would react in Diels–Alder fashion. However, the facial selectivity, which has important stereochemical

consequences, and the regioselectivity of the cycloaddition of quinone **2** with (*E*)-β-ocimene presented unanswered concerns. We expected that the preferred conformation of quinone **2** would be cup-shaped, so that the diene would add to **2** from the more accessible convex α-face. This speculation was supported by both the NMR studies of St. Jacques and Vaziri, which found that benzocycloheptenes strongly favor a chair conformation,[27] and by MM3 calculations,[28] which indicate that the chair cycloheptene conformer of **2** is >3.0 kcal/mol lower in steric energy than the boat conformation (Fig. 3: **i**, 37.54 kcal/mol; **ii**, 40.78 kcal/mol). The magnitude of this energy difference suggests that the equilibrium between these conformers strongly favors the cup-shaped conformation (**i**).

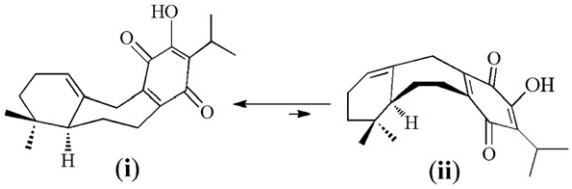
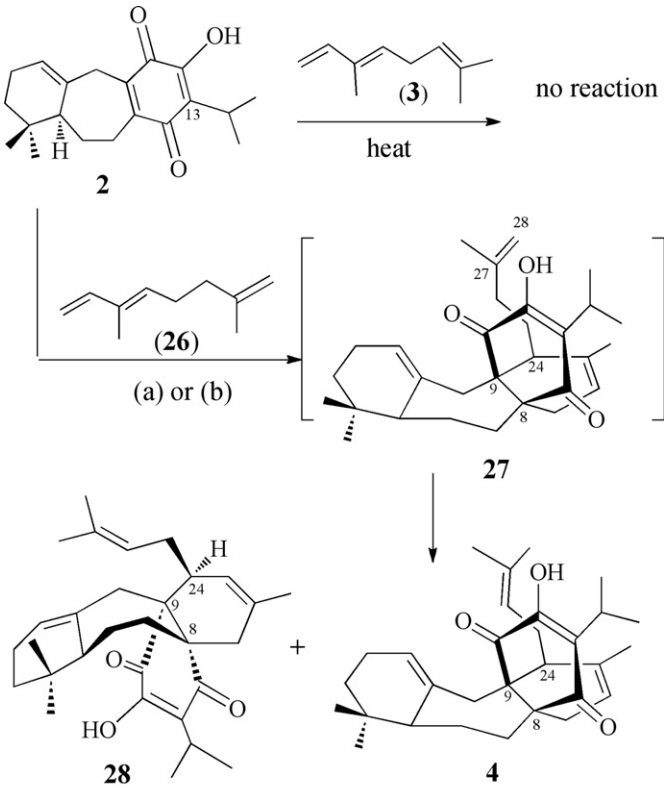



**Fig. 3.** Two conformations of quinone **2**.

It was hoped that in the cycloaddition transition state the steric interactions between the substituents of asymmetrically functionalized dienes, such as (*E*)-β-ocimene (**3**), and the C-13 isopropyl group would control the regiochemistry of the Diels–Alder reaction (Scheme 7). Unfortunately, (*E*)-β-ocimene (**3**) failed to react with **2** under a variety of thermal conditions.[29] Common techniques used to overcome a sluggish Diels–Alder reaction are to carry out the cycloaddition either in the presence of a Lewis acid catalyst[30] or under high pressure,[31] or a combination of both conditions. Although (*E*)-β-ocimene is thermally stable,[32] at temperatures above 50 °C even mild Lewis acids cause it to rearrange into its various allo-ocimene isomers, which then react to form undesired products. This rapid consumption of the (*E*)-β-ocimene under thermal and Lewis acid-catalysis precluded the formation of a Diels–Alder product. On the other hand, substituting (*E*)-α-ocimene (**26**) as the diene slowed the rate of diene decomposition and gave a 30% yield of adduct **4** when diethylaluminium chloride was used at rt to promote the cycloaddition. It is important to note that under these conditions the C-27,C-28 disubstituted double bond of the Diels–Alder adduct **27** isomerized to the trisubstituted position (cf. C-26,C-27) after the cycloaddition had taken place. A 79% yield of tetracycle **4** was obtained when **2** was treated in a sealed tube at 45 °C for 24 h with (*E*)-α-ocimene in the presence of the mild Lewis acid tris-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)-europium [Eu(fod)$_3$].[33] This reaction also gave a low yield of an isomeric C-8,C-9 Diels–Alder adduct (**28**), the result of addition of the diene to the β-face of quinone **2**.

Several important observations were made in the course of studying this Diels–Alder reaction. First, the Diels–Alder reaction required at least 10 mol % of the Lewis acid (relative to the quinone) at either 0 °C or rt. Stoichiometric quantities of the Lewis acid prompted rapid cycloaddition and migration of the C-22,C-23 double bond to the tetrasubstituted position. While the isomerization of the C-27,C-28 double bond—after the cycloaddition occurred—could not be suppressed, we found that the undesired isomerization of the C-22,C-23 double bond could be minimized if the reaction was monitored. Further work showed that trienes **3** and **26** do not undergo Diels–Alder reactions, either thermally or with Lewis acid catalysis, when the C-12 hydroxyl group is protected as either a methyl ether, a trimethylsilyl ether, or as an acetate.[34,35] These results suggest that complexation between the Lewis acid, the α-hydroxy group and the C-11 carbonyl group of **2** (cf. chelate **iii**, Fig. 4) is




**Reagents and Yields:** (a) **26** and $Et_2AlCl$ at 25 °C, 30% of **4**; 0% of **28**; (b) **26** and $Eu(fod)_3$ at 45 °C, 79% of **4** and 9% of **28**.

**Scheme 7.**

necessary for the Diels–Alder reaction to occur. Moreover, the resonance structure **iv** derived from **iii** governs the regioselectivity observed.[36] Finally, cycloadduct **28**, which has the undesired stereochemistry at the C-8 and C-9 quaternary centers, was produced only when the Lewis acid-catalyzed Diels–Alder reaction was heated; hence the formation of this unwanted isomer could be avoided.

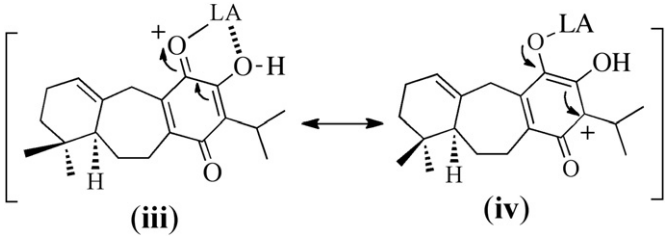
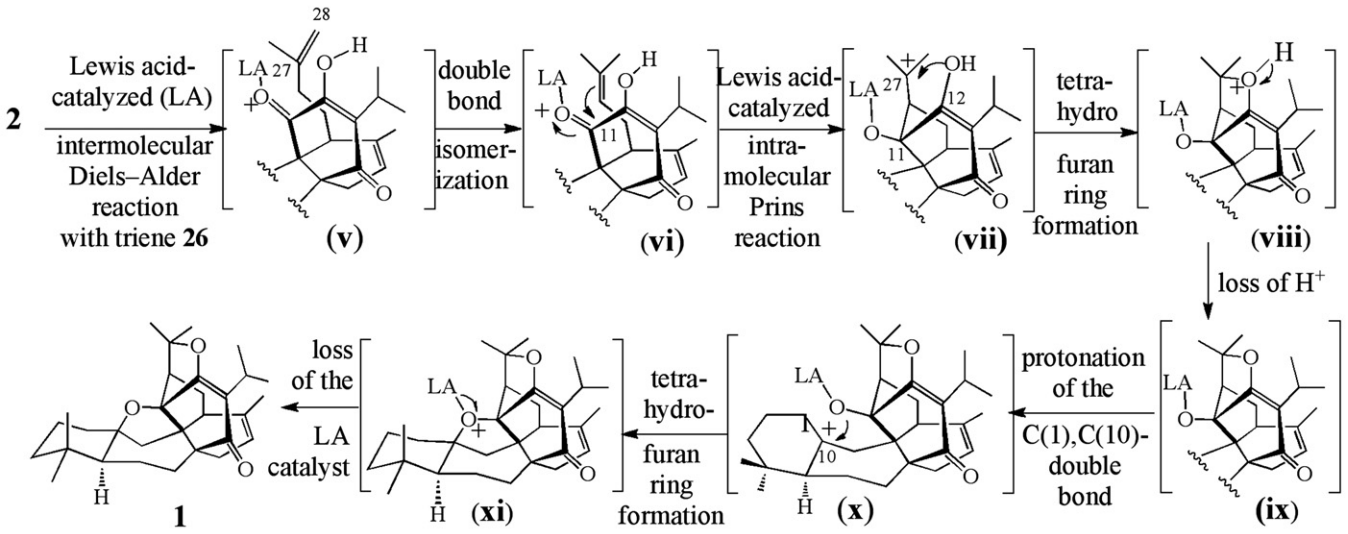



**Fig. 4.** Lewis acid-activation of quinone **2**.

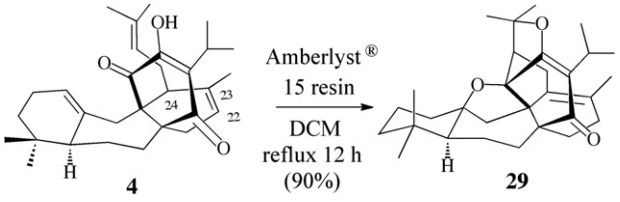
With the Diels–Alder adduct in hand, we next sought to determine the conditions needed for the intramolecular ene reaction to form the E-ring. In our retrosynthetic analysis we assumed that formation of the E-, F-, and G-rings would require separate steps. However, the need to use a Lewis acid to catalyze the Diels–Alder reaction suggested that these rings, complete with the correct stereogenic centers, could be formed in a series of tandem reactions (Scheme 8). Intermediates **v**→**xi** help to explain the bond formations that occur during this proposed cascade as well as the multiple functions of the catalyst. After the Lewis acid




**Scheme 8.**

promotes the intermolecular Diels–Alder reaction, it causes the C-27,C-28 disubstituted double bond to isomerize (cf. **v**→**vi**). Since ene reactions are facilitated by Lewis acids,[37] the nucleophilic addition of the C-26,C-27 double bond to the C-11 carbonyl group would also benefit from Lewis acid activation (cf. **vi**). Formation of the C-11,C-26 bond generates a tertiary carbocation at C-27, which is trapped by the C-12 hydroxyl group. This sequence, **vi**→**vii**→**viii**, is best described as an intramolecular Lewis acid-catalyzed Prins reaction. Formation of the heterocyclic F-ring would liberate the proton needed to add to the C-1,C-10 double bond, and permits the formation of the second tetrahydrofuran ring (cf. **ix**→**x**→**xi**→**1**).

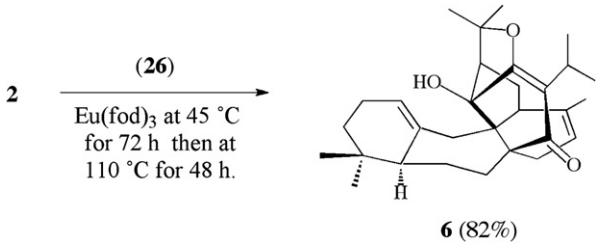
Our quest became to discover the appropriate reaction conditions needed to form the D-, E-, F-, and G-rings in a single step. We decided to examine first the Prins reaction using Amberlyst® 15 resin as a protic acid as catalyst (Scheme 9).[38] We were delighted to find that heating Diels–Alder adduct **4** at 42 °C for 12 h with this acidic resin achieved both the desired Prins reaction and bis-tetrahydrofuran formation (cf. **29**). While the realization of the polycyclization cascade was welcome, the migration of the C-22,C-23 trisubstituted double bond to the C-23,C-24 position was not. Perhaps one day triterpene **29** will be isolated from nature.[39] Clearly, the use of a weaker acid catalyst than the Amberlyst® 15 resin was needed to catalyze the Prins reaction and thereby initiate the polycyclization cascade.




**Scheme 9.**

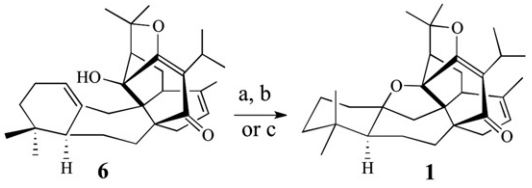
The next Lewis acid tested was the Eu(fod)$_3$ reagent previously used to achieve the Diels–Alder reaction (Scheme 10). After heating the Eu(fod)$_3$-catalyzed Diels–Alder reaction at 45 °C for 24 h, the reaction mixture had to be warmed to 110 °C before consumption of the Diels–Alder adduct was observed. Heating the reaction mixture at that temperature for an additional 48 h resulted in the isolation of alcohol **6** in 82% yield.

Brief reaction of alcohol **6** with Amberlyst® 15 resin or with pyridinium *p*-toluenesulfonate (PPTS)[40] in DCM achieved the final ring closure in high yield without the migration of the C-22,C-23 trisubstituted double bond (Scheme 11). Our synthetic




**Scheme 10.**

(±)-perovskone displays $^1$H and $^{13}$C NMR, IR, and MS spectra that are indistinguishable from those reported for the natural material.[5]

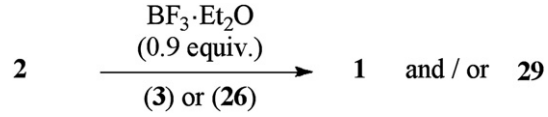



**Reagents and Yields:** (a) Amberlyst® 15-ion exchange resin, DCM, reflux for 25 min, 90%; (b) pyridinium *p*-toluene-sulfonate (PPTS), DCM, reflux for 25 min, 90% (c) PPTS, $C_6H_6$, 25 °C, 150 min, 90%.

**Scheme 11.**

Having achieved an efficient synthesis of racemic perovskone, the siren call to find conditions whereby quinone **2** would produce perovskone in a one-pot reaction was irresistible. Thus, a systematic study of the solvent, the choice of catalyst, and the reaction temperatures required was undertaken (Table 2). While toluene and DCM were suitable solvents, quinone **2** and triene **3** (or **26**) were insoluble in acetonitrile. When THF was used as the solvent, only the Diels–Alder reaction occurred. The use of weak Lewis acids required heating in order to promote the Diels–Alder and the

**Table 2**
Optimization of the cascade reaction




| Diene | Reaction conditions | Yield of **1** and/or **29** |
|---|---|---|
| **3** | (a) 0 °C (1.5 h)→50 °C (10 h) in toluene | 46%/26% |
| **3** | (b) 0 °C (1.5 h)→50 °C (7 h) in DCM | 50%/15% |
| **26** | (c) 0 °C (1.5 h)→50 °C (10 h) in toluene | 0%/71% |

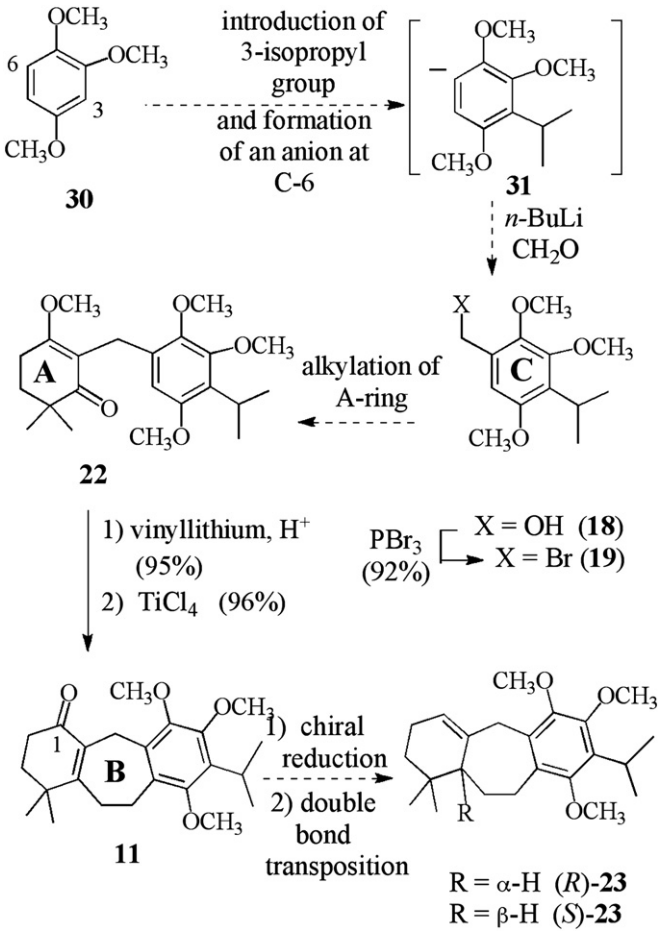
Prins reactions; unfortunately, these conditions would promote the isomerization and hence decomposition of (*E*)-β-ocimene (**3**). We reasoned that the use of stronger Lewis acids at low temperatures would produce only the cycloadduct derived from addition of the diene to the α-face of the quinone and that short reaction times would be required. Indeed, the use of nearly a stoichiometric quantity of $BF_3{\cdot}Et_2O$ in toluene at 0 °C allowed the Diels–Alder reaction of **2** with (*E*)-β-ocimene to be complete within 90 min; lower reaction temperatures required longer reaction times.

Previous work had shown that the Prins reaction occurs at a higher reaction temperature than the [4+2]-cycloaddition. We reasoned that the use of a strong Lewis acid would lower the reaction temperature necessary to initiate the Prins reaction and that shorter reaction times would be required. Indeed, warming the crude Diels–Alder reaction mixture to only 50 °C caused the polycyclization cascade to occur; this temperature was maintained overnight. Under these conditions a 46% yield of perovskone was isolated along with a 26% yield of **29**, in which the trisubstituted double bond had isomerized to the tetrasubstituted position. Repeating this reaction using DCM as the solvent gave perovskone in 50% yield, while the yield of compound **29** was reduced to 14%. Using $BF_3{\cdot}Et_2O$ as the catalyst and toluene as the solvent, (*E*)-α-ocimene (**26**) rapidly formed the desired Diels–Alder adduct; however, isomerization of the C-22,C-23 trisubstituted double bond of the adduct could not be avoided and occurred prior to formation of the heterocyclic F- and G-rings. These conditions led to the formation of **29** in 71% yield (unoptimized).

We explored other ideas to improve the cascade reaction. The C-12 hydroxyl group of quinone **2** is also a vinylogous carboxylic acid and could therefore serve as the only catalyst needed for the Diels–Alder and polycyclization cascade. However, simply heating quinone **2** and (*E*)-β-ocimene (**26**) together at 200 °C gave only a trace amount of the [4+2]-adduct. Similar results were obtained when **2** and **3** were kept at 12 kbar for 24 h. Grieco and co-workers have established that lithium perchlorate in diethyl ether is a powerful medium for promoting Diels–Alder reactions.[41] They found that **2** and triene **26** in $LiClO_4{\cdot}Et_2O$ formed a 2:1 mixture of adducts **4** and **28**, respectively, in 50% yield using 5 M lithium perchlorate–diethyl ether as both catalyst and solvent. Finally, we attempted to verify the proposed biosynthesis of perovskone by treating geranyl pyrophosphate with quinone **2**, our icetexone equivalent. Unfortunately, the geranyl pyrophosphate formed a complex mixture of acyclic and cyclic terpenes without producing any of the desired cycloaddition adduct.[42]

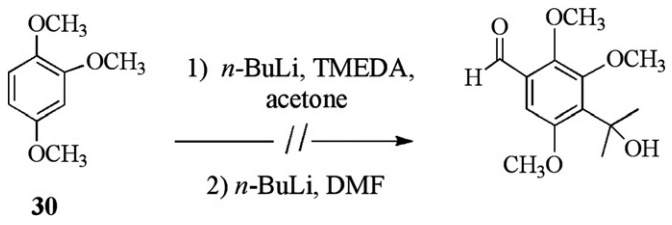
Although our synthesis of (±)-perovskone from vanillin required only 16 steps and proceeded in 9% overall yield, a more efficient route was desired. Since the C-5 chiral center in **2** controls the stereochemistry for each new chiral center produced in the tandem polycyclizations leading to perovskone (cf. Scheme 1), the ability to prepare quinone **2** in optically active form was essential for us to prepare (+)-perovskone.

The retrosynthetic analysis for a synthesis of optically active quinone (**2**) is generalized in Scheme 12. Our selection of 1,2,4-trimethoxybenzene (**30**) as a more attractive starting material was based on the work of Sundberg and co-workers, who reported an efficient one-pot procedure for the synthesis of pentasubstituted benzenes derived from **30**[43] which selectively functionalized of the 3- and 6-positions with either identical or different electrophiles.[44,45] Given this, the introduction of an isopropyl group at the 3-position, followed by metalation of the 6-position and trapping this anion (cf. **31**) with formaldehyde, should produce benzyl alcohol **18**. Previously, 4,4-dimethylcyclohexane-1,3-dione (**20**) was *C*-alkylated with bromide **19** and then *O*-alkylated with iodomethane to give enone **22** in 67% yield. We can envision other strategies to couple the A and C rings to give enone **22**. The addition of vinyllithium to enone **22**, followed by cyclialkylation to form the cycloheptane ring, produces key intermediate **11**. For clarity's sake, our strategy for converting prochiral enone **11** into the required enantiomer of **2** is postponed until after our second synthesis of **11** has been discussed.



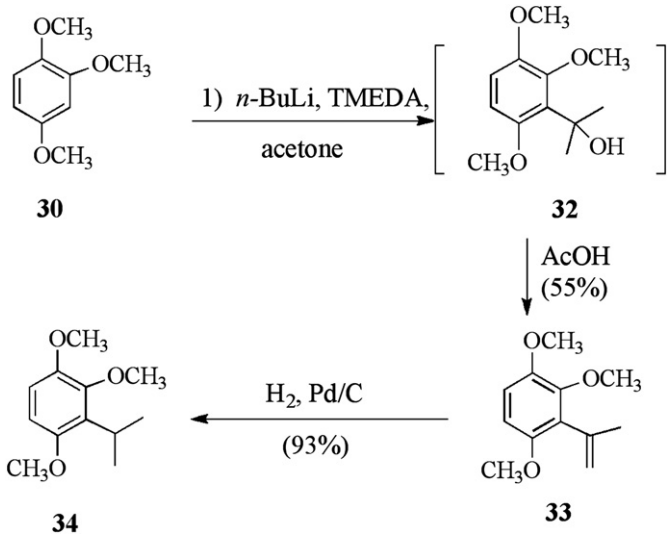

**Scheme 12.**

In 1984, Crowthers and co-workers found that treatment of 1,2,4-trimethoxybenzene (**30**) with *n*-butyllithium followed by the addition of an electrophile affords only the 3-substituted product.[43] When that product is treated with a second equivalent of *n*-butyllithium and TMEDA, metalation occurs selectively at the 6-position provided that the newly introduced C-3 substituent does not react with the *n*-butyllithium used for deprotonation. Based on these precedents, a one-pot bis-functionalization of **30** was attempted (Scheme 13). A 1:1 mixture of **30** and TMEDA was treated with 1.1 equiv of *n*-butyllithium, followed by an equal of acetone; a second equivalent of *n*-butyllithium was followed by the addition of 1.1 equiv of DMF. Unfortunately, these conditions gave a complex mixture of products.



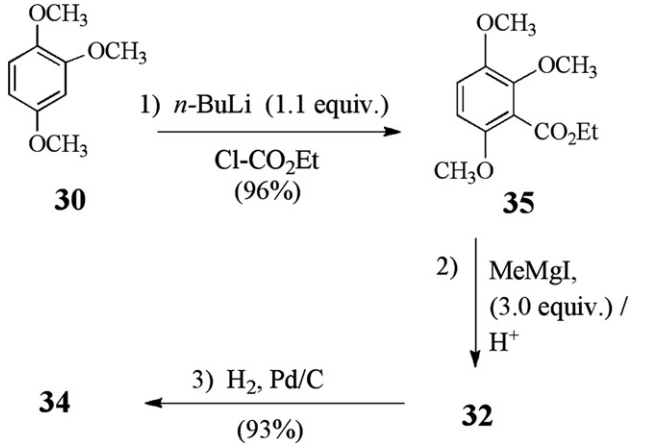

Scheme 13.

Instead of functionalizing **30** at two sites in a one-pot process, we decided to focus on introducing the isopropyl group at the 3-position before functionalizing the 6-position (Scheme 14). In 1993, we converted veratrole to isopropylveratrole in three steps and a 50% overall yield.[46] Thus, metalation of **30**, followed by the addition of acetone and quenching the reaction with acetic acid, produced olefin **33** in 55% yield along with a 35% yield of recovered **30**.[47] Hydrogenation of **33** using 10% palladium on carbon at atmospheric pressure afforded tetrasubstituted benzene derivative **34** in 93% yield.



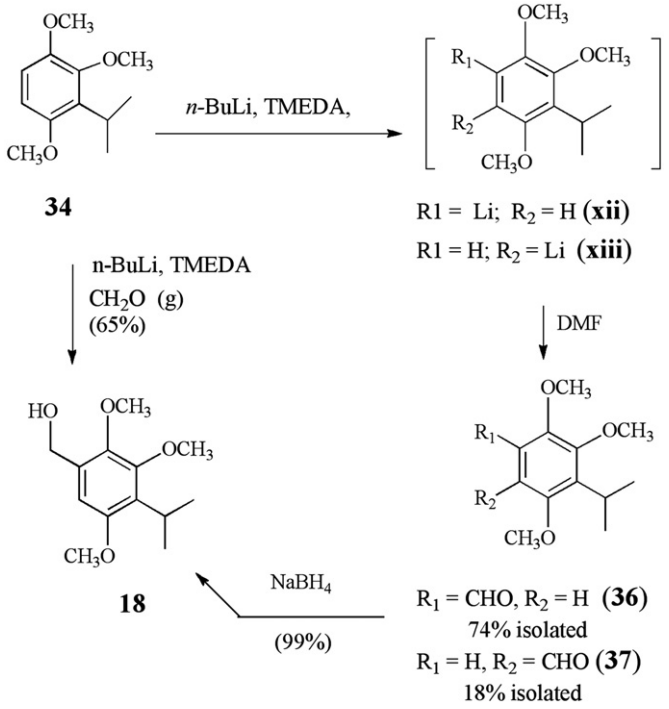

Scheme 14.

The introduction of an isopropyl group at the 3-position of **30** was significantly improved when ethyl chloroformate was used instead of acetone (Scheme 15). Treatment of **30** with *n*-butyllithium, followed by addition of ethyl chloroformate, produced benzoate **35** in 96% yield. The addition of excess of methylmagnesium iodide to **35**, followed by an acidic workup, gave tertiary alcohol **32** in high yield. Hydrogenation of **32** in the presence of HCl afforded tetrasubstituted benzene **34** in 93% yield.[48] This three-step reaction sequence was carried out on a scale of greater than 50 g without isolation of the intermediates.



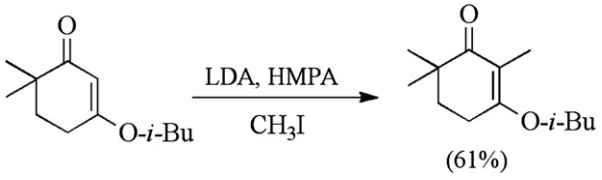

Scheme 15.

In our hands, metalation of **34** occurred at both the 6- and the 5-positions (Scheme 16), although significantly favoring the 6-position. Addition of excess DMF to the mixture of aryllithium anions (**xii**) and (**xiii**) gave isomeric benzaldehydes **36** and **37** in 74% and 18% yield, respectively; these aldehydes were easily separated by chromatography. Reduction of aldehyde **36** with $NaBH_4$ gave a nearly quantitative yield of alcohol **18**. Alternatively, anions (**xii**) and (**xiii**) could be trapped with gaseous formaldehyde to produce alcohol **18** in 65% yield after chromatographic separation of the isomeric alcohol derived from anion **xiii**. Alcohol **18** was then converted to bromide **19** in 92% yield using $PBr_3$.




Scheme 16.

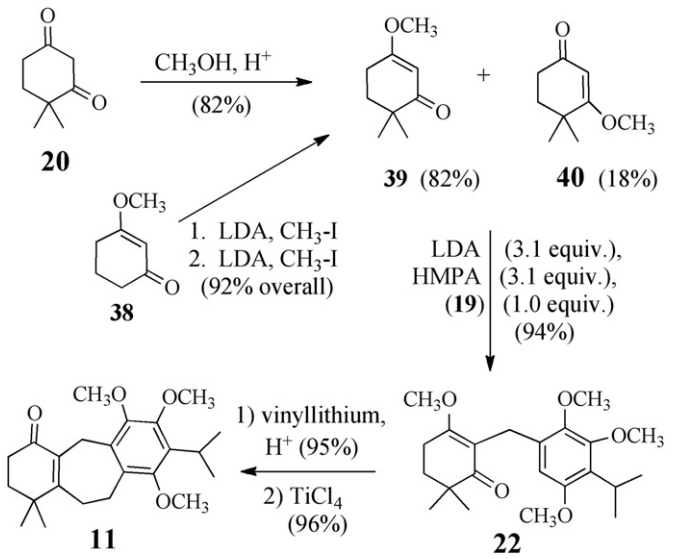
Enolates derived from enones alkylate with alkyl halides at the α-position. In particular Smith and co-workers methylated 3-isobutoxy-6,6-dimethylcyclohexen-2-en-1-one at the α-position in 61% yield using LDA and HMPA (Scheme 17).[49] Since benzyl halides are good electrophiles, we were confident that this alkylation would couple the A and C rings units.




Scheme 17.

Enone **39** was prepared in 82% yield by heating commercially available dione **20** with methanol and TsOH with azeotropic removal of water (Scheme 18); although column chromatography

separated **39** from isomer **40** their $R_f$ values were very close.[50] We found that **39** could be prepared on a 20 g scale using the Stork–Danheiser protocol[51] by alkylating 3-methoxycyclohex-2-en-1-one (**38**) twice with iodomethane in a 92% overall yield after distillation.

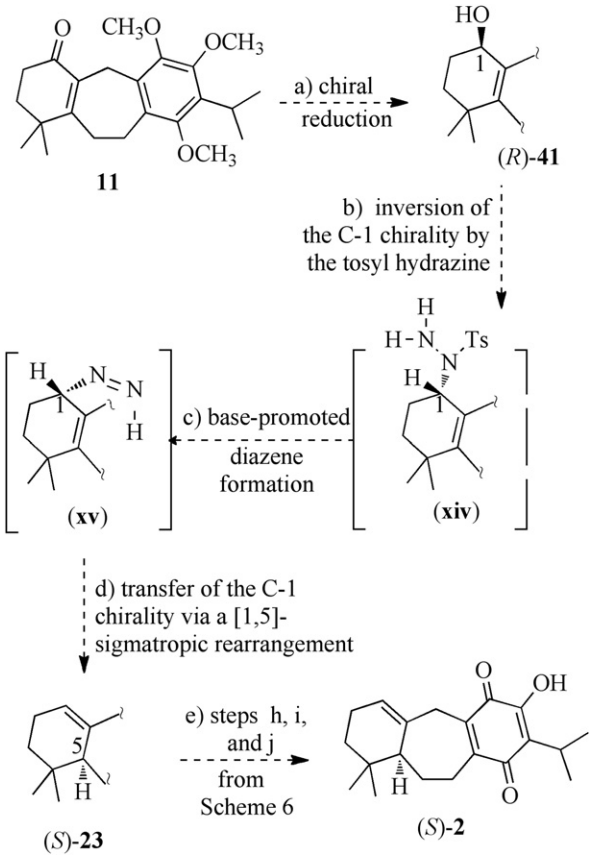



**Scheme 18.**

Enone **39** was treated with LDA using Smith's conditions and the resulting dienolate was treated with bromide **19**. Surprisingly, alkylation product **22** was obtained in only 32% yield, along with >65% of unreacted bromide **19** and recovered enone **39**. This observation caused us to carry out the alkylation using bromide **19** as the limiting reagent. Indeed, **22** was prepared in 94% yield by using a threefold excess of the dienolate relative to bromide **19**; the excess **39** was recovered via distillation. The conversion of bicyclic enone **22** to tricyclic enone **11** used the same two steps worked out in our initial synthesis. Thus, the preparation of enone **11** from 1,2,4-trimethoxybenzene required nine steps [**30**→**35**→**32**→**34**→**36**→**18**→**19**→**22**→**12**→**11**] and proceeded in 52% overall yield. While enone **11** could be prepared using only seven transformations [**30**→**33**→**34**→**18**→**19**→**22**→**12**→**11**], this shorter route gave only a 29% overall yield. Nevertheless, both sequences are an improvement over our first route, which required 12 steps to convert vanillin into enone **11** and proceeded in 15% overall yield.

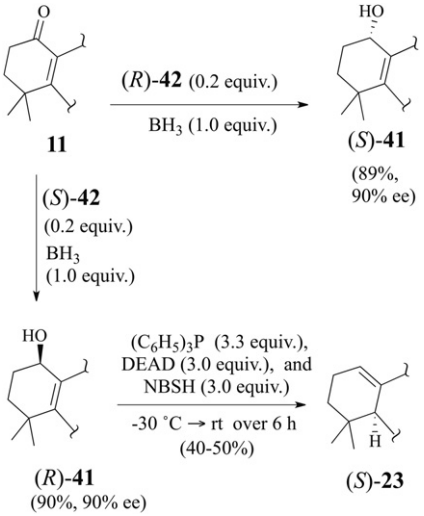
We foresaw that quinone (*S*)-**2** could be synthesized as summarized in Scheme 19.[52] Several methods now exist for the asymmetric reduction of ketones[53] including α,β-disubstituted cyclohex-2-en-1-ones.[54] Access to allylic alcohol (*R*)-**41** would allow us to prepare (*S*)-**2** via a modification of the one-pot Wolff-Kisner reduction developed by Myers and Zheng.[55] In the first step of their modified process, an allylic alcohol is converted into a hydrazine derivative such as **xiv** using a Mitsunobu reaction (cf. **41**→**xiv**→**xv**). The $S_N2$ displacement of triphenylphosphine oxide by nitrobenzenesulfonylhydrazine (NBSH)[59] inverts the configuration at C-1 and the base present converts intermediate **xiv** into diazene **xv**. Once formed, diazene **xv** undergoes an intramolecular [1,5]-sigmatropic rearrangement to release a molecule of nitrogen with the transfer of a hydride to C-5 and the movement of the C-5,C-10 double bond to the C-1,C-10 position.[56] The three remaining transformations needed to convert (*S*)-**23** to quinone (*S*)-**2** were developed in our synthesis of (±)-perovskone (**1**) and occurred in high yield (cf. Scheme 6).

The commercial availability of (*S*)-methyl-CBS-oxaborolidine [(*S*)-**42**] and (*R*)-methyl-CBS-oxaborolidine [(*R*)-**42**] coupled with




**Scheme 19.**

their high selectivity for preparing chiral alcohols from ketones and enones led us to utilize these reagents for the synthesis of allylic alcohols (*R*)- and (*S*)-**41** (Scheme 20). These reductions occurred in high chemical yield (90%). The $^{19}F$ NMR analysis of the Mosher esters[57] of alcohols (*R*)-**41**, (*S*)-**41**, and (±)-**41** indicated a 90% ee for (*R*)-**41**. We attempted to selectively hydrolyze only one of the enantiomers of the acetate of (*R*)-**41** using pig liver esterase to enhance the enantiomeric purity of (*R*)-**41**.[58] However, this acetate exhibited severe solubility problems despite the large variety of co-solvent systems studied. Fortunately, three recrystallizations of the 90% ee enriched (*R*)-**41** gave material



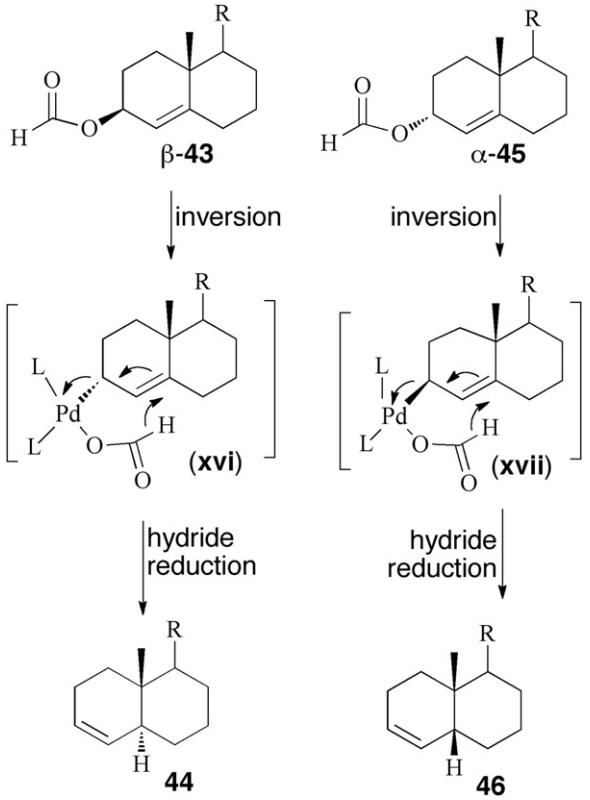

**Scheme 20.**

consisting of a single enantiomer of 99% ee based on the $^{19}F$ NMR analysis of its Mosher ester.

The addition of alcohol (*R*)-**41** to the complex formed by treating triphenylphosphine (TPP) with diethylazodicarboxylate (DEAD) at −30 °C, followed by the addition of NBSH, gave disappointing yields of alkene (*S*)-**23**. Myers and Zheng observed that hindered secondary alcohols required the use of a large excess of reagents in a concentrated solution. Unfortunately, these conditions can also result in elimination byproducts. They circumvented this problem by using *N*-methyl morpholine (NMM) as solvent instead of THF.

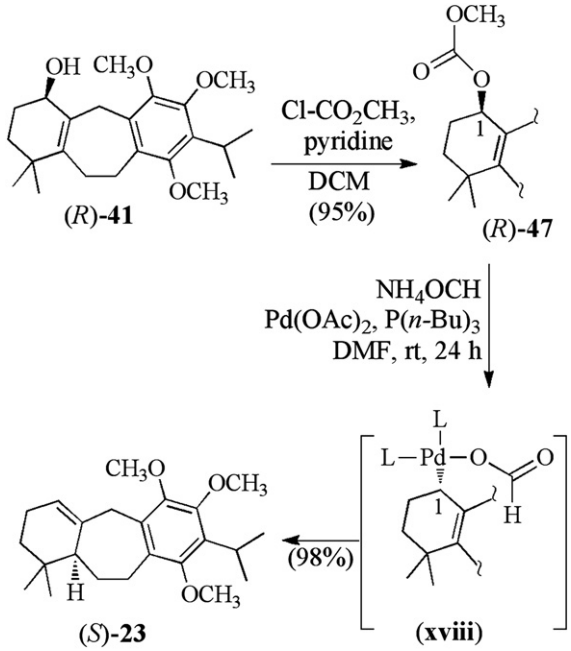
The application of Myers' reductive transposition to alcohol (*R*)-**41** was a demanding test of the generality of this procedure since tetrasubstituted secondary allylic alcohols were not previously studied. For a 100 mg scale reaction the best solvent system was a 1:1 mixture of THF/NMM; less concentrated solutions resulted in much lower yield. A threefold excess of TPP, DEAD, and NBSH at a concentration of approximately 0.25 M with respect to the alcohol gave the best yield (60%) of (*S*)-**23**. In general, the Mitsunobu inversion of (*R*)-**41** occurred at −10 °C or 0 °C but the overall yield of the 1,3-transposition varied from 40% to 45% when more than 1 g of alcohol (*R*)-**41** was used.

The palladium-catalyzed hydrogenolysis of allylic acetates, ethers, or carbonates by hydrides produces alkenes with transposition of the position of the double bond. In 1993, Mandai and Tsuji used the palladium-catalyzed hydrogenolysis of allylic formates to control the stereochemistry of ring junctions (Scheme 21).[60] In their study, allylic formate **43** gave *trans*-decalin **44**, whereas allylic formate **45** produced *cis*-decalin **46**. The initial step of this transformation is the formation of a π−allylpalladium complex, which occurs with inversion of the stereochemistry at the allylic position. The subsequent migration of the hydride from the α-palladium formate **xvi** to the ring junction carbon occurred from the α-face to produce a *trans*-fused decalin. Similarly, the 3 α-allylic formate (α-**45**) undergoes hydride transfer from the β-face of the β-palladium formate **xvii** to produce *cis*-declin **46**. We were hopeful that this hydrogenolysis was applicable to the conversion of (*R*)-**41** to (*S*)-**23**.



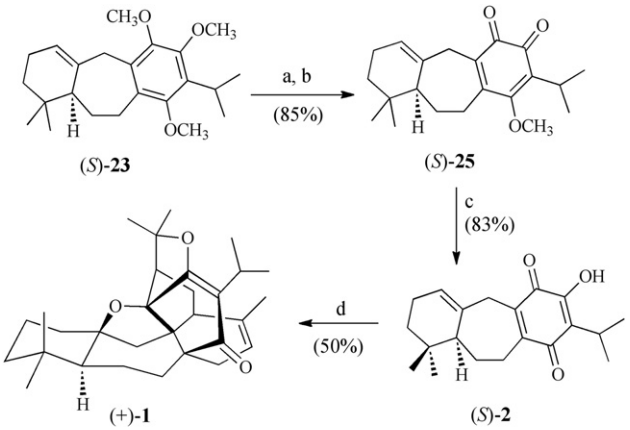

**Scheme 21.**

As shown in Scheme 22, (*R*)-**41** was treated with methyl chloroformate and pyridine to generate carbonate (*R*)-**47**. The reaction of carbonate **47** with 6 equiv of ammonium formate, 0.2 equiv of $Pd(OAc)_2$, and 0.2 equiv of $PBu_3$ at rt in dry DMF gave optically pure olefin (*S*)-**23** in 98% yield. We found that a 1:1 ratio of the $PBu_3$ to the $Pd(OAc)_2$ allowed the reaction to occur at rt overnight, whereas higher ratios of $PBu_3$ to the $Pd(OAc)_2$ slowed down the reaction and required heating, which resulted in lower overall yield. In general, this transposition was carried out on 2−3 g scales in 98% yield.




**Scheme 22.**

With tricycle (*S*)-**23** in hand, all that remained to complete a syntheses of quinone (*S*)-**2** was to deprotect the C-11 and C-12 methyl ethers, and to oxidize the intermediate catechol to *o*-quinone **25** (Scheme 23). Treatment of **25** with either mild acid or mild base isomerized *o*-quinone (*S*)-**25** to *p*-quinone (*S*)-**2**. The reaction




**Reagents and yields:** (a) NaSEt, 90 °C (86%); (b) $NH_4Ce(NO_3)_6$ (99%); (c) NaOH (98%); (d) (**3**), 0 °C (1.5 h) → 50°C (7 h) in DCM (50%).

**Scheme 23.**

of (*S*)-**2** with (*E*)-β-ocimene (**3**) and $BF_3 \cdot Et_2O$ using the optimized conditions (Table 2) afforded (+)-perovskone in 50% yield having an $[\alpha]_D^{23}$ of +91.4, which compares favorably with the $[\alpha]_D^{25}$ of +94.0 reported by Ahmad and co-workers for natural perovskone.[5]

## 3. Conclusions

Sixteen transformations were needed to convert vanillin into (±)-perovskone in a 9% overall yield. This synthesis featured a one-pot reaction, which assembled three rings, four bonds, and five stereocenters in 82% yield. The final step was an acid-catalyzed olefin hydration, which occurred in 90% yield. In contrast, the conversion of 1,2,4-trimethoxybenzene into (+)-perovskone required fifteen steps and occurred in 18% overall yield. In this improved synthesis, the polycyclization cascade created four rings, five bonds, and six stereocenters in a one-pot reaction in 50% yield. The chemistry discovered in the course of the synthesis of (±)- and (+)-perovskone has facilitated the synthesis of other complex terpenes,[52] most recently a four-step synthesis of (+)-salvadione-B, a related pentacyclic triterpene.[61] Additional applications of the chemistry learned during this study are forthcoming.

## 4. Experimental section

### 4.1. General procedures

All reactions were run under an atmosphere of nitrogen and monitored by TLC analysis until the starting material was completely consumed. Unless otherwise indicated, all ethereal workups consisted of the following procedure: the reaction was quenched at rt with saturated aqueous ammonium chloride. The aqueous phase organic solvent was removed under reduced pressure on a rotary evaporator and the residue was taken up in ether, washed with brine and dried over anhydrous $MgSO_4$. Filtration, followed by concentration at reduced pressure on a rotary evaporator and at 1 Torr to constant weight, afforded a crude residue, which was purified by flash chromatography using NM silica gel 60 (230–400 mesh ASTM) and distilled reagent grade solvents.

$^1H$ and $^{13}C$ NMR spectral data were obtained in $CDCl_3$ on a Varian AMX-400 or a Bruker AM-250 MHz spectrometer and were calibrated using trace $CHCl_3$ ($\delta$ 7.27 and 77.23 ppm). $^{19}F$ NMR spectra were obtained in $CDCl_3$ on a Bruker AMX-400 MHz spectrometer and were calibrated using trifluoroacetic acid as an external standard (0 ppm). Infrared spectra were obtained on a Perkin–Elmer 1600 series FT-IR spectrometer and the absorption frequencies are reported in wavenumbers ($cm^{-1}$). Mass spectra were obtained on a Perkin–Elmer SCIEX API1 Plus spectrometer using electrospray ionization. Microanalysis was performed by Atlantic Microlab, Inc., Atlanta, GA.

The following abbreviations are used throughout this section: hexanes (H), diethyl ether (E), and methyl *tert*-butyl ether (MTBE).

*4.1.1. 11-Hydroxy-12-methoxy-9(**10**→**20**)-5aH-abeo-abieta-1(**10**),8,11,13-tetraene (**9a**) and 12-hydroxy-11-methoxy-9(**10**→**20**)-5aH-abeo-abieta-1(**10**),8,11,13-tetraene (**9b**).* (a) *Using NaSEt*: Ethanethiol (16.80 g, 0.29 mol) was added dropwise to a cold solution (0 °C) of sodium hydride (3.20 g, 0.13 mol, 80% dispersion in oil) suspended in 35 mL of freshly distilled DMF. The resulting mixture was stirred at rt for a 2-h period, followed by the addition of a solution of 1.60 g of barbatusol methyl ether (**8**) (4.47 mmol) dissolved in 20 mL of dry DMF. The reaction mixture was heated to 50 °C for 12 h, and then cooled to 0 °C and cautiously neutralized with 2 N aqueous HCl. Standard ethereal workup, followed by purification by chromatography on silica gel (elution with H/E, 10:1→5:1), gave 1.26 g (86%) of phenols **9a** and **9b** as an inseparable 3:2 mixture, which was homogeneous by TLC analysis [H/E, 5:1, $R_f$ **8**=0.92, $R_f$ **9a**/**9b**=0.74]. Analysis of the $^1H$ NMR spectrum, particularly the set of olefinic signals at 5.68 and 5.60 and the methoxy signals at 3.78 and 3.80, indicates that **9a** and **9b** were produced in a 3:2 ratio.

(b) *Using NaS-i-Pr*: The above procedure was repeated except that isopropyl mercaptan (80 mL, 0.88 mmol) was added to sodium hydride (29 mg, 0.70 mmol) in 2 mL of DMF. To this solution of sodium isopropylthiolate was added **8** (29 mg, 0.09 mmol) and the resulting mixture was heated at 65 °C for 48 h. Standard ethereal workup, followed by chromatography, gave 21 mg (75%) of phenols **9a** and **9b** as an inseparable 3:2 mixture, respectively. Analysis of the $^1H$ NMR spectrum, particularly the set of olefinic signals at 5.68 and 5.60 and the methoxy signals at 3.78 and 3.80, indicates that **9a** and **9b** were produced in a 3:2 ratio.

(c) *Using NaS-t-Bu*: The above procedure was repeated except that *tert*-butyl mercaptan (100 mL, 0.88 mmol) was added to sodium hydride (29 mg, 0.70 mmol) in 2 mL of DMF. To this solution of sodium *tert*-butylthiolate was added **8** (30 mg, 0.90 mmol) and the resulting mixture was heated at 50 °C for 48 h. Standard ethereal workup, followed by chromatography, gave 14.5 mg (52%) of phenols **9a** and **9b** as an inseparable 2:1 mixture, respectively. Analysis of the $^1H$ NMR spectrum, particularly the set of olefinic signals at 5.68 and 5.60 and the methoxy signals at 3.78 and 3.80, indicates that **9a** and **9b** were produced in a 2:1 ratio.

(d) *Using L-Selectride*: To a solution of bis-ether **8** (20 mg, 0.125 mmol) dissolved in 4.0 mL of dry glyme was added 375 mL of L-Selectride (1.0 M, 3.75 mmol) and the resulting mixture was refluxed (90 °C) until TLC analysis indicated that the demethylation was complete (24 h). The reaction mixture was cooled to 0 °C and diluted with 50 mL of ether. The resulting mixture was quenched carefully with water. Standard ethereal workup, followed by chromatography (elution with H/E, 10:1) gave 17 mg of **9a** (92%): $^1H$ NMR (250 MHz) $\delta$ 6.66 (s, 1H), 5.60 (s, 1H), 3.78 (s, 3H), 3.20 (heptet, 1H, *J*=7 Hz), 3.03 (d, 1H, *J*=14.4 Hz), 2.7–2.8 (m, 2H), 1.9–2.15 (m, 3H), 1.79 (d, 1H, *J*=12 Hz), 0.92–0.99 (m, 2H), 0.87 (s, 3H). This data suggests that the following diagnostic data corresponds to isomer **9b**: $^1H$ NMR (250 MHz) $\delta$ 6.68 (s, 1H), 5.68 (s, 1H), 3.80 (s, 3H).

*4.1.2. 2,3,5-Trimethoxybenzoic acid (**14**).* 1-Bromo-2,3,5-trimethoxybenzene (**13**) (13.25 g, 53.60 mmol) was dissolved in 130 mL of dry ether and was cooled to −78 °C. *t*-Butyllithium (110 mmol, 65 mL of 1.7 M solution in pentane) was added and the resulting solution was kept at −78 °C over a 90-min period and then warmed to −20 °C. The reaction mixture was treated with solid $CO_2$ (>5 g) and stirred at −20 °C for a 30-min period. The reaction was quenched with water and the phases were separated. The aqueous phase was acidified with 10% aqueous HCl, extracted with ether and the combined ethereal extracts were dried over anhydrous $MgSO_4$. After filtration and evaporation of the solvent, the crude acid was recrystallized from hexanes to afford 13.65 g (89%) of acid **14** as white needles, which were homogeneous by TLC analysis (H/E, 1:1, $R_f$ **13**=0.69, $R_f$ **14**=0.14): mp 101–101.5 °C; $^1H$ NMR (250 MHz) $\delta$ 3.82 (s, 3H), 3.89 (s, 3H), 4.01 (s, 3H), 6.71 (d, 1H, *J*=3.0 Hz), 7.16 (d, 1H, *J*=3.0 Hz) [the carboxylic acid proton was not observed]; $^{13}C$ NMR (62.9 MHz) 165.3 (s), 156.4 (s), 152.8 (s), 142.5 (s), 121.8 (s), 106.3 (d), 104.6 (d), 62.3 (q), 56.1 (q), 55.8 (q) ppm; IR (Nujol) 1738, 1605 $cm^{-1}$; MS (*m*/*z*) 212 (100%), 197 (96%), 137 (67%). Elemental analysis for $C_{10}H_{12}O_5$. Calculated: C, 56.59%, H, 5.70%. Found: C, 56.63%, H, 5.71%.

*4.1.3. 4-(1-Methylethyl)-2-hydroxy-3,5-dimethoxybenzoic acid (**15**) and 4-(1-methylethyl)-2,3,5-trimethoxybenzoic acid (**16**).* To a solution of 10.23 g of acid **14** (48.2 mmol) in 70 mL of 98% $H_2SO_4$ was added 6.60 g of 2-propanol (0.11 mol) at rt. The resulting mixture was heated to 45 °C and an additional 116.8 mL of 2-propanol (0.22 mol) was added to the reaction mixture in two portions

over a 30-min period. The resulting reaction mixture was held at 45 °C for 2 h. Standard ethereal workup provided 12.18 g of a crude residue that NMR analysis indicated consisted of 18% benzoic acid **15** and 55% yield of tris-ether **16**. This crude mixture was used directly without further purification or characterization.

*4.1.4. Methyl 4-(1-Methylethyl)-2,3,5-trimethoxybenzoate (**17**).* To a solution of the above crude mixture (900 mg, 3.54 mmol) dissolved in ACS reagent grade acetone (6 mL) was added anhydrous potassium carbonate (980 mg, 7.09 mmol) and iodomethane (1.25 g, 8.80 mmol). The resulting heterogeneous mixture was refluxed for 8 h, cooled to rt, and diluted with brine (10 mL). Standard ethereal workup furnished 932 mg of a crude ester **17**. Chromatography (elution with H/E, 5:1) provided 920 mg (97%) of ester **17**, which was homogeneous by TLC analysis (H/E, 3:1, $R_f$ **17**=0.75): $^1$H NMR (250 MHz) $\delta$ 1.30 (d, 6H, $J$=6.9 Hz), 3.55 (heptet, 1H, $J$=6.9 Hz), 3.80 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 7.02 (s, 1H); $^{13}$C NMR (62.9 MHz) 166.4 (s), 154.1 (s), 152.5 (s), 147.7 (s), 135.7 (s), 122.1 (s), 107.6 (d), 61.4 (q), 61.0 (q), 55.6 (q), 52.1 (q), 25.4 (d), 20.7 (q) ppm; IR (film) 1732 cm$^{-1}$; MS (*m*/*z*) 268 (88%), 221 (100%). Elemental analysis for $C_{14}H_{20}O_5$. Calculated: C, 62.66%, H, 7.52%. Found: C, 62.50%, H, 7.56%.

*4.1.5. 4-(1-Methylethyl)-2,3,5-trimethoxyphenylmethyl alcohol (**18**).* A suspension of $LiAlH_4$ (1.56 g, 40.00 mmol) in 100 mL of anhydrous ether was cooled to 0 °C. A solution of ester **17** (10.00 g, 37.00 mmol) in 50 mL of dry ether was added dropwise and the resulting mixture was allowed to warm to rt over a 4-h period. Standard ethereal workup afforded 9.67 g of a residue. Purification using chromatography (elution with H/E, 3:1) gave 8.82 g (98%) of alcohol **18**, which was homogeneous by TLC analysis (H/E, 2:1, $R_f$ **17**=0.47, $R_f$ **18**=0.14): $^1$H NMR (300 MHz) $\delta$ 1.29 (d, 6H, $J$=7.0 Hz), 2.55 (br s, 1H), 3.48 (heptet, 1H, $J$=7.0 Hz), 3.78 (s, 3H), 3.81 (s, 3H), 3.83 (s, 3H), 4.65 (s, 2H), 6.60 (s, 1H); $^{13}$C NMR (75.5 MHz) 154.6 (s), 151.5 (s), 144.8 (s), 131.5 (s), 130.1 (s), 106.3 (d), 61.3 (t), 60.7 (q), 60.7 (q) [note the preceding signals overlap], 55.6 (q), 25.1 (d), 21.1 (q) ppm; IR (film) 3387 cm$^{-1}$; MS (*m*/*z*) 240 ($M^+$). Elemental analysis for $C_{13}H_{20}O_4$. Calculated: C, 64.96%, H, 8.39%. Found: C, 65.00%, H, 8.42%.

*4.1.6. 2-(1-Methylethyl)-1,3,4-trimethoxy-5-bromomethylbenzene (**19**).* To a cold solution (0 °C) of 5.68 g of alcohol **18** (23.50 mmol) in 50 mL of dry ether was carefully added phosphorus tribromide (3.82 g, 14.11 mmol) and the mixture was stirred for 5 min. Standard ethereal workup, followed by chromatography (elution with H/E, 10:1), gave 6.58 g (92%) of bromide **19**, which was homogeneous by TLC analysis (H/E, 2:1, $R_f$ **18**=0.17, $R_f$ **19**=0.83): $^1$H NMR (250 MHz) $\delta$ 1.83 (d, 6H, $J$=7.2 Hz), 3.48 (heptet, 1H, $J$=7.2 Hz), 3.78 (s, 3H), 3.81 (s, 3H), 3.90 (s, 3H), 4.54 (s, 2H), 6.58 (s, 1H); $^{13}$C NMR (62.9 MHz) 154.5 (s), 151.8 (s), 145.6 (s), 131.7 (s), 128.5 (s), 107.7 (d), 60.6 (q), 60.6 (q) [note the preceding signals overlap], 55.6 (q), 28.7 (t), 25.2 (d), 21.0 (q) ppm; IR (film) 1601 cm$^{-1}$; MS (*m*/*z*) 304 (11%), 302 (11%), 223 (100%). Elemental analysis for $C_{13}H_{19}O_3Br$. Calculated: C, 51.65%, H, 6.34%. Found: C, 51.33%, H, 6.27%.

*4.1.7. 4,4-Dimethyl-2-[4-(1-methylethyl)-2,3,5-trimethoxyphenylmethyl]-1,3-cyclohexanedione (**21**).* 4,4-Dimethylcyclohexane-1,3-dione (**20**) (2.78 g, 19.83 mmol, Aldrich), $K_2CO_3$ (1.37 g, 9.90 mmol), bromide **19** (3.00 g, 9.90 mmol), and KI (822 mg, 4.95 mmol) were dissolved in a mixture of 3 mL of water and 1.5 mL of THF. The reaction mixture was stirred at rt for a 24-h period. The aqueous solution was first extracted with ether (2×50 mL) and the combined ethereal extracts were washed with 100 mL of saturated aqueous $NaHCO_3$. The resulting organic phase was extracted with 5% aqueous NaOH (2×50 mL) and the resulting aqueous solutions were acidified with 10% aqueous HCl and extracted with ether (3×50 mL). The ethereal extracts were dried over anhydrous $MgSO_4$ and concentrated. The crude residue was chromatographed (elution with H/E, 3:1) to afford 2.51 g (68%) of **21**, which was homogeneous by TLC analysis (H/E, 4:1, $R_f$ **21**=0.24): mp 81–83 °C; $^1$H NMR (250 MHz) $\delta$ 1.08 (s, 6H), 1.27 (d, 6H, $J$=6.9 Hz), 1.75 (t, 2H, $J$=6.5 Hz), 2.40 (t, 2H, $J$=6.5 Hz), 3.46 (heptet, 1H, $J$=6.9 Hz), 3.49 (s, 2H), 3.73 (s, 3H), 3.79 (s, 3H), 3.84 (s, 3H), 6.66 (s, 1H); $^{13}$C NMR (62.9 MHz) 202.7 (s), 170.4 (s), 155.5 (s), 150.8 (s), 142.3 (s), 131.1 (s), 128.5 (s), 112.6 (s), 108.2 (d), 61.6 (q), 61.0 (q), 55.6 (q), 39.5 (t), 35.2 (s), 34.1 (t), 25.7 (q), 25.0 (d), 24.9 (t), 21.1 (q) ppm; IR (film) 1734, 1705, 1603 cm$^{-1}$; Elemental analysis for $C_{21}H_{28}O_5$. Calculated: C, 69.59%, H, 8.34%. Found: C, 69.32%, H, 8.41%.

*4.1.8. 3-Methoxy-6,6-dimethyl-2-[4-(1-methylethyl)-2,3,5-trimethoxyphenylmethyl]-2-cyclohexenone (**22**).* To a suspension of degreased NaH (60%, 565 mg, 23.51 mmol) in 20 mL of dry DMF at 0 °C was added dione **21** (7.13 g, 19.60 mmol) in 40 mL of DMF over a 30-min period. The resulting solution was warmed to rt and then stirred for 30 min. Dimethyl sulfate (2.70 g, 21.50 mmol) was then added and the resulting mixture was stirred at rt for 12 h. The reaction mixture was diluted with ether and quenched with water. The resulting organic phase was washed sequentially with aqueous 10% HCl and saturated aqueous $Na_2CO_3$, dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude residue was chromatographed (elution with H/E, 3:1) to give 7.30 g of **22** (99%), which was homogeneous by TLC analysis (H/E, 2:1, $R_f$ **21**=0.19, $R_f$ **22**=0.58): $^1$H NMR (250 MHz) $\delta$ 1.13 (s, 6H), 1.25 (d, 6H, $J$=7.0 Hz), 1.88 (t, 2H $J$=6.2 Hz), 2.64 (t, 2H, $J$=6.2 Hz), 3.45 (heptet, 1H, $J$=7.0 Hz), 3.61 (s, 2H), 3.63 (s, 3H), 3.76 (s, 3H), 3.81 (s, 3H), 3.82 (s, 3H), 6.16 (s, 1H); $^{13}$C NMR (62.9 MHz) 202.7 (s), 170.6 (s), 154.1 (s), 151.3 (s), 145.1 (s), 131.9 (s), 127.2 (s), 115.7 (s), 106.1 (d), 60.7 (q), 60.1 (q), 55.4 (q), 54.8 (q), 39.4 (s), 34.3 (t), 24.9 (d), 24.5 (q), 22.0 (t), 21.4 (q), 21.3 (q) ppm; IR (film) 1615 cm$^{-1}$. Elemental analysis for $C_{22}H_{32}O_5$. Calculated: C, 70.17%, H, 8.57%. Found: C, 70.06%, H, 8.88%.

*4.1.9. 3-Ethenyl-4,4-dimethyl-2-[4-(1-methylethyl)-2,3,5-trimethoxyphenylmethyl]-2-cyclohexenone (**12**).* A solution of 7.50 g (20.00 mmol) of enone **22** and $CeCl_3$ (161 mg, 0.66 mmol) in 40 mL of ether at rt was treated dropwise with 70 mL (70.00 mmol) of vinylmagnesium bromide (1.0 M in THF) over a 30-min period. The reaction mixture was stirred at rt for 13 h. The reaction mixture was quenched with ice and then diluted with 100 mL of ether. The resulting mixture was placed in a separatory funnel and the ethereal phase was shaken for a 5-min period with 200 mL of a 10% aqueous HCl solution. Standard ethereal workup, followed by chromatography (elution with H/E, 3:1), provided 6.93 g (95%) of conjugated dienone **12**, which was homogeneous by TLC analysis (H/E, 2:1, $R_f$ **22**=0.15, $R_f$ **12**=0.57): mp 104–105 °C; $^1$H NMR (250 MHz) $\delta$ 1.23 (s, 6H), 1.26 (d, 6H, $J$=7.2 Hz), 1.93 (t, 2H, $J$=6.7 Hz), 2.55 (t, 2H, $J$=6.7 Hz), 3.43 (heptet, 1H, $J$=7.2 Hz), 3.66 (s, 3H), 3.68 (s, 2H), 3.81 (s, 6H), 5.15 (d, 1H, $J$=17.9 Hz), 5.35 (d, 1H, $J$=11.5 Hz), 6.13 (s, 1H), 6.36 (dd, 1H, $J$=17.9, 11.5 Hz); $^{13}$C NMR (62.9 MHz) 195.4 (s), 163.5 (s), 154.0 (s), 151.5 (s), 144.9 (s), 133.4 (d), 132.3 (s), 131.7 (s), 127.6 (s), 119.7 (t), 106.1 (d), 60.7 (q), 59.9 (q), 55.4 (q), 37.3 (t), 35.5 (s), 34.4 (t), 27.2 (q), 26.2 (t), 24.9 (d), 21.2 (q) ppm; IR (film) 1670, 1600 cm$^{-1}$; MS (*m*/*z*) 372 (5%), 210 (100%), 195 (53%). Elemental analysis for $C_{23}H_{32}O_4$. Calculated: C, 74.15%, H, 8.66%. Found: C, 74.26%, H, 8.71%.

*4.1.10. 11,12,14-Trimethoxy-9(**10**→**20**)-5aH-abeo-abieta-5(**10**),8,11,13-tetraen-1-one (**11**).* To a solution of **12** (3.00 g, 8.06 mmol) in 40 mL of dry DCM at −78 °C was added 3.06 mL of $TiCl_4$ (16.12 mmol) and the reaction mixture was stirred at −78 °C for 20 min and then warmed to rt over a 30-min period. Standard ethereal workup, followed by chromatography (elution H/E, 4:1),

provided 2.89 g (96%) of enone **11**, which was homogeneous by TLC analysis (H/E, 1:1, $R_f$ **12**=0.43, $R_f$ **11**=0.38): mp 120–121 °C; $^1$H NMR (250 MHz) δ 1.16 (s, 6H), 1.32 (d, 6H, *J*=7.2 Hz), 1.79 (t, 2H, *J*=6.7 Hz), 2.49 (t, 2H, *J*=6.7 Hz), 2.65 (br t, 2H, *J*=6.4 Hz), 3.00 (br t, 2H, *J*=6.4 Hz), 3.37 (heptet, 1H, *J*=7.2 Hz), 3.65 (s, 3H), 3.74 (s, 3H), 3.86 (s, 3H), 3.88 (s, 2H); $^{13}$C NMR (100.6 MHz) 20.5 (t), 22.3 (q), 24.2 (t), 26.1 (d), 26.9 (q), 29.5 (t), 34.5 (t), 36.6 (s), 37.3 (t), 60.6 (q), 60.8 (q), 62.0 (q), 129.0 (s), 131.9 (s) 131.9 (s) [note: the preceding signals overlap], 132.8 (s) 132.8 (s) [note the preceding signals overlap], 147.5 (s), 151.2 (s), 165.4 (s), 197.7 (s) ppm; IR (film) 1664 cm$^{-1}$; MS (*m*/*z*) 372 ($M^+$). Elemental analysis for $C_{23}H_{32}O_4$. Calculated: C, 74.15%, H, 8.66%. Found: C, 73.90%, H, 8.61%.

*4.1.11. 11,12,14-Trimethoxy-9(**10**→**20**)-5aH-abeo-abieta-1(**10**),8,11,13-tetraene (**23**).* A mixture of enone **11** (2.60 g, 6.99 mmol) and *p*-tosylhydrazine (1.43 g, 7.69 mmol) dissolved in 25 mL of absolute ethanol was stirred at rt for a 12-h period. Evaporation of the solvent and elution of the residue through a plug of silica gel afforded the crude hydrazone, which was used without further purification or characterization (H/E, 1:1, $R_f$ hydrazone=0.38, $R_f$ **11**=0.34).

The above hydrazone was stirred in 10 mL of DMF and 10 mL of sulfolane containing 10 mg of bromocresol green. The resulting mixture was warmed to 90 °C and sodium cyanoborohydride (2.20 g, 350 mmol) was added, followed by sufficient 2 M aqueous HCl to give a tan color. Heating was continued for 90 min during which time several portions of 2 M aqueous HCl were added to maintain the proper acidity, indicated by the tan color. The reaction mixture was diluted with 25 mL of hexanes and the resulting solution was refluxed for a 1-h period and then cooled. Standard ethereal workup afforded 1.78 g of a crude residue. Chromatography on silica gel (elution with H/E, 10:1) gave 1.61 g (64%) of trisubstituted olefin **23**, which was homogeneous by TLC analysis (H/E, 1:1, $R_f$ hydrazone=0.32, $R_f$ **23**=0.80): mp 101–103 °C; $^1$H NMR (250 MHz) δ 0.89 (s, 3H), 0.93 (s, 3H), 1.05–1.42 (m, 9H), 1.33 (d, 3H, *J*=7.1 Hz), 1.34 (d, 3H, *J*=7.1 Hz), 1.75–1.83 (m, 1H), 1.92–2.15 (m, 3H), 2.35 (d, 1H, *J*=15.0 Hz), 2.59 (ddd, 1H, *J*=12.5, 8.7 Hz, 3.7 Hz), 3.05 (d, 1H, *J*=15 Hz), 3.16 (ddd, 1H, *J*=16.2, 8.7 Hz, 3.7 Hz), 3.41 (heptet, 1H, *J*=7.1 Hz), 3.65 (s, 3H), 3.78 (s, 3H), 3.87 (s, 3H), 5.50 (br s, 1H); $^{13}$C NMR (62.9 MHz) 151.2 (s), 150.6 (s), 146.5 (s), 138.1 (s), 133.7 (s), 131.9 (s), 130.6 (s), 130.1 (s), 121.3 (d), 62.2 (q), 60.2 (q), 51.3 (q), 35.2 (t), 31.9 (s), 31.4 (t), 29.6 (t), 27.3 (d), 27.1 (d), 25.8 (q), 25.8 (q) [note: the two preceding signals overlap], 23.1 (t), 22.2 (q), 22.1 (q) ppm; IR (film) 2934 cm$^{-1}$. Elemental analysis for $C_{23}H_{34}O_3$. Calculated: C, 77.04%, H, 9.56%. Found: C, 77.15%, H, 9.66%.

*4.1.12. 11,12-Dihydroxy-14-methoxy-9(**10**→**20**)-5aH-abeo-abieta-1(**10**),8,11,13-tetraene (**24**).* Ethanethiol (16.8 g, 0.29 mol) was added dropwise to a cold solution (0 °C) of sodium hydride (3.2 g, 0.13 mol, 80% dispersion in oil) suspended in 35 mL of freshly distilled DMF. The resulting mixture was then stirred at rt for a 2-h period, followed by the addition of a solution of 1.60 g of ether **23** (4.47 mmol) dissolved in 20 mL of dry DMF. The reaction mixture was heated to 90 °C for 24 h, and then cooled to 0 °C and cautiously neutralized with 2 M aqueous HCl. Standard ethereal workup, followed by purification by chromatography on silica gel (elution with H/E, 10:1→5:1), gave 1.26 g (86%) of catechol **24**, which was homogeneous by TLC analysis [H/E, 5:1, $R_f$ **23**=0.91, $R_f$ **24**=0.30]: $^1$H NMR (300 MHz) δ 0.87 (s, 3H), 0.92 (s, 3H), 1.09–1.38 (m, 9H), 1.37 (d, 1H, *J*=7.1 Hz), 1.38 (d, 1H, *J*=7.1 Hz), 1.81 (dd, 1H, *J*=13.8, 4.5 Hz), 1.93–2.11 (m, 3H), 2.55–2.65 (m, 1H), 3.05–3.15 (m, 2H), 3.44 (heptet, 1H, *J*=7.1 Hz), 3.62 (d, 1H, *J*=12.4 Hz), 3.62 (s, 3H), 5.48 (br s, 1H); $^{13}$C NMR (75.5 MHz) 148.8 (s), 141.9 (s), 137.7 (s), 136.8 (s), 126.3 (s), 125.9 (s), 124.6 (s), 121.2 (d), 62.5 (q), 50.6 (d), 35.4 (t), 32.0 (s), 31.4 (t), 29.9 (t), 27.2 (q), 27.2 (q), 25.5 (d), 25.3 (t), 23.1 (t), 21.2 (q), 21.2 (q) [note: the two preceding signals overlap] ppm; IR (film) 3392 cm$^{-1}$. Elemental analysis for $C_{21}H_{30}O_3$. Calculated: C, 76.33%, H, 9.15%. Found: C, 72.69%, H, 9.20%.

*4.1.13. (±)-12-Hydroxy-9(**10**→**20**)-5aH-abeo-abieta-1(**10**),8(**9**),12(**13**)-trien-11,14-dione (**2**).* (a) *Via the* in situ *oxidation/acid hydrolysis procedure*: To a mixture of catechol **24** (740 mg, 2.24 mmol) and ammonium cerium nitrate (2.00 g, 3.65 mmol) dissolved in 20 mL of a 1:1 mixture of water and ether was stirred vigorously for a 1-h period at rt. The ethereal phase was separated and concentrated to a residue. The crude residue was dissolved in THF (10 mL) and 1 mL of 10% aqueous $H_2SO_4$ was added. The resulting mixture was stirred vigorously at rt for a 5-h period. Standard ethereal workup, followed by chromatography (elution with H/E, 10:1), afforded 700 mg (99%) of quinone **2**, which was homogeneous by TLC analysis (H/E, 19:1, $R_f$ **24**=0.64, $R_f$ **2**=0.16): mp 158 °C; $^1$H NMR (250 MHz) δ 0.86 (s, 3H), 0.90 (s, 3H), 1.08–1.47 (m, 9H), 1.21 (d, 6H, *J*=7.2 Hz), 1.82 (br d, 1H, *J*=10.9 Hz), 1.90–2.10 (m, 3H), 2.44–2.51 (m, 1H), 2.87 (d, 1H, *J*=15.5 Hz), 3.00–3.10 (m, 1H), 3.20 (heptet, 1H, *J*=7.2 Hz), 3.58 (d, 1H, *J*=15.5 Hz), 5.48 (s, 1H), 7.06 (s, 1H); $^{13}$C NMR (62.9 MHz) 183.6 (s), 166.7 (s), 149.9 (s), 146.8 (s), 138.9 (s), 134.7 (s), 124.6 (s), 122.8 (d), 50.3 (d), 33.7 (t), 32.2 (s), 31.4 (t), 27.1 (d), 27.1 (t), 26.4 (q), 24.6 (t) [note: the two preceding signals overlap], 24.4 (q), 23.1 (t), 19.9 (q) ppm; IR (film) 3378, 1636 cm$^{-1}$. Elemental analysis for $C_{20}H_{26}O_3$. Calculated: C, 76.40%, H, 8.33%. Found: C, 76.08%, H, 8.22%.

(b) *Via the* in situ *oxidation/saponification procedure*: To a mixture of catechol **24** (554 mg, 1.65 mmol) and ammonium cerium nitrate (1.50 g, 2.73 mmol) dissolved in 20 mL of a 1:1 mixture of water and ether was stirred vigorously for 1 h at rt. To the ethereal phase were added 10 mL of aqueous 10% NaOH and 10 mL of THF. The resulting homogeneous mixture was stirred vigorously at rt for a 5-min period. Standard ethereal workup, followed by chromatography (elution with H/E, 10:1), afforded 520 mg (98%) of quinone **2**, which was identical to that characterized above.

*4.1.14. $EtAlCl_2$-catalyzed Diels–Alder of **2** with (E)-α-ocimene (**26**) to give Diels–Alder adducts (**4**).* A mixture of quinone **2** (450 mg, 1.43 mmol), (*E*)-α-ocimene (1.50 g, 11.0 mmol), 50 mg of $EtAlCl_2$, and 2.0 mL of dry benzene was stirred at rt for 12 h. The reaction mixture was concentrated under vacuum and the residue was purified using silica gel chromatography (elution with H/E, 10:1) to provide 168 mg (30%) of crystalline alcohol **4**, which was homogeneous by TLC analysis (H/E, 10:1, $R_f$ **2**=0.85, $R_f$ **4**=0.60).

*4.1.15. $Eu(fod)_3$-catalyzed Diels–Alder of **2** with (E)-α-ocimene (**26**) to give Diels–Alder adducts (**4**) and isomer (**28**).* A mixture of quinone **2** (450 mg, 1.43 mmol), (*E*)-α-ocimene (1.50 g, 11.0 mmol), 50 mg of $EtAlCl_2$, and 2.0 mL of dry benzene was stirred at rt for 12 h. Eventually the reaction mixture was heated at 45 °C for 6 h. The reaction mixture was concentrated under vacuum and the residue was purified using silica gel chromatography (elution with H/E, 10:1) to provide 517 mg (79%) of crystalline alcohol **4**, which was identical to that previously characterized.

Continued elution afforded 59 mg (9%) of an isomeric alcohol **28**, which was homogeneous by TLC analysis (H/E, $R_f$ **28**=0.41): mp 145–146 °C; $^1$H NMR (300 MHz) δ 0.87 (s, 3H), 0.88 (s, 3H), 0.99 (d, 3H, *J*=7.1 Hz), 1.07 (d, 3H, *J*=7.1 Hz), 1.05–1.17 (m, 1H), 1.38 (m, 1H), 1.47 (s, 3H), 1.61 (s, 3H), 1.62 (s, 3H), 1.60–2.11 (m, 9H), 2.22 (d, 1H, *J*=13.7 Hz), 2.31 (m, 1H), 2.82 (m, 1H), 2.91 (d, 1H, *J*=13.7 Hz), 2.93 (heptet, 1H, *J*=7.1 Hz), 5.24 (s, 1H), 5.45 (s, 1H); $^{13}$C NMR (75.5 MHz) 203.8 (s), 172.0 (s), 138.7 (s), 137.3 (s), 125.5 (d), 120.9 (d), 120.0 (s), 90.3 (s), 88.4 (s), 52.9 (s), 52.5 (d), 52.1 (d), 51.8 (s), 44.1 (d), 43.4 (t), 34.9 (t), 33.6 (t), 31.8 (s), 31.4 (t), 28.0 (q), 27.2 (q), 26.9 (d), 25.4 (q), 24.7 (t), 24.2 (q), 23.9 (t), 23.7 (t), 21.0 (q), 19.6

(q), 19.0 (q) ppm; IR (film) 3414, 1668, 1609 $cm^{-1}$. Elemental analysis for $C_{30}H_{42}O_3$. Calculated: C, 79.94%, H, 9.40%. Found: C, 79.74%, H, 9.27%.

*4.1.16. Europium-catalyzed Diels–Alder reaction of **2** with (E)-α-ocimene (**26**) to give alcohol **6**.* A mixture of quinone **2** (450 mg, 1.43 mmol), (*E*)-α-ocimene (**26**) (1.50 g, 11.0 mmol), 50 mg of tris-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)-europium, and 2.0 mL of dry benzene was stored at rt in a sealed tube for 3 days. The sealed reaction vessel was warmed to 45 °C and heated at that temperature for a 48-h period. Finally, the reaction mixture was warmed to 100–110 °C and heated at that temperature for an additional 48 h. The reaction mixture was concentrated under vacuum and the residue was purified using silica gel chromatography (elution with H/E, 10:1) to provide 519 mg (82%) of crystalline alcohol **6**, which was homogeneous by TLC analysis (H/E, 10:1, $R_f$ **2**=0.60, $R_f$ **6**=0.40): mp 155–156 °C; $^1$H NMR (250 MHz) $\delta$ 0.78 (s, 3H), 0.90 (s, 3H), 1.02 (d, 3H, *J*=6.9 Hz), 1.08 (d, 3H, *J*=6.9 Hz), 1.15–1.40 (m, 3H), 1.43 (s, 3H), 1.46–1.55 (m, 2H), 1.58 (s, 3H), 1.66 (s, 3H), 1.70–2.11 (m, 8H), 2.54–2.58 (m, 3H), 2.70 (d, 1H, *J*=14.6 Hz), 2.95 (heptet, 1H, *J*=6.9 Hz), 3.95 (s, 1H), 3.36 (m, 1H), 5.85 (s, 1H); $^{13}$C NMR (62.7 MHz) 202.1 (s), 170.8 (s), 142.0 (s), 136.9 (s), 126.5 (d), 121.6 (d), 120.7 (s), 89.5 (s), 89.1 (s), 53.4 (d), 51.6 (s), 50.4 (s), 50.0 (d), 49.8 (d), 49.5 (t), 34.7 (t), 33.6 (t), 32.9 (s), 32.4 (t), 28.5 (q), 27.8 (q), 27.2 (t), 25.3 (q), 24.4 (q), 23.9 (t), 23.3 (d), 23.2 (t), 20.7 (q), 20.1 (q), 19.7 (q) ppm; IR (film) 3500, 1627, 1607 $cm^{-1}$. Elemental analysis for $C_{30}H_{42}O_3$. Calculated: C, 79.94%, H, 9.40%. Found: C, 77.70%, H, 9.37%.

*4.1.17. The Amberlyst reaction to give tetrasubstituted perovskone isomer (**29**).* To a solution of alcohol **4** (80 mg, 0.48 mmol) dissolved in 8 mL of freshly distilled $CH_2Cl_2$ was added 200 mg of Amberlyst® 15 resin. The resulting mixture was refluxed for 12 h, cooled to rt, and filtered. The filtrate was concentrated and the resulting residue was purified by chromatography (elution with H/E, 10:1) to give 72 mg (90%) of crystalline **29**, which was homogeneous by TLC analysis (H/E, $R_f$ **4**=0.50, $R_f$ **29**=0.50): mp 153–154 °C; $^1$H NMR (250 MHz) $\delta$ 0.79 (s, 3H), 0.82 (s, 3H), 0.85 (m, 1H), 1.01 (d, 3H, *J*=7 Hz), 1.10 (d, 3H, *J*=7 Hz), 1.12 (m, 1H), 1.24 (m, 1H) 1.30 (m, 1H,), 1.32 (m, 1H), 1.34 (s, 3H), 1.36 (m, 1H), 1.42 (m, 1H), 1.50 (s, 3H), 1.55 (m, 1H), 1.60 (m, 1H), 1.70 (m, 1H), 1.4 (m, 1H), 1.80 (m, 1H), 2.00 (m, 1H), 2.11 (m, 1H), 2.34 (m, 1H), 2.42 (br t, 1H), 2.53 (d, 1H, *J*=13.5 Hz), 2.72 (m, 1H), 3.08 (heptet, 1H, *J*=7 Hz), 5.32 (m, 1H); $^{13}$C NMR (62.7 MHz) 202.0 (s), 168.8 (s), 131.1 (s), 130.6 (s), 121.6 (s), 97.0 (s), 90.1 (s), 88.9 (s), 56.2 (s), 54.2 (d), 53.0 (d), 48.5 (s), 47.4 (t), 42.1 (t), 41.9 (t), 41.5 (t), 34.5 (t), 33.6 (s), 32.0 (d), 29.5 (q), 29.0 (t), 26.7 (t), 24.7 (q), 24.2 (q), 22.0 (q), 21.9 (t), 20.3 (q), 20.1 (q), 19.3 (t), 19.0 (q) ppm; IR (film) 1624 $cm^{-1}$. Elemental analysis for $C_{30}H_{42}O_3$. Calculated: C, 79.84%, H, 9.40%. Found: C, 79.84%, H, 9.04%.

*4.1.18. Cyclization of alcohol (**6**) to perovskone (**1**) using Amberlyst® 15 resin.* To a solution of alcohol **6** (80 mg, 0.48 mmol) dissolved in 8 mL of freshly distilled DCM was added 200 mg of Amberlyst® 15 resin. The resulting mixture was refluxed for 25 min, cooled, and filtered. The filtrate was concentrated and the resulting residue was purified by chromatography (elution with H/E, 10:1) to give 72 mg (90%) of crystalline (±)-perovskone (**1**), which was homogeneous by TLC analysis (H/E, 10:1, $R_f$ **6**=0.35, $R_f$ **1**=0.42): mp 135–136 °C; $^1$H NMR (400 MHz) $\delta$ 0.81 (s, 3H), 0.84 (s, 3H), 1.03 (d, 3H, *J*=7.2 Hz), 1.12 (d, 3H, *J*=7.2 Hz), 1.24–1.34 (m, 4H), 1.36 (s, 3H), 1.39–1.48 (m, 3H), 1.52 (s, 3H), 1.56–1.66 (m, 5H), 1.67(s, 3H), 1.70–1.84 (m, 3H), 2.02 (dd, 1H, *J*=13.6, 8.0 Hz), 2.13 (dt, 1H, *J*=15.2, 7.2 Hz), 2.35 (dd, 1H, *J*=12.4, 3.2 Hz), 2.42(br t, 1H, *J*=8.8 Hz), 2.56 (d, 1H, *J*=13.6 Hz), 2.73 (dd, 1H, *J*=14.8, 7.2 Hz), 3.11 (heptet, 1H, *J*=7.2 Hz), 5.34 (d, 1H, *J*=6.8 Hz); $^{13}$C NMR (400 MHz) 18.60 (t), 18.71 (q), 19.13 (q), 19.53 (q), 20.58 (t), 20.84 (q), 23.18 (d), 23.35 (q), 26.08 (q), 31.04 (q), 32.47 (t), 32.62 (s), 34.55 (t), 40.12 (t), 40.95 (t), 41.71 (t), 47.25 (s), 47.55 (d), 52.79 (d), 52.82 (d), 52.90 (s), 53.26 (t), 87.74 (s), 88.36 (s), 95.30 (s), 119.10 (d), 122.87 (s), 135.34 (s), 168.63 (s), 200.35 (s) ppm; IR (neat) 2922, 2852, 1628, 1460, 1368, 1265, 740, 703 $cm^{-1}$; Elemental analysis for $C_{30}H_{42}O_3$. Calculated: C, 79.96%, H, 9.39%. Found: C, 79.64%, H, 9.35%.

*4.1.18.1. (**2**)+(**3**)→(**1**)+(**29**) Using reaction conditions (a) [Table 2].* $BF_3\cdot Et_2O$ (3 μL, 0.9 equiv) was added to a solution of quinone **2** (40 mg, 0.13 mmol) and (*E*)-β-ocimene (**3**) (140 mg, 1.04 mmol) in freshly distilled dry toluene (0.50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 90 min and then heated at 50 °C for 10 h. The volatiles were removed in vacuo and the resulting crude residue was directly chromatographed (elution with H/E, 10:1) to give 27 mg (46%) of perovskone and 15 mg (26%) of tetrasubstituted isomer **29**.

*4.1.18.2. (**2**)+(**3**)→(**1**)+(**29**) Using reaction conditions (b) [Table 2].* $BF_3\cdot Et_2O$ (6 μL, 0.9 equiv) was added to a solution of quinone **2** (23 mg, 0.073 mmol) and (*E*)-β-ocimene (**3**) (71 mg, 0.52 mmol) in freshly distilled dry DCM (0.50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 90 min and then heated at 50 °C for 7 h. The volatiles were removed in vacuo and the resulting crude residue was directly chromatographed (elution with H/E, 10:1) to give 16.5 mg (50%) of perovskone and 5 mg (15%) of tetrasubstituted isomer **29**.

*4.1.18.3. (**2**)+(**3**)→(**29**) Using reaction conditions (c) [Table 2].* $BF_3\cdot Et_2O$ (10 μL, 0.9 equiv) was added to a solution of quinone **2** (26 mg, 0.082 mmol) and (*E*)-α-ocimene (**29**) (78 mg, 0.58 mmol) in freshly distilled dry toluene (0.50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 90 min and then heated at 50 °C for 10 h. The volatiles were removed in vacuo and the resulting crude residue was directly chromatographed (elution with H/E, 10:1) to give 21 mg (71%) of only **29**, the tetrasubstituted C(23),C(24)-isomer of perovskone.

*4.1.18.4. (**2**)+(**3**)→No reaction.* Quinone **2** (26 mg, 0.082 mmol) and triene **29** (78 mg, 0.58 mmol) were placed in a sealed tube (neat) and heated at 200 °C for a 12-h period. $^1$H NMR and TLC analysis of the crude reaction mixture indicated that only trace amounts of Diels–Alder adduct **4** had been produced.

*4.1.18.5. (**2**)+(**26**)+$LiClO_4$→(**4**)+(**28**).* Quinone **2** (25 mg, 0.080 mmol) and (*E*)-β-ocimene were dissolved in a 5 M solution of $LiClO_4\cdot Et_2O$. The resulting mixture was stirred at rt for a10-h period. Standard ethereal workup produced a 2:1 mixture of Diels–Alder adducts **4** and **29**, respectively.

*4.1.18.6. (**2**)+(**29**) at 12 kbar→No reaction.* Quinone **2** (25 mg, 0.080 mmol) and (*E*)-β-ocimene were reacted at 12 kbar for 24 h. Workup afford a low yield of the Diels–Alder adducts **4** and **28**, in an undetermined ratio.

*4.1.19. 3-(1-Methylethylenyl)-1,2,4-trimethoxybenzene (**33**).* 1,2,4-Trimethoxybenzene (**30**) (1.00 g, 5.95 mmol) was dissolved in anhydrous THF (30 mL) and the resulting solution cooled to 0 °C. *n*-Butyllithium (1.9 M, 3.4 mL, 6.55 mmol) was added dropwise over a 5-min period and the reaction mixture was allowed to warm to rt over a 30-min period. After 2 h, the mixture was cooled to 0 °C and anhydrous acetone (380 mg, 6.55 mmol) in THF (10 mL) was added dropwise. The reaction mixture was refluxed for a 3-h period, cooled to 0 °C, and then quenched by the dropwise addition of acetic acid (15 mL). Standard ethereal workup, followed by chromatography (elution with pet ether/E, 6:1), afforded 681 mg (55%) of olefin **33** that was homogeneous by TLC analysis (pet ether/E, 6:1, $R_f$ **30**=0.31, $R_f$ **33**=0.22): $^1$H NMR (400 MHz) $\delta$ 2.08 (s, 3H), 3.78 (s,

3H), 3.81 (s, 3H), 3.85 (s, 3H), 4.91 (s, 1H), 5.32 (s, 1H) 6.59 (d, 1H, *J*=8.9 Hz), 6.78 (d,1H, *J*=8.9 Hz).

*4.1.20. 3-(1-Methylethyl)-1,2,4-trimethoxybenzene (**34**).* Alkene **33** (681 mg, 3.27 mmol) and 10% Pd/C (50 mg) were dissolved in 5 mL of ethanol and placed under an atmosphere of hydrogen for a 13-h period at rt. Excess hydrogen gas was removed under a water aspirator and the palladium catalyst was removed by filtration through Celite. Standard ethereal workup, followed by chromatography (elution with pet ether/E, 6:1), gave 641 mg (93%) of **34** that was homogeneous by TLC analysis (pet ether/ether, 6:1, $R_f$ **33**=0.67, $R_f$ **34**=0.22): $^1$H NMR (400 MHz) $\delta$ 1.33 (d, 6H, *J*=7.0 Hz), 3.55 (heptet, 1H, *J*=7.1 Hz), 3.77 (s, 3H), 3.81 (s, 3H), 3.82 (s, 3H), 6.57 (d, 1H, *J*=8.9 Hz), 6.70 (d, 1H, *J*=8.9 Hz); $^{13}$C NMR (100.6 MHz) 21.4 (q), 25.4 (d), 56.0 (q), 56.3 (q), 61.2 (q), 106.4 (d), 109.6 (d), 131.0 (s), 147.5 (s), 148.0 (s), 153.0 (s) ppm; IR (film) 2985, 2952, 2832 cm$^{-1}$; MS (*m*/*z*) 210 (M$^+$).

*4.1.21. Ethyl 2,3,6-trimethoxybenzoate (**35**).* 1,2,4-Trimethoxybenzene **30** (82.30 g, 0.49 mol) was dissolved with mechanical stirring in anhydrous THF (1.2 L) and then cooled to 0 °C. *n*-Butyllithium (210 mL, 2.5 M, 0.53 mol) was added dropwise over a 1-h period and the reaction mixture was allowed to warm to rt. After 2 h, the mixture was cooled to 0 °C and then transferred via a cannula into a solution of ethyl chloroformate (200 mL, 2.1 mol) in THF (500 mL). The resulting mixture was stirred at rt for a 3-h period. Standard ethereal workup, followed by chromatography (elution with H/E, 1:1), afforded 112.90 g (96%) of benzoate **35** that was homogeneous by TLC analysis (H/E, 1:1, $R_f$ **30**=0.41, $R_f$ **35**=0.22): $^1$H NMR (400 MHz) $\delta$ 1.38 (t, 3H, *J*=7.1 Hz), 3.78 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 4.41 (q, 2H, *J*=7.1 Hz), 6.60 (d,1H, *J*=9.0 Hz), 6.88 (d, 1H, *J*=9.0 Hz); $^{13}$C NMR (100.6 MHz) 14.3 (q), 56.3 (q), 56.6 (q), 61.4 (t), 61.5 (q), 106.4 (d), 114.2 (d), 119.6 (s), 146.9 (s), 146.9 (s) [note: the preceding signals overlap], 150.5 (s), 166.0 (s) ppm; IR (film) 2938, 2838, 1732 cm$^{-1}$; MS (*m*/*z*) 240 (M$^+$).

*4.1.22. 3-(1-Methyl-1-hydroxyethyl)-1,2,4-trimethoxybenzene (**32**).* To a mechanically stirred solution of ester **35** (55.01 g, 0.23 mol) in anhydrous THF (700 mL) was added dropwise at 0 °C a solution of freshly prepared methylmagnesium iodide (0.81 mol) in 300 mL of THF. The resulting mixture was stirred for 2 h at rt and then quenched by the dropwise addition of water (100 mL), followed by 100 mL of saturated aqueous $NH_4Cl$. Standard ethereal workup gave 37.5 g of alcohol **32** as a crude oil, which was homogeneous by TLC analysis and was used directly in the next reaction without purification: $^1$H NMR (500 MHz) $\delta$ 1.64 (s, 6H), 3.80 (s, 6H), 3.82 (s, 3H), 5.92 (s, 1H), 6.62 (d, 1H, *J*=8.9 Hz), 6.77 (d, 1H, *J*=8.9 Hz); $^{13}$C NMR (400 MHz) 151.4 (s), 148.0 (s), 147.3 (s), 129.9 (s), 110.5 (d), 107.3 (d), 74.2 (s), 61.3 (q), 56.2 (q), 56.15 (q), 31.2 (q) ppm.

*4.1.23. 3-(1-Methylethyl)-1,2,4-trimethoxybenzene (**34**) from (**32**).* Tertiary alcohol **32** (37.50 g) and 10% Pd/C (2.40 g) were stirred in a mixture of ethanol (200 mL) and 10% HCl (40 mL) under an atmosphere of hydrogen for a 48-h period at rt. Excess hydrogen gas was removed under a water aspirator and the palladium catalyst was removed by filtration through Celite. Standard ethereal workup, followed by chromatography (elution with pet ether/E, 6:1), gave 35.60 g (93%) of **34** that was homogeneous by TLC analysis (pet ether/E, 6:1, $R_f$ **32**=0.67, $R_f$ **34**=0.22), which was identical to that previously characterized.

*4.1.24. 3-(1-Methylethyl)-2,3,5-trimethoxybenzaldehyde (**36**) and 3-(1-methylethyl)-2,4,5-trimethoxybenzaldehyde (**37**).* To compound **34** (7.50 g, 35.7 mmol) and anhydrous TMEDA (5.4 mL, 35.8 mmol) dissolved in anhydrous MTBE (100 mL) was added dropwise 25.0 mL of *n*-butyllithium (1.6 M, 40.0 mmol) at 0 °C. The reaction mixture was slowly warmed to rt, stirred for 30 min, cooled to 0 °C and then added via a cannula to a solution of anhydrous DMF (15 mL, 193.7 mmol) in MTBE (50 mL) and stirred at rt for 6.5 h. Standard ethereal workup, followed by chromatography (elution with H/E, 8:1), gave 6.31 g (74%) of **36**, which was homogeneous by TLC analysis (H/E, 8:1, $R_f$ **34**=0.50, $R_f$ **36**=0.35): $^1$H NMR (250 MHz) $\delta$ 1.33 (d, 6H, *J*=7.5 Hz), 3.57 (heptet, 1H, *J*=7.6 Hz), 3.83 (s, 3H), 3.87 (s, 3H), 3.95 (s, 3H), 7.04 (s, 1H), 10.34 (s, 1H); $^{13}$C NMR (62.9 MHz) 20.8 (q), 25.8 (d), 55.7 (q), 61.0 (q), 62.5 (q), 103.2 (d), 127.4 (s), 139.0 (s), 151.6 (s), 152.1 (s), 155.1 (s), 189.4 (d) ppm; IR (film) 2991, 2957, 2871, 1688 cm$^{-1}$; MS (*m*/*z*) 239 (MH$^+$).

Continued elution (H/E, 8:1) afforded 1.50 g (18%) of the isomeric aldehyde **37**, which was homogeneous by TLC analysis (H/E, 8:1, $R_f$ **37**=0.23): $^1$H NMR (250 MHz) $\delta$ 1.36 (d, 6H, *J*=7.5 Hz), 3.46 (heptet, 1H, *J*=7.6 Hz), 3.85 (s, 3H), 3.88 (s, 3H), 3.94 (s, 3H), 7.25 (s, 1H), 10.28 (s, 1H); $^{13}$C NMR (62.9 MHz) 21.7 (q), 25.5 (d), 55.9 (q), 61.0 (q), 65.5 (q), 107.9 (d), 124.6 (s), 135.7 (s), 150.2 (s), 155.1 (s), 157.1 (s), 189.5 (d) ppm; IR (film) 2955, 2869, 1681 cm$^{-1}$; MS (*m*/*z*) 239 (MH$^+$).

*4.1.25. 4-(1-Methylethyl)-2,3,5-trimethoxybenzyl alcohol (**18**).* (a) *Via sodium borohydride reduction of benzaldehyde* **36**: Aldehyde **36** (2.00 g, 8.4 mmol) was dissolved in anhydrous ethanol (30 mL) and cooled to 0 °C. Sodium borohydride (381 mg, 10.1 mmol) was added in small portions over a 30-min period, and the reaction mixture was stirred at rt for 2 h. Water (10 mL) was added, and the ethanol removed under reduced pressure. Treatment of the residue with cold 5% aqueous HCl (20 mL), followed by standard ethereal workup, provided 2.01 g (99%) of **18**, which was homogeneous by TLC analysis (H/E, 6:1, $R_f$ **36**=0.63, $R_f$ **18**=0.03) and was identical to that characterized previously.

(b) *Via metalation of* **34** *and reaction with formaldehyde*: *n*-Butyllithium (1.6 M, 3.3 mL, 5.2 mmol) was added to a mixture of compound **34** (1.03 g, 4.76 mmol) and TMEDA (0.72 mL, 4.76 mmol) in anhydrous MTBE (40 mL) at 0 °C. The reaction mixture was then stirred for 2 h at rt. Gaseous formaldehyde, generated by heating paraformaldehyde at 130 °C, was then bubbled into the reaction mixture for a 5-min period. Water (10 mL) was added, followed by 5% aqueous HCl (20 mL). Standard ethereal workup, followed by chromatography (elution with H/E, 3:1), afforded 767 mg (65%) of alcohol **18**, which was homogeneous by TLC analysis (H/E, 1:1, $R_f$ **34**=0.85, $R_f$ **18**=0.35) and identical to that characterized previously.

*4.1.26. 3-Methoxy-6,6-dimethylcyclohex-2-enone (**39**).* 4,4-Dimethylcyclohexane-1,3-dione (**20**) (10.02 g, 71.3 mmol) and *p*-TsOH (136 mg, 0.71 mmol) were refluxed in benzene (50 mL) and methanol (10 mL) using a Dean–Stark trap for a 20-h period. The reaction mixture was cooled to rt and then quenched with 5% $Na_2CO_3$ (50 mL). Standard ethereal workup, followed by chromatography (elution with H/E, 3:2), provided 9.82 g (82%) of enone **39**, which was homogeneous by TLC analysis (H/E, 1:1, $R_f$ **20**=0.35, $R_f$ **39**=0.52): $^1$H NMR (400 MHz) $\delta$ 1.13 (s, 6H), 1.37 (t, 3H, *J*=7.0 Hz), 1.81 (t, 2H, *J*=6.4 Hz), 2.44 (t, 2H, *J*=6.4 Hz), 3.90 (q, 2H, *J*=7.0 Hz), 5.30 (s, 1H); $^{13}$C NMR (100.6 MHz) 14.3 (q), 24.7 (q), 26.4 (q), 35.1 (t), 40.3 (s), 64.3 (t), 101.1 (d), 176.1 (s), 204.8 (s) ppm; IR (film) 2980, 2927, 2868, 1651, 1611 cm$^{-1}$; MS (*m*/*z*) 268 (M$^+$). Continued elution (H/E, 3:2) gave 2.15 g (18%) of enone **40**.

*4.1.27. 3-Methoxy-6,6-dimethyl-2-[4-(1-methylethyl)-2,3,5-trimethoxyphenylmethyl]-2-cyclohexenone (**22**) from enone (**39**).* Diisopropylamine (15.0 mL, 107 mmol) and freshly distilled HMPA (19.2 mL, 110 mmol) were added to dry THF (250 mL). The mixture was cooled to −78 °C and *n*-butyllithium (2.5 M, 43.0 mL, 108 mmol) was added dropwise. After stirring for 30 min at −78 °C,

enone **39** (18.02 g, 107 mmol) dissolved in THF (75 mL) was added dropwise. The resulting mixture was stirred 8 h at −78 °C and then allowed to warm to 0 °C over a 2-h period. Bromide **19** (10.52 g, 34.7 mmol) in THF (50 mL) was added portionwise, and the reaction mixture was allowed to stir for a 12-h period at rt. Following standard ethereal workup, the HMPA and excess enone were separated from the crude residue via distillation (100–120 °C at 3 mmHg). The remaining residue was chromatographed (elution with pet ether/ethyl acetate, 3:1) to afford 12.65 g (94%) of enone **22** that was homogeneous by TLC analysis (pet ether/EtOAc, 3:1, $R_f$ **19**=1.00, $R_f$ **22**=0.43) and was identical to that previously characterized. The conversion of **22**→**12**→**11** is described above.

*4.1.28. (±)-11,12,14-Trimethoxy-9(**10**→**20**)-5aH-abeo-abieta-1(**10**),8,11,13-tetraen-1-ol (**41**).* Enone **11** (2.01 g, 5.35 mmol) dissolved in anhydrous THF (25 mL) was added dropwise to a suspension of $LiAlH_4$ in THF (75 mL) at 0 °C. After stirring 30 min at 0 °C, the reaction mixture was quenched by the successive dropwise addition of wet ether (50 mL), water (25 mL), and 1 M aqueous HCl (50 mL). Standard ethereal workup, followed by chromatography (elution with H/E, 3:1), afforded 1.78 g (89%) of alcohol (±)-**41** that was homogeneous by TLC analysis (H/E, 3:1, $R_f$ **11**=0.31, $R_f$ **41**=0.23): $^1$H NMR (400 MHz) $\delta$ 1.00 (s, 3H), 1.03 (s, 3H), 1.33 (s, 3H), 1.35 (s, 3H), 1.57–1.64 (m, 1H), 1.68–1.74 (m, 1H), 1.83–1.89 (m, 2H), 2.39–2.51 (m, 2H), 2.91–3.00 (m, 2H), 3.38 (heptet, 1H, $J$=7.0 Hz), 3.58 (s, 1H), 3.60 (s, 1H), 3.66 (s, 3H), 3.80 (s, 3H), 3.86 (s, 3H) 4.05 (br t, 1H); $^{13}$C NMR (100.6 MHz) 22.4 (q), 24.9 (t), 26.1 (d), 26.7 (q), 27.0 (t), 27.7 (t), 28.3 (q), 28.6 (t), 34.5 (t), 35.3 (s), 60.5 (q), 60.6 (q), 61.9 (q), 70.6 (d), 129.4 (s), 131.3 (s), 132.4 (s), 132.5 (s), 143.0 (s), 146.6 (s), 150.7 (s), 151.6 (s) ppm; MS ($m/z$) 374 ($M^+$).

(*S*)-Methoxytrifluoromethylphenylacetyl chloride (50 mL, 0.27 mmol) was added to dry pyridine (0.5 mL), followed by the addition of anhydrous DCM (0.8 mL). Racemic alcohol **41** (50 mg, 0.13 mmol) was added, and the resulting mixture was stirred for a 72-h period at rt. After cooling to 0 °C, the reaction mixture was diluted with ether (25 mL) and washed successively with 10% aqueous $NH_4Cl$ (2×10 mL), 5% aqueous $NaHCO_3$ (2×10 mL), water (10 mL), and brine (10 mL). The ethereal phase was then dried over anhydrous $Na_2SO_4$ and filtered. Concentration under reduced pressure gave a crude ester that was purified by chromatography (elution with pet ether/ether, 10:1) to afford 73 mg (93%) of the Mosher esters derived from (*R*)-**41** and (*S*)-**41** (pet ether/E, 10:1, $R_f$ **41**=0.08, $R_f$ **Mosher esters**=0.83): $^{19}$F NMR (400 MHz) $\delta$ 4.79 (49%) and 4.83 (51%). This LAH reduction does not produce racemic material as a 2% ee was observed!

*4.1.29. (R)-11,12,14-Trimethoxy-9(**10**→**20**)-5aH-abeo-abieta-1(**10**),8,11,13-tetraen-1-ol [(R)-**41**].* (*S*)-Methyl-CBS-oxazaborolidine [(*S*)-**41**] (1 M, 2.7 mL, 2.7 mmol) and borane-methyl sulfide (1.3 mL, 13.4 mmol) were dissolved in anhydrous THF (100 mL). Enone **11** (5.00 g, 13.4 mmol) was dissolved in anhydrous THF (50 mL) and added dropwise over a 2-h period at rt. The reaction mixture was stirred for 4 h and then cooled to 0 °C. Excess hydride was destroyed by the slow, dropwise addition of cold methanol (50 mL). Following the removal of the volatile components under reduced pressure, the reaction mixture was worked up using standard ethereal workup, except that two washes with 75 mL of 25% aqueous $NH_4Cl$ were included. The resulting ethereal extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to afford 4.53 g (90%) of alcohol (*R*)-**41** that was homogeneous by TLC analysis (H/E, 3:1, $R_f$ **9**=0.31, $R_f$ (*R*)-**41**=0.23): $[\alpha]_D^{24}$ +33.3 ($c$ 31.0 mg/ml, $CHCl_3$). $^1$H NMR (400 MHz) $\delta$ 0.99 (s, 3H), 1.03 (s, 3H), 1.33 (s, 3H), 1.35 (s, 3H), 1.57–1.64 (m, 1H), 1.68–1.74 (m, 1H), 1.82–1.91 (m, 1H), 2.03 (br s, 1H), 2.39–2.51 (m, 2H), 2.91–2.97 (m, 2H), 3.38 (heptet, 1H, $J$=7.0 Hz), 3.58 (s 1H), 3.60 (s, 1H), 3.65 (s, 3H), 3.79 (s, 3H), 3.86 (s, 3H) 4.05 (br t, 1H); $^{13}$C NMR (100.6 MHz) 22.4 (q), 24.9 (t), 26.0 (d), 26.7 (q), 26.9 (t), 27.7 (t), 28.2 (q), 28.6 (t), 34.5 (t), 35.3 (s), 60.4 (q), 60.5 (q), 61.9 (q), 70.5 (d), 129.4 (s), 131.3 (s), 132.4 (s), 132.5 (s), 142.9 (s), 146.6 (s), 150.7 (s), 151.5 (s) ppm; MS ($m/z$) 374 ($M^+$).

(*S*)-Methoxytrifluoromethylphenylacetyl chloride (50 mL, 0.27 mmol) was added to dry pyridine (0.5 mL), followed by the addition of anhydrous DCM (0.8 mL). Alcohol (*R*)-**41** (50 mg, 0.13 mmol) was added, and the resulting mixture was stirred for a 72-h period at rt. After cooling to 0 °C, the reaction mixture was diluted with ether (25 mL) and washed successively with 10% aqueous $NH_4Cl$ (2×10 mL), 5% aqueous $NaHCO_3$ (2×10 mL), water (10 mL), and brine (10 mL). The ethereal phase was then dried over anhydrous $Na_2SO_4$ and filtered. Concentration under reduced pressure afforded a crude ester that was examined directly by $^{19}$F NMR spectroscopy. Chromatography (elution with pet ether/E, 10:1) afforded 77 mg (98%) of a Mosher ester that was homogeneous by TLC analysis (H/E, 10:1, $R_f$ (*R*)-**41**=0.08, $R_f$ **Mosher ester**=0.83): $^1$H NMR (400 MHz) $\delta$ 0.99 (s, 3H), 1.02 (s, 3H), 1.33–1.36 (m, 6H), 1.41–1.50 (m, 2H), 1.72–1.77 (m, 1H), 1.89–1.98 (m, 1H), 2.36–2.43 (m, 1H), 2.55–2.62 (m, 1H), 2.83–3.00 (m, 2H), 3.39 (heptet,1H, $J$=7.0 Hz), 3.50 (br s, 2H), 3.60 (s, 3H), 3.66 (s, 3H), 3.71 (s, 3H), 3.84 (s, 3H), 5.53 (br t, 1H), 7.37–7.40 (m, 3H), 7.58–7.60 (m, 2H). $^{19}$F NMR (400 MHz) $\delta$ 4.79 (90%) and 4.83 (10%).

Recrystallization of the 90% enriched (*R*)-**41** (3×using EtOAc/pet ether) gave crystalline material, which was again converted into its Mosher ester via the procedure described above. $^{19}$F NMR (400 MHz) $\delta$ 4.79 (99%) and 4.83 (1%).

*4.1.30. (S)-11,12,14-Trimethoxy-9(**10**→**20**)-5aH-abeo-abieta-1(**10**),8,11,13-tetraen-1-ol [(S)-**41**].* (*R*)-Methyl-CBS-oxazaborolidine [(*R*)-**43**] (1 M, 1.1 mL, 1.1 mmol) and borane-methyl sulfide (0.51 mL, 5.38 mmol) were dissolved in anhydrous THF (50 mL). Enone **11** (2.00 g, 5.38 mmol) was dissolved in THF (25 mL) and added dropwise over a 1-h period at rt. The reaction mixture was stirred for 4 h and then cooled to 0 °C. Excess hydride was destroyed by the slow, dropwise addition of cold methanol (25 mL). Following the removal of the volatile components under reduced pressure, the mixture was worked up using standard ethereal workup, except two washes with 25 mL of 25% aqueous $NH_4Cl$ were included. Recrystallization from petroleum ether afforded 1.78 g (89%) of alcohol (*S*)-**41** that was homogeneous by TLC analysis (H/E, 3:1, $R_f$ **11**=0.31, $R_f$ (*S*)-**41**=0.23) and exhibited identical spectral data as for alcohol (*R*)-**41**.

(*S*)-Methoxytrifluoromethylphenylacetyl chloride (50 mL, 0.27 mmol) was added to dry pyridine (0.5 mL), followed by the addition of anhydrous DCM (0.8 mL). Alcohol (*S*)-**41** (50 mg, 0.13 mmol) was added, and the resulting mixture was stirred for a 72-h period at rt. After cooling to 0 °C, the reaction mixture was diluted with ether (25 mL) and washed successively with 10% aqueous $NH_4Cl$ (2×10 mL), 5% aqueous $NaHCO_3$ (2×10 mL), water (10 mL), and brine (10 mL). The ethereal phase was then dried over anhydrous $Na_2SO_4$ and filtered. Concentration under reduced pressure afforded a crude ester that was examined directly by $^{19}$F NMR spectroscopy. Chromatography (elution with H/E, 10:1) afforded 78 mg (99%) of a Mosher ester that was homogeneous by TLC analysis (H/E, 10:1, $R_f$ (*S*)-**41**=0.08, $R_f$ **ester**=0.83): $^1$H NMR (400 MHz) $\delta$ 1.01 (s, 3H), 1.08 (s, 3H), 1.32–1.36 (m, 6H), 1.40–1.51 (m, 2H), 1.59–1.66 (m, 1H), 1.84–1.91 (m, 1H), 1.99–2.07 (m, 1H), 2.29–2.38 (m, 1H), 2.57–2.64 (m, 1H), 2.82–2.97 (m, 2H), 3.30 (d,1H, $J$=8.6 Hz), 3.38 (heptet, 1H, $J$=7.0 Hz), 3.60 (s, 3H), 3.66 (s, 3H), 3.71 (s, 3H), 3.84 (s, 3H), 5.53 (br t, 1H), 7.38–7.45 (m, 3H), 7.63–7.65 (m, 2H). $^{19}$F NMR (400 MHz) $\delta$ 4.79 (10%) and 4.83 (90%). Since alcohol (*S*)-**41** was prepared only to establish the enantiomeric purity of the (*R*)-**41**, further enrichment of this material through recrystallization was not carried out.

*4.1.31. Acetylation of (±)-**41**.* To (±)-alcohol **41** (280 mg, 0.67 mmol) dissolved in pyridine (0.8 mL) were added DMAP (9 mg, 0.07 mmol, 0.09 equiv) and acetic anhydride (94 mL, 1.0 mmol, 1.5 equiv) at 0 °C. After stirring for 1 h water (1 mL) was added. The resulting mixture was stirred at rt for a 1-h period. The crude reaction mixture was extracted with EtOAc and the organic phase was washed with saturated aqueous $CuSO_4$, saturated aqueous $NaHCO_3$, brine and dried over anhydrous $Na_2SO_4$. Concentration under reduced pressure afforded a crude oil, which was chromatographed (elution with H/E, 9:1) to give 273 mg (98%) of the acetate of **41**. $^1$H NMR (400 MHz) $\delta$ 1.02 (s, 3H), 1.04 (s, 3H), 1.32 (d, 3H, $J$=6.8 Hz), 1.34 (d, 3H, $J$=6.8 Hz), 1.55–1.62 (m, 1H), 1.68–1.74 (m, 1H), 1.85–1.94 (m, 1H), 2.09 (s, 3H), 2.47 (br s, 2H), 2.85–3.0 (m, 2H), 3.38 (heptet, 1H, $J$=6.8 Hz), 3.4 (s, 2H), 3.66 (s, 3H), 3.72 (s, 3H), 3.86 (s, 3H), 5.26 (br s, 1H); $^{13}$C NMR (400 MHz) 171.4 (s), 151.2 (s), 150.6 (s), 146.7 (s), 145.4 (s), 132.4 (s), 131.9 (s), 129.5 (s), 127.1 (s), 72.8 (d), 61.8 (q), 60.3 (q), 60.2 (q), 35.1 (s), 34.5 (t), 28.0 (q), 27.2 (t), 26.5 (q), 25.9 (d), 25.6 (t), 24.7 (t), 22.3 (q), 22.1 (q), 21.5 (q) ppm.

*4.1.32. (S)-11,12,14-Trimethoxy-9(**10**→**20**)-5aH-abeo-abieta-1(**10**),8,11,13-tetraene [(S)-**23**] from (R)-**41**.* To triphenylphosphine (4.40 g, 16.8 mmol) dissolved in anhydrous NMM (12 mL) was added DEAD (2.4 mL, 15.2 mmol) at −30 °C. After 10 min, alcohol (*R*)-**41** (1.90 g, 5.08 mmol) dissolved in anhydrous THF (12 mL) was added dropwise and the reaction mixture was stirred at −30 °C for 15 min. NBSH (3.31 g, 15.2 mmol) was added portionwise, and the mixture was stirred at −30 °C for a 2-h period. The temperature was slowly increased to −20 °C and stirred for a 2-h period. The temperature was slowly increased to −10 °C and stirred for a 1-h period. The reaction mixture was then slowly warmed to rt and stirred overnight. Standard ethereal workup, followed by chromatography (elution with pet ether/E, 30:1) and recrystallization using hexane afforded 891 mg (49%) of (*S*)-**23** (TLC, pet ether/E, 10:1, $R_f$ (*R*)-**41**=0.08, $R_f$ **23**=0.86): $[\alpha]_D^{24}$ −87.1 (*c* 13.7 mg/ml, $CHCl_3$); $^1$H NMR (400 MHz) $\delta$ 0.95 (s, 3H), 0.99 (s, 3H), 1.06–1.29 (m, 2H), 1.39–1.44 (m, 6H), 1.82–2.17 (m, 4H), 2.60–2.68 (m, 1H), 3.08–3.18 (m, 2H), 3.45–3.51 (heptet, 1H, $J$=7.0 Hz), 3.70 (s, 3H), 3.84 (s, 3H), 3.93 (s, 3H), 5.57 (br s, 1H); $^{13}$C NMR (100.6 MHz) 22.4 (q), 22.4 (q) [note: the preceding signals overlap], 23.4 (t), 26.1 (d), 27.4 (q), 27.7 (q), 29.8 (t), 31.6 (t), 32.2 (s), 35.4 (t), 51.6 (q), 60.5 (q), 62.5 (q), 121.6 (d), 130.3 (s), 132.1 (s), 136.9 (s), 136.9 (s) [note: the preceding signals overlap], 138.4 (s), 146.7 (s), 150.9 (s), 151.5 (s) ppm; MS (*m*/*z*) 359 ($MH^+$).

*4.1.33. Preparation of carbonate (R)-**47** from alcohol (R)-**41**.* Alcohol (*R*)-**41** was dissolved in 3 mL of anhydrous DCM (200 mg, 0.534 mmol) at rt and placed under an atmosphere of Argon. The solution was charged with methyl chloroformate (165 mL, 2.14 mmol), followed by the dropwise addition of pyridine (151 mL, 1.87 mmol). Gas evolution was observed during the addition of the pyridine, as well as the formation of a white solid that soon dissolved back into solution. The reaction was monitored by TLC analysis and upon completion was concentrated and purified by silica gel chromatography without ethereal workup [pet ether/E, 4:1] to give a nearly quantitative yield of carbonate **47**: $^1$H NMR (400 MHz) $\delta$ 5.12 (br t, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.74 (s, 3H), 3.65 (s, 3H), 3.51 (d, 2H, $J$=16.4 Hz), 3.45 (d, 2H, $J$=16.4 Hz), 3.38 (m, 2H), 3.01–2.84 (m, 3H), 2.46 (t, 2H, $J$=5.6 Hz), 1.78 (m, 2H), 1.6 (m, 2H), 1.33 (d, 6H, $J$=7.6 Hz), 1.04 (s, 3H), 1.01 (s, 3H); $^{13}$C NMR (400 MHz) 156.3, 151.4, 150.9, 147.1, 146.6, 132.7, 131.9, 129.7, 126.6, 62.0, 60.6, 60.5, 54.7, 35.4, 34.4, 28.3, 27.8, 27.4, 26.4, 26.1, 25.7, 24.8, 22.4; IR (film) 1750, 1240 cm$^{-1}$; MS-HR (*m*/*z* calculated)=432.2512, (*m*/*z* observed)=432.2421.

*4.1.33.1. (S)-**23** from carbonate **47**.* $Pd(OAc)_2$ (21 mg, 0.92 mmol) was placed in a 10 mL round bottom flask containing 2 mL of freshly distilled DMF, placed under Argon, and stirred to dissolution. After stirring for 5 min, *n*-$Bu_3P$ (23.0 mL, 0.092 mmol, 0.2 equiv) was added and stirred for a 5-min period (or until the red color of the solution darkens to almost black). At this point (*R*)-**47** (200 mg, 0.462 mmol) dissolved in 2 mL of anhydrous DMF was added as well as ammonium formate (175 mg, 2.77 mmol, 6 equiv) that had been finely crushed with a mortar and pestle. The reaction was allowed to stir overnight. Standard ethereal workup gave a crude oil, which was purified by silica gel chromatography [elution with pet ether/E, 4:1] to give (*S*)-**23** (200 mg, 98% yield), which was identical to that previously characterized.

*4.1.33.2. (S)-**23**→(S)-**24**→(S)-**25**→(S)-**2**.* To a solution of ethanethiol (7.5 mL, 101 mmol, 20.0 equiv) in 80 mL of DMF at 0 °C was added NaH (60% in mineral oil, 3.00 g, 75 mmol, 15 equiv) in five portions under a $N_2$ atmosphere. The reaction mixture bubbles vigorously after each addition of NaH and a viscous foam formed. The resulting mixture was stirred at 0 °C for 30 min until it became a clear brown solution. Alkene (*S*)-**23** (1.80 g, 5 mmol) was dissolved in DMF (20 mL) and added to the NaSEt solution slowly. The resulting mixture was heated for 4 days, at 90–95 °C; temperatures >95 °C caused decomposition. TLC analysis revealed that the (*S*)-**23** had been fully deprotected. The reaction mixture was cooled to 0 °C and aqueous HCl (a 5% solution) was added to acidify the reaction mixture. It was then extracted three times with EtOAc. The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. The organic phase was concentrated to give 1.89 g of a crude foam, which was purified by column chromatography (elution with pet ether/E, 4:1) to afford 1.46 g (88%) of hydroquinone (*S*)-**24** as a dark brown foam: $[\alpha]_D^{24}$ −91.5 (*c* 6.4 mg/ml, benzene). The $^1$H NMR, $^{13}$C NMR, IR and MS for (*S*)-**24** were the same as (±)-**24**.

To a solution of hydroquinone (*S*)-**24** (1.46 g, 4.42 mmol) in diethyl ether/water (40/40 mL) at rt was added ceric(IV) ammonium nitrite (CAN) (4.85 g, 8.84 mmol, 2.0 equiv). The resulting mixture was stirred for 4 h at rt. Water (10 mL) was then added and the ether layer was separated. The aqueous layer was extracted with ether (3×20 mL). The combined ethereal extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated to afford 1.50 g of (*S*)-**25** as a red solid.

The above product was dissolved in THF (35 mL) and was treated with 10% aqueous $H_2SO_4$ (15 mL) for 1 h. Diethyl ether (50 mL) was added and the organic phase was separated. The aqueous layer was extracted twice with ether (20 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated to give 1.50 g of a crude red solid. Column chromatography (elution with pet ether/E, 8:1) provided 1.32 g (95%) of *p*-quinone (*S*)-**2** with $[\alpha]_D^{24}$ −155.2 (*c* 0.0051 g/ml, $CHCl_3$): $^1$H NMR (400 MHz) $\delta$ 0.87 (s, 3H), 0.91 (s, 3H), 1.11–1.21 (m, 2H), 1.22 (d, 6H, $J$=6.8 Hz), 1.31–1.40 (m, 1H), 1.57 (d, 1H, $J$=2.4 Hz), 1.82 (dd, 1H, $J$=11.2, 4.0 Hz), 1.94–2.02 (m, 3H), 2.49 (ddd, 1H, $J$=14.8, 9.6, 2.8 Hz), 2.98 (d, 1H, $J$=16.0 Hz), 3.06 (ddd, 1H, $J$=14.8, 8.0, 2.8 Hz), 3.21 (heptet, 1H, $J$=6.8 Hz), 3.59 (d, 1H, $J$=15.6 Hz), 5.49 (br t, 1H, $J$=3.6 Hz), 7.06 (s, 1H); $^{13}$C NMR (400 MHz) 19.96 (q), 19.96 (q), 23.14 (t), 24.43 (d), 24.70 (t), 26.47 (q), 27.20 (t), 27.24 (q), 31.53 (t), 32.26 (s), 33.73 (t), 50.37 (d), 122.83 (d), 124/72 (s), 134.84 (s), 138.98 (s), 146.86 (s), 150.02 (s), 183.64 (s), 186.71 (s) ppm; HRMS: $[M+H]^+$ observed=315.1956; $[M+H]^+$ calculated=315.1960; IR (neat) 3348, 2961, 2934, 1872, 1638, 1391, 1321, 1287, 1128, 1038, 758 cm$^{-1}$.

*4.1.33.3. (S)-**2**→(S)-**6**→(S)-**1**.* A mixture of *p*-quinone (*S*)-**2** (45 mg, 0.143 mmol), *E*-β-ocimene (**26**) (170 mg, 1.25 mmol, 8.7 equiv), and $Eu(fod)_3$ (5 mg) in 1.3 mL of anhydrous benzene was placed in a sealed tube reaction vessel. The tube was placed under a nitrogen atmosphere and sealed. The resulting reaction mixture was stirred at rt for 64 h, then stirred at 40 °C–45 °C for 69 h, and then stirred at 100 °C–110 °C for an additional 48-h period. The reaction mixture was cooled to rt and 3 mg of additional $Eu(fod)_3$

was added. The mixture was sealed and heated at 100 °C for another 72-h period. The benzene was removed from the crude mixture (via a pipette) and placed on a silica gel column. Elution with pet ether/E (30:1 and then 20:1) afforded 51.6 mg (82%) of alcohol (*S*)-**6**: $[\alpha]_D^{24}$ +26.8 (*c* 0.37 mg/ml, benzene); $^1$H NMR (400 MHz) $\delta$ 0.79 (s, 3H), 0.91(s, 3H), 1.02 (d, 3H, *J*=7.2 Hz), 1.08 (d, 3H, *J*=7.2 Hz), 1.20–1.28 (m, 1H), 1.32–1.40 (m, 1H), 1.43 (s, 3H), 1.48–1.56 (m, 3H), 1.59 (s, 3H), 1.67 (s, 3H), 1.76–1.86 (m, 1H), 1.88–1.98 (m, 2H), 1.98–2.14 (m, 4H), 2.37–2.56 (m, 4H), 2.70 (d, 1H, *J*=14.4 Hz), 2.96 (heptet, 1H, *J*=7.2 Hz), 3.95 (s, 1H), 5.07–5.08 (m, 1H), 5.85 (s, 1H); $^{13}$C NMR (400 MHZ) 19.90 (q), 20.31 (q), 20.92 (q), 23.51 (t), 23.60 (q), 24.18 (t), 24.62 (d), 25.58 (q), 27.47 (t), 50.09 (d), 50.25 (d), 50.71 (s), 51.88 (s), 53.69 (d), 89.71 (s), 89.73 (s), 120.91 (s), 121.90 (d), 127.06 (d), 137.10 (s), 142.26 (s), 171.00 (s), 202.32 (s) ppm; HRMS: $[M+H]^+$ observed=451.3226; $[M+H]^+$ calculated=451.3212; IR (neat) 3473, 2957, 2870, 1670, 1629, 1456, 1386, 1275, 1192, 1119, 1035, 838 cm$^{-1}$.

To a solution of alkene **6** (51.6 mg, 0.115 mmol) in DCM (10 mL) was added 100 mg of Amberlyst® 15 ion-exchange resin. The resulting mixture was refluxed under a nitrogen atmosphere for 1 h. The Amerlyst® 15 resin was removed by filtrations and the DCM was concentrated under vacuum. Column chromatography of the resulting residue (elution with pet ether/E, 8:1) gave 46.4 mg (90%) of pure (+)-perovskone: $[\alpha]_D^{24}$ +90.2 (*c* 0.0108 g/ml, $CHCl_3$); $^1$H NMR (400 MHz) $\delta$ 0.81 (s, 3H), 0.84 (s, 3H), 1.03 (d, 3H, *J*=7.2 Hz), 1.12 (d, 3H, *J*=7.2 Hz), 1.24–1.34 (m, 4H), 1.36 (s, 3H), 1.39–1.48 (m, 3H), 1.52 (s, 3H), 1.56–1.66 (m, 5H), 1.67(s, 3H), 1.70–1.84 (m, 3H), 2.02 (dd, 1H, *J*=13.6, 8.0 Hz), 2.13 (dt, 1H, *J*=15.2, 7.2 Hz), 2.35 (dd, 1H, *J*=12.4, 3.2 Hz), 2.42(br t, 1H, *J*=8.8 Hz), 2.56 (d, 1H, *J*=13.6 Hz), 2.73 (dd, 1H, *J*=14.8, 7.2 Hz), 3.11 (heptet, 1H, *J*=7.2 Hz), 5.34 (d, 1H, *J*=6.8 Hz); $^{13}$C NMR (400 MHz) 18.60 (t), 18.71 (q), 19.13 (q), 19.53 (q), 20.58 (t), 20.84 (q), 23.18 (d), 23.35 (q), 26.08 (q), 31.04 (q), 32.47 (t), 32.62 (s), 34.55 (t), 40.12 (t), 40.95 (t), 41.71 (t), 47.25 (s), 47.55 (d), 52.79 (d), 52.82 (d), 52.90 (s), 53.26 (t), 87.74 (s), 88.36 (s), 95.30 (s), 119.10 (d), 122.87 (s), 135.34 (s), 168.63 (s), 200.35 (s) ppm; IR (neat) 2922, 2852, 1628, 1460, 1368, 1265, 740, 703 cm$^{-1}$; HRMS: $[M+H]^+$observed=451.3230, $[M+H]^+$calculated=451.3212.

*4.1.33.4. (S)-**2**→(S)-**1**.* A solution of (*S*)-quinone **2** (64 mg, 0.203 mmol, 1.0 equiv), (*E*)-α-ocimene (**3**) (222 mg, 1.63 mmol, 8 equiv), and freshly distilled $BF_3{\cdot}Et_2O$ (8.5 mg, 17.4 μL, 0.9 equiv) was added to a solution of quinone (*S*)-**2** (26 mg, 0.082 mmol) and in freshly distilled dry DCM (1.00 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 90 min and then heated at 50 °C for 10 h. The volatiles were removed in vacuo and the resulting crude residue was directly chromatographed (elution with H/E, 98:2 to 95:5) to give 52 mg (57%) of (+)-perovskone, which was identical to that characterized via the two step sequence.

## Acknowledgements

Appreciation is extended to the National Science Foundation (CHE-0010128) for support of the (+)-perovskone synthesis. Thanks are extended to Scott Handy and Professor Paul Grieco (Montana State University) for their study of the Diels–Alder reaction of quinone **2** and (*E*)-β-ocimene (**3**) with $LiClO_4{\cdot}Et_2O$. The efforts of Professor Takeshi Kitahara (University of Tokyo) to examine the same Diels–Alder reaction at12 kbar are also gratefully acknowledged.

The following Stork group members have greatly influenced my scientific career: Patrick McCurry (undergraduate research), Paul Grieco (doctoral research), Sam and Sarah Danishefsky, and Dick Hill (my colleague at UGA since 1981). While at Columbia with Professor Stork (1979–1981) I lived for those Saturday mornings when Gilbert would ask me to help him clean out a refrigerator/freezer and he would proceed to tell me the history and his dreams for every sample we encountered. Thank you, Gilbert, for all the fond memories and your mentoring!

## Supplementary data

$^1$H and $^{13}$C NMR spectra for the following have been provided: compounds **30**, **31**, **18**, **19**, **22**, **23**, **33**, **34**, **35**, **36**, **37**, **39**, **41**, and **25**. Tables of crystal data, atomic coordinates, bond lengths, angles, and the ORTEP for byproduct **29**, the isomer of perovskone are also available. This material is available free of charge via the internet at http://pubs.acs.org. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.09.072.

## References and notes

1. Fujita, E.; Node, M. *Prog. Chem. Org. Nat. Prod.* **1986**, *46*, 77–157.
2. (a) Chopra, R. N.; Nayar, S. L.; Chopra, I. C. *Glossary of Indian Medicinal Plants*; CSIR: New Delhi, 1956; p 189; (b) Kirtikar, K. R.; Basu, B. D. *Indian Medicinal Plants*; Indian: Allahabad, 1918; p 1031.
3. Hasan, M.; Iqbal, R.; Ullah, I. *Islamabad J. Sci.* **1978**, *5*, 22–25.
4. (a) Younas, M. C.; Mortier, F. *Bull. Sec. Pharm. Nancy.* **1971**, *90*, 16; (b) Younas, M. C. *Bull. Sec. Pharm. Nancy.* **1971**, *88*, 15.
5. Parvez, A.; Choudhary, M. I.; Akhter, F.; Noorwala, M.; Mohammad, F. V.; Hasan, N. M.; Zamir, T.; Ahmad, V. U. *J. Org. Chem.* **1992**, *57*, 4339–4340.
6. Majetich, G.; Zhang, Y. *J. Am. Chem. Soc.* **1994**, *116*, 4979–4980.
7. For recent reviews of tandem reactions in organic synthesis, see: (a) Fustero, S.; Sanchez-Rosello, M.; del Pozo, C. *Pure Appl. Chem.* **2010**, *82*, 669–677; (b) Grondal, C.; Jeanty, M.; Ender, D. *Nature Chem.* **2010**, *2*, 167–178; (c) Li, X.-W.; Wang, Z.-Y.; Zheng, L.-Y. *Youji Huaxue* **2006**, *26*, 1144–1149; (d) McCarrol, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2224–2248; (e) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136; (f) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103–13159; (g) Ho, T.-L. *Tandem Organic Reactions*; Wiley: New York, NY, 1992.
8. Watson, W. H.; Taira, Z. *Tetrahedron Lett.* **1976**, *29*, 2501–2504.
9. For reviews, see: (a) Laschat, S. *Angew. Chem., Int. Ed. Engl.* **1966**, *35*, 280–291; (b) Ichihara, A.; Oikawa, H. *Curr. Org. Chem.* **1998**, *2*, 365–394; (c) Stocking, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078–3115; (d) Oikawa, H.; Suzuki, K.; Naya, A.; Katayama, K.; Ichihara, A. *J. Am. Chem. Soc.* **1994**, *116*, 3605–3606.
10. Majetich, G.; Zhang, Y.; Feltman, T. L.; Duncan, S., Jr. *Tetrahedron Lett.* **1993**, *34*, 445–448.
11. (a) Kelecom, A. *Tetrahedron* **1983**, *39*, 3603–3608; (b) Koft, E. R. *Tetrahedron* **1987**, *43*, 5775–5780.
12. (a) Feutrill, G. I.; Mirrington, R. N. *Tetrahedron Lett.* **1970**, *16*, 1327–1328; (b) Chakraborti, A. K.; Sharma, L.; Nayak, M. K. *J. Org. Chem.* **2002**, *67*, 6406–6414.
13. Majetich, G.; Zhang, Y.; Wheless, K. *Tetrahedron Lett.* **1994**, *35*, 8727–8730.
14. (a) Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, *71*, 229–246; (b) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227–231; (c) McKillop, A.; Young, D. W. *Synth. Commun.* **1977**, *7*, 467–474; (d) Saunders, B. C.; Stark, B. P. *Tetrahedron* **1967**, *23*, 1867–1872; (e) Smith, L. I.; Byers, D. J. *J. Am. Chem. Soc.* **1941**, *63*, 612–617.
15. Dorn, H. W.; Warren, W. H.; Bullock, J. C. *J. Am. Chem. Soc.* **1939**, *61*, 145–147.
16. Mackenzie, A. R.; Moody, C. J.; Rees, C. W. *Tetrahedron* **1986**, *42*, 3259–3268.
17. Stetter, H.; Dierichs, W. *Chem. Ber.* **1952**, *85*, 1061–1067.
18. Imamoto, T.; Kusumoto, T.; Yokoyama, M. *J. Chem. Soc., Chem. Commun.* **1982**, *18*, 1042–1043.
19. (a) Bruson, H. A.; Kroeger, J. W. *J. Am. Chem. Soc.* **1940**, *62*, 36–44; (b) Barclay, L. R., Part II In *Cyclialkylations of Aromatics*; Olah, G., Ed.; Friedel–Crafts and Related Reactions; Interscience Publishers: New York, NY, 1964; Vol. II, p 785.
20. For the use of dienones in cyclialkylations to prepare functionalized 6,7,6-fused tricycles, see: (a) Majetich, G.; Hicks, R.; Zhang, Y.; Tian, X.; Feltman, T. L.; Fang, J.; Duncan, S., Jr. *J. Org. Chem.* **1996**, *61*, 8169–8185; (b) For the preparation of functionalized 6,6,6-fused systems using this annulation strategy, see: Majetich, G.; Liu, S.; Fang, J.; Siesel, D.; Zhang, Y. *J. Org. Chem.* **1997**, *62*, 6928–6951; (c) For examples of the cyclialkylation of dienone-furans, see: Majetich, G.; Zhang, Y.; Liu, S. *Tetrahedron Lett.* **1994**, *35*, 4887–4890.
21. Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662–3668.
22. (a) Letcher, R. M.; Sasho, M.; Akai, S.; Wada, A.; Kita, Y. *Tetrahedron* **1984**, *40*, 4539–4548; (b) Tamura, Y.; Sasho, M.; Akai, S.; Kishimoto, H.; Sekihachi, J.; Kita, Y. *Tetrahedron Lett.* **1986**, *27*, 195–198.
23. Jacob, P., III; Callery, P. S.; Shulgin, A. T.; Castagnoli, N., Jr. *J. Org. Chem.* **1976**, *41*, 3627–3629.
24. Maier, M. E.; Bayer, A. *Eur. J. Org. Chem.* **2006**, *17*, 4034–4043.
25. For examples, see: (a) Benchikn le-Hocine, M.; Do Khac, D.; Fetizon, M.; Guir, F.; Guo, Y.; Prange, T. *Tetrahedron Lett.* **1992**, *33*, 1443–1446; (b) Taschner, M. J. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; Jai: Greenwich, CT, 1989; Vol. 1, pp 1–102.
26. Engler, T. A.; Sampath, U.; Naganathan, S.; Vander Velde, D.; Takusagawa, F.; Yohannes, D. *J. Org. Chem.* **1989**, *54*, 5712–5727.
27. (a) St.-Jacques, M.; Vaziri, C. *Org. Magn. Reson.* **1972**, *4*, 77–78; (b) Menard, D.; St.-Jacques, M. *Tetrahedron* **1983**, *39*, 1041–1060.
28. Allinger, N. L.; Yuh, Y.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551–8582.

29. The Diels–Alder reactions of functionalized quinones with functionalized dienes under thermal conditions generally fail. For examples, see: Hollinshead, D. M.; Howell, S. C.; Ley, S. V.; Mahon, M.; Ratcliffe, N. M.; Worthington, P. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1579–1586 and references cited therein.
30. (a) Jurczak, J.; Tkacz, M. *J. Org. Chem.* **1979**, 3347–3352; (b) Dauben, W. G.; Bunce, R. A. *J. Org. Chem.* **1982**, 4875–4878; (c) Trost, B. M.; O'Krongly, D.; Belletier, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595–7596; (d) Takeshita, A. H.; Liu, J. F.; Kato, N. *J. Chem. Soc. Perkin 1* **1994**, 1433–1437.
31. Yates, D.; Eaton, P. E. *J. Am. Chem. Soc.* **1960**, *82*, 4436–4437.
32. (a) Wolinsky, J.; Chollar, B.; Baird, M. D. *J. Am. Chem. Soc.* **1962**, *84*, 2775–2779; (b) Vig, O. P.; Vig, B.; Anad, R. C. *Indian J. Chem.* **1969**, *7*, 1111–1113.
33. For other Eu(fod)$_3$-promoted Diels–Alder reactions, see: (a) Gandhi, R. P.; Ishar, M. P. S.; Wali, A. *J. Chem. Soc., Chem. Commun.* **1988**, *16*, 1074–1075; (b) Lamy-Schelkens, H.; Giomi, D.; Ghosez, L. *Tetrahedron Lett.* **1989**, 5887–5890; (c) Castellino, S.; Sims, J. J. *Tetrahedron Lett.* **1984**, *25*, 4059–4062.
34. *o*-Methoxyquinones chelate with titanium-based Lewis acids, see: Seebach, D.; Teschner, M. *Chem. Ber.* **1976**, *109*, 1601–1616.
35. The acetylation and silylation of **2** were achieved using standard conditions. The methyl ether of quinone **2** was prepared either via a Williamson ether synthesis [NaH/$CH_3I$/DMF (35%)].
36. For a related Lewis acid-catalyzed Diels–Alder reaction of an α-hydroxyquinone, see: Trost, B. M.; Ippen, J.; Vladuchick, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 8117–8118.
37. Snider, B. B.; Zhang, Q. W. *J. Org. Chem.* **1991**, *56*, 4908–4913.
38. Majetich, G.; Khetani, V. *Tetrahedron Lett.* **1990**, *31*, 2243–2246.
39. The structure assigned to undesired **29** was verified by means of a single-crystal X-ray diffraction study. Data relevant to this analysis can be found in the Supplemental Section of this manuscript.
40. Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772–3774.
41. (a) Grieco, P. A.; Beck, J. P.; Handy, S. T.; Saito, N.; Daeuble, J. F. *Tetrahedron Lett.* **1994**, *37*, 6783–6786; (b) Grieco, P. A. *Aldrichimica Acta* **1991**, *24*, 59–66.
42. (a) Miller, J. A.; Wood, H. C. S. *J. Chem. Soc. C* **1968**, 1837–1838; (b) Haley, R. C.; Miller, J. A.; Wood, H. C. S. *J. Chem. Soc. C* **1969**, 264–265.
43. Crowther, G. P.; Sundberg, R. J.; Sarpeshkar, A. M. *J. Org. Chem.* **1984**, *49*, 4657–4663.
44. For the preparation of hexasubstituted benzenes from **30**, see: Cabbiddu, S.; Contini, L.; Fattuoni, C.; Costantino, F.; Gelli, G. *Tetrahedron* **1991**, *47*, 9279–9288.
45. Conformational or stereoelectronic effects may explain the observed regioselectivity, see: Carreno, M. C.; Ruano, J. L.; Toledo, M. A.; Urbano, A. *Tetrahedron: Asymmetry* **1997**, *8*, 913–921.
46. Majetich, G.; Liu, S. *Synth. Commun.* **1993**, *23*, 2331–2335.
47. Aryllithiums derived from **30** can often act as a base towards ketones, such as acetone, in these metallations, see: Slocum, D. W.; Moon, R.; Thompson, D. S.; Coffey, D. S.; Li, J. D.; Slocum, M. G.; Liegel, A.; Gayton-Garcia, R. *Tetrahedron Lett.* **1994**, *35*, 385–388.
48. The one-pot conversion of **32** to **34** using hydrogenation at one atmosphere in the presence of HCl has been improved on by using higher reaction pressures, see: Martinez-Solorio, D.; Jennings, M. P. *Org. Lett.* **2009**, *11*, 189–192.
49. Smith, A. B.; Levenberg, P. A.; Jerris, P. J.; Scarborough, R. M.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 1501–1513.
50. (a) Clerici, A.; Passtori, N.; Porta, O. *Tetrahedron* **2001**, *57*, 217–225; (b) Zimmerman, H. E.; Wang, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 2205–2216.
51. Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775–1776.
52. Although (*S*)-**23** was used in our synthesis of (+)-salvadione-A [Majetich, G.; Wang, Y.; Li, Y.; Vohs, J. K.; Robinson, G. H. *Org. Lett.* **2003**, *5*, pp 3847–3850] and our synthesis of (−)-barbatusol [Majetich, G.; Zou, G.; Grove, J. *Org. Lett.* **2008**, *10*, pp 81–84], the publication of this work was held in reserve for an opportunity to honor Professor Stork.
53. Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.
54. (a) Calco, D.; Port, M.; Deelpech, B.; Lett, R. *Tetrahedron Lett.* **1996**, *37*, 1023–1024; (b) Mori, K.; Amaike, M.; Itou, M. *Tetrahedron* **1993**, *49*, 1871–1878.
55. Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1988**, *29*, 6409–6412.
56. The mechanism of this reduction was proposed in 1949, see: (a) Lardelli, G.; Jeger, O. *Helv. Chim. Acta* **1949**, *32*, 1817–1835; (b) Fischer, R.; Lardelli, G.; Jeger, O. *Helv. Chim. Acta* **1950**, *33*, 1335–1338; (c) Fischer, R.; Lardelli, G.; Jeger, O. *Helv. Chim. Acta* **1951**, *34*, 1577–1585; (d) Hutchins, R.; Kacher, M.; Rua, L. *J. Org. Chem.* **1975**, *40*, 923–926; (e) Hutchins, R.; Natale, N. *J. Org. Chem.* **1978**, *43*, 2299–2301.
57. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.
58. Mori, K.; Puapoomchareon, P. *Liebigs Ann. Chem.* **1991**, 1053–1056.
59. Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507.
60. Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *Tetrahedron* **1993**, *49*, 5483–5493.
61. Majetich, G.; Zou, G.; Hu, S. Synthesis of (+)-salvadione-B, in preparation.