Tandem Use of Cobalt-Mediated Reactions to Synthesize (+)-Epoxydictymene, a Diterpene Containing a *Trans*-Fused 5−5 Ring System

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Abstract: The diterpene (+)-epoxydictymene has been synthesized in 20 steps using the asymmetry of (*R*)-pulegone and several substrate-controlled diastereoselective reactions to prepare the natural product in its natural configuration. Three of the four rings were assembled with two consecutive intramolecular reactions involving dicobalt hexacarbonyl complexes of alkynes: a Lewis acid-promoted Nicholas reaction and a Pauson−Khand reaction. The construction of the strained *trans*-3-oxabicyclo[3.3.0]octane ring system of the natural product presented a significant challenge. To this end, several radical and anionic cyclizations were studied, the latter leading to (+)-epoxydictymene.

Isolated and fully characterized in 1983 (Scheme 1), the diterpene epoxydictymene[1] (**1**) contains an 8-membered ring[2] with five asymmetric centers as its central structural element and is one of four terpene natural products[3−5] containing the strained *trans*-fused 5−5 ring system[6,7] (Figure 1). This structural and stereochemical complexity, along with epoxydictymene's similarity to carbocyclic systems previously prepared using two reactions of dicobalthexacarbonyl clusters of alkynes,[8−10] led us to explore this cobalt chemistry in the preparation of the natural product. These studies, reported herein, led to the first total synthesis of a natural product containing a *trans*-5−5 moiety.[11]

Our synthetic strategy is outlined in Scheme 2. Epoxydictymene possesses few functional groups, and therefore a protecting group strategy was not a chief concern. On the contrary, because of this dearth of functionality, we reasoned that synthesis of the natural product might involve temporary functional group introduction to facilitate carbon−carbon bond formation. Accordingly, tetracyclic enone **2** became an appealing target since a reductive methylation might install the quaternary methyl group at C1. Whether this transformation would construct the *trans*-5−5 ring system, however, was uncertain. In contrast to 6−6 fused systems, the *trans*-5−5 is much less stable than the *cis* (approximately 6 kcal/mol)[6] and, consequently, possesses a degree of strain and conformational rigidity not usually associated with 5-membered rings. Further, the difference in the heats of formation of the parent *cis*- and *trans*-3-oxabicyclo[3.3.0]octanes, the 5−5 ring system present in epoxydictymene, has been calculated to be over 10 kcal/mol.[12] Nevertheless, as we and others had prepared similar fused 5−5 enones via intramolecular Pauson−Khand reactions,[10,13,14] cobalt cluster **3** was a logical precursor to **2**. Our experience with the Lewis acid-promoted Nicholas reaction[8,9] suggested that **4**, fashioned with a displacement of a triflate derived from **5** by an acetylide derived from propargylic acetal **6**, should be the initial focus of our synthetic efforts.

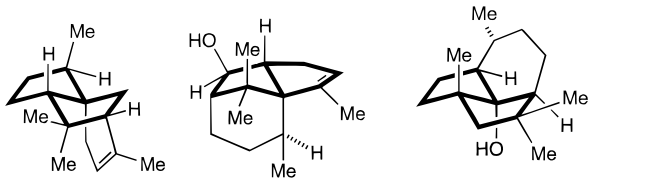
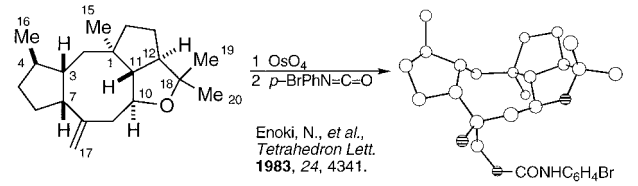


Figure 1. Three sesquiterpene natural products containing the *trans*-bicyclo[3.3.0]octane ring system (bold lines).

Scheme 1



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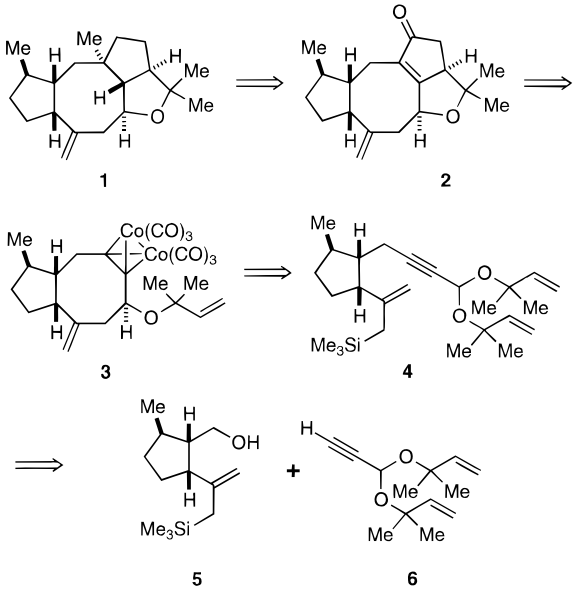
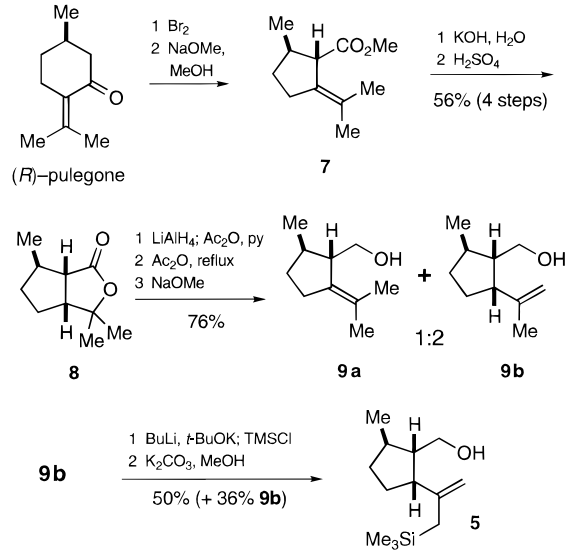
Scheme 2

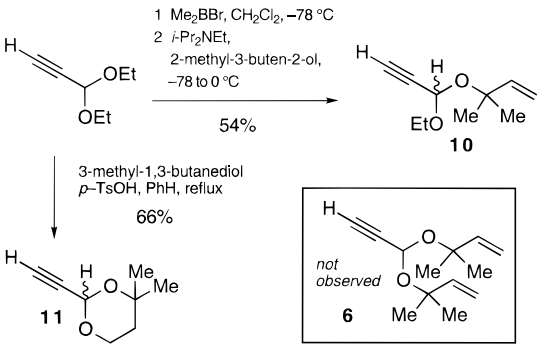


Scheme 3

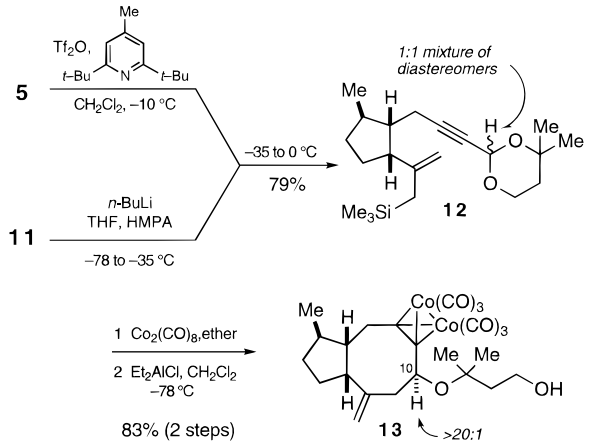


Synthesis and Coupling of the Two Fragments. All of the asymmetry in the synthesis is derived from (*R*)-pulegone, and its conversion to allylsilane **5** is depicted in Scheme 3. Wolinsky and co-workers demonstrated[15] that Favorskii ring contraction of pulegone affords ester **7** stereospecifically, favoring the diastereomer in which the methyl and carboxymethyl groups are oriented *trans* to each other. Saponification of the ester and subsequent acid-catalyzed cyclization to the fused *cis*-5−5 system established the configuration of C7 (epoxydictymene numbering) in 56% overall yield for the four steps. Reduction of the lactone to the diol and acetylation of the primary alcohol allowed for selective dehydration of the tertiary alcohol, effected in boiling acetic anhydride. Saponification of the acetate yielded a 1:2 mixture of primary alcohols **9a** and **9b** (desired) that were separated chromatographically after selective epoxidation (MCPBA) of the tetrasubstituted olefin of the former. Subjecting **9b** to 300 mol % of Schlosser's base[16] and quenching the resulting dianion with chlorotrimethylsilane afforded, after hydrolysis of the silyl ether, a 50% yield of allylsilane **5**, along with a 36% yield of recovered **9b**.

Scheme 4



Scheme 5



Unfortunately, all attempts to prepare propargylic acetal **6** by protic acid-catalyzed transacetalization of propiolaldehyde diethyl acetal and 2-methyl-3-buten-2-ol were unsuccessful. Thus, a similar compound, mixed acetal **10**, was prepared by bromodimethylborane treatment[17] of propiolaldehyde diethyl acetal and subsequent trapping of the bromomethyl propargyl ether *in situ* with 2-methyl-3-buten-2-ol, giving **10** in 54% yield (Scheme 4). Since it was unclear whether this mixed acetal would exhibit the necessary site selectivity in the 8-membered ring formation, 1,3-dioxane **11** (racemic) was also prepared. Similar 1,3-dioxanes had been reported to exhibit complete site selectivity in the desired sense in Lewis acid-catalyzed addition reactions.[18] In contrast to attempts to prepare **6** under protic acid catalysis, *p*-toluenesulfonic acid successfully promoted the reaction between propiolaldehyde diethyl acetal and 3-methyl-1,3-butanediol, giving **11** in 66% yield. The intramolecularity of the second transacetalization step in this case, as well as reduced steric interaction in the product acetal (as compared to that in **6**), are likely contributors to the success of the reaction.

Coupling of **5** and cyclic acetal **11** was achieved under carefully controlled conditions. Thus, activation of the alcohol of allylsilane **5** with trifluoromethanesulfonic anhydride in the presence of a hindered pyridine base afforded a triflate that was treated immediately with a lithium anion derived from **11** (Scheme 5). A 79% yield of the coupled product **12** was obtained as a 1:1 diastereomeric mixture at the acetal carbon. Treatment of **12** in ether with dicobalt octacarbonyl incorporated the alkyne into a dicobalt hexacarbonyl complex in greater than 90% yield. This compound is typical of such clusters, being deep red in color, moderately air-sensitive, but nevertheless stable enough to be purified using silica gel chromatography.

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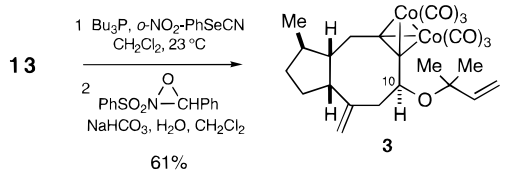
Table 1. Effect of Lewis Acid and Solvent on the Yield and Selectivity of the Cyclization of the Cobalt Complex Derived from **14** (Scheme 7)

entry	Lewis acid	solvent	temp (°C)/time	yield (%)	**15**:**3** (site selectivity)
1	Et_2AlCl	$PhMe/CH_2Cl_2$	−78/1 h	0	na
2	Et_2AlCl	$PhMe/CH_2Cl_2$	−78 to 0/1 h	50	80:20
3	$TiCl_4$	CH_2Cl_2	−78/30 min	73	na
4	$EtAlCl_2$	$PhMe/CH_2Cl_2$	−78/30 min	50−78	78:22
5	TMSOTf	CH_2Cl_2	−78/15 min	87	70:30
6	TMSOTf	THF	−78/15 min	63	0:100
7	TMSOTf	Et_2O	−78/15 min	91	91:9
8	TBDMSOTf	CH_2Cl_2	−78/15 min	85	65:35
9	TESOTf	CH_2Cl_2	−78/15 min	87	63:37
10	HOTf	CH_2Cl_2	−78/15 min	73	50:50

[a] All reactions were performed at 0.005 M in the solvent indicated, and 110 mol % of Lewis acid was used in each case.

Scheme 6

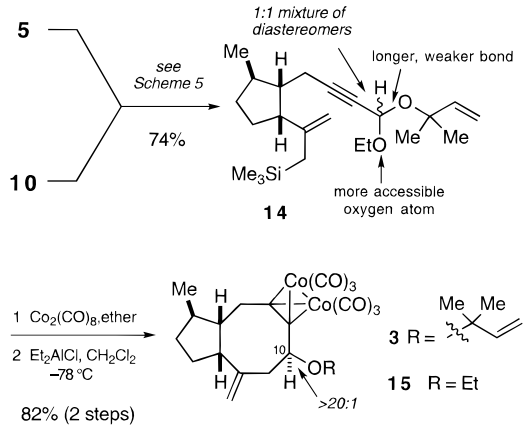


Lewis Acid-Mediated Nicholas Cyclizations and Pauson−Khand Reactions of Alkyne−Cobalt Complexes. The preparation of 8-membered rings by direct cyclization of acyclic precursors is often a low-yielding process, primarily as a result of unfavorable torsional strain and transannular interactions engendered in the cyclization process.[2] However, low-temperature treatment of the cobalt complex derived from **12** with a stoichiometric amount of Et_2AlCl in dichloromethane afforded a 91% yield of the fused 5−8 ring system of epoxydictymene as cobalt complex **13**. Although the cyclization substrate is a 1:1 mixture of diastereomers, ^1H NMR analysis detected only a single diastereomer of **13** in the crude product mixture. Since the yield of the reaction was greater than 50%, equilibration at the acetal carbon leading to C10 was necessarily faster than cyclization.[9] In addition to a high level of diastereoselection, complete site selectivity was observed.

Mild conditions were required for the conversion of the primary alcohol to terminal olefin **3** in the presence of the substitutionally and oxidatively labile dicobalthexacarbonyl cluster (Scheme 6). The method of Grieco and Nicolaou proved to be most compatible with this system.[19,20] Accordingly, *o*-nitrophenyl selenocyanate, when combined with tributylphosphine in dichloromethane, displaced the hydroxyl group in good yield. A trace of a second compound, consistent with replacement of one of the liganded CO molecules of the cobalt complex with tributylphosphine, was detected in the product mixture. Oxidation and elimination of the selenoether was effected with the phenyloxaziridine of Davis under biphasic conditions, giving olefin **3** in 61% overall yield for the two steps. A series of NOE DIFF experiments was consistent with the configuration of C10 shown, the same as that found at the corresponding carbon in epoxydictymene.

Having demonstrated the feasibility of the Lewis acid-mediated cyclization approach to the synthesis of the fused 5−8 system of epoxydictymene, we next explored a similar procedure with racemic acyclic acetal **10** with the hope of providing a more direct route to Pauson−Khand educt **3**. The key question in this case was whether the acyclic acetal would exhibit the same high level of site and diastereoselectivity in the cyclization reaction. As depicted in Scheme 7, the yield of coupled product

Scheme 7



involving allylsilane **5** and **10** was similar to that observed with cyclic acetal **11** (Scheme 5). As before, the coupled product **14** was isolated as a 1:1 mixture of diastereomers at C10. However, the cobalt complex derived from this alkyne was more resistant to Lewis acids than that derived from **12**, and several conditions were screened until the optimum cyclization protocol was found. In further contrast to the cyclization of the substrate containing the cyclic acetal, the cyclization involving the acyclic mixed acetal was not entirely site selective. That is, while the major product obtained in this reaction was identical to terminal olefin **3**, the minor product, ethyl ether **15**, was consistent with cyclization after loss of the tertiary allylic alcohol of the acetal.

The Lewis acids that were tested are listed in Table 1, along with the yield and site selectivity of each cyclization. Et_2AlCl (entry 1), which efficiently induced cyclization in the cyclic acetal case, failed to afford any of the cyclized material under the same conditions with the alkyne−cobalt cluster derived from **14**. At higher temperatures, this Lewis acid did induce cyclization with a 4:1 level of selectivity, but in a diminished yield of 50%. The more potent titanium tetrachloride afforded an uncyclized product that was consistent with hydrolysis of the acetal to the aldehyde (^1H NMR analysis). $EtAlCl_2$, intermediate in Lewis acidity, did effect fairly effective cyclization in several instances (entry 4), but with inconsistent yields and varying amounts of the aldehyde side product. The most consistent and efficient results for this reaction were obtained with silyl triflates, with a striking solvent dependence observed for TMSOTf. In dichloromethane (entry 5), a 2.3:1 ratio of desired **3** to undesired cyclization product **15** was obtained, while the experiment conducted in THF afforded none of the desired product, a low yield of **15**, and the aldehyde as the major product. With ether as solvent, the highest yield (91%) and selectivity (10:1) were observed, and no aldehyde side product was formed (entry 7). The steric bulk of the alkyl groups on the silyl triflate had minimal effects on the selectivity

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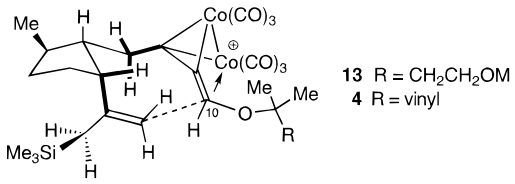


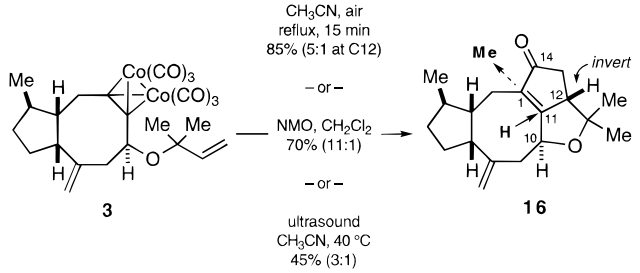
Figure 2. Proposed transition structure in the Lewis acid-catalyzed conversions of **12** to **13** (Scheme 5) and **15** to **3** (Scheme 7). The bonds depicted with untapered bold lines are some of those involved in the minimized g^+/g^- interactions. The orientation of the hydrogen atom of C10 toward the incipient 8-membered ring both minimizes steric interaction between the larger alkoxy substituent and the rest of the molecule and affords the desired configuration of C10 in the product.

and yield in reactions performed in dichloromethane (entries 8 and 9) suggesting that triflic acid, generated in the reaction by trace amounts of water, might be effecting catalysis in the conditions screened. Triflic acid did indeed promote cyclization, but not in the same yield or selectivity, affording a 1:1:1 mixture of desired product, undesired cyclization product, and aldehyde under otherwise identical reaction conditions (entry 10). As it was the highest yielding and most site-selective combination, TMSOTf in ether was used in all subsequent cyclizations.

The cyclizations of cobalt complexes derived from **12** and **14** illustrate the interplay of two competing factors that determine which alkoxy group is preferentially removed by the Lewis acid. In the acyclic acetal case, the ethoxy oxygen is likely to be more accessible for complexation, but the C10−O bond of the tertiary alkoxy substituent is probably longer and therefore weaker than the C10−OEt bond.[21] In the cyclizations of the cobalt complex derived from **12** (Scheme 5), where complete site selectivity was observed, the cyclic nature of the acetal suggests the appealing explanation that oxygen accessibility is the more important factor by far. However, several groups have studied addition reactions of acyclic and cyclic acetals and found that the *mechanism* of the reaction is dependent on Lewis acid, nucleophile, the structure of the acetal, and solvent.[22−26]

An analysis of the high level of diastereoselectivity observed in these cyclizations is depicted in Figure 2. Two critical factors appear to dominate this aspect of the reaction. Minimization of steric interactions in the transition state can be achieved with the conformation shown. Also of importance is the fluxional nature of such cationic cobalt complexes. In intermolecular Lewis acid-mediated Nicholas reactions, equilibration occurs at the propargylic center (C10 in this case) via what is thought to be a fluxional cationic intermediate, and thus any stereochemical information at this site in the substrate is lost upon treatment with a Lewis acid.[9] Assuming that this equilibration is operative in this intramolecular process and that it is fast relative to cyclization, then the stereochemical induction observed in the cyclization may be representative of the ratio of the activation energies of the two diastereomeric cyclization pathways (Curtin−Hammett principle). Positioning of the hydrogen atom at C10 toward the interior of the cyclizing system and the larger alkoxy substituent away from this forming ring leads to the desired configuration at C10.

Scheme 8



Of the methods for initiating intramolecular Pauson−Khand reactions, thermal,[13] oxidative,[10] and ultrasonic[27,28] conditions proved to be effective in converting cobalt complex **3** into tetracyclic enone **16** (Scheme 8). Earlier investigations in our laboratory[10] led to the development of a high yielding, room temperature procedure that employs *N*-methylmorpholine *N*-oxide in the oxidative initiation of cyclization, probably by oxidative dissociation of one of the CO ligands of the cobalt complex to CO_2, vacating a coordination site for the olefin, and ultimately leading to enone. Under these conditions, cobalt complex **3** gave a 70% yield of the desired enone **16** as an 11:1 mixture of diastereomers at C12. NOE DIFF experiments performed on the major enone product provided two insights into stereochemistry. While the C12 configuration opposite to that desired was favored in the Pauson−Khand reaction, these NMR experiments supported the earlier assignment of configuration at C10 following Lewis acid cyclization. X-ray crystallographic analysis of subsequent derivatives confirmed this stereochemical assignment. Under an atmosphere of air, the thermally induced Pauson−Khand cyclization of **3** was higher yielding but less diastereoselective (5:1 at C12), again with the undesired diastereomer prevailing. All attempts at epimerization of C12 were unsuccessful.

Reductive and Deconjugative Methylation Attempts. With a tetracyclic precursor of epoxydictymene in hand, there remained four tasks for completion of the synthesis: face-selective delivery of a hydrogen to C11, stereoselective installation of the angular methyl group at C1, inversion of the C12 configuration, and reduction of the C14 carbonyl (Scheme 8). The first strategy explored attempted to solve the first two of these issues in a single step (Scheme 9). Dissolving metal reduction of the enone followed by alkylation of the enolate with iodomethane afforded tetracyclic ketone **17** in high yield. A *cis* fusion of the 5−5 system of **17** was formed exclusively, opposite to results usually observed in dissolving metal reductions of homologous 6−6 enones, which favor the *trans*-fused product.[29−32] While the fusion of these two rings to the 8-membered ring may also exert a reinforcing effect on the facial selectivity of this reduction, formation of the *cis* fusion is generally observed in dissolving metal reductions of similar 5−5 enones.[33,34] Of greater importance to the synthesis of the natural product was that the methyl group attached to C1 had been installed in the incorrect configuration.

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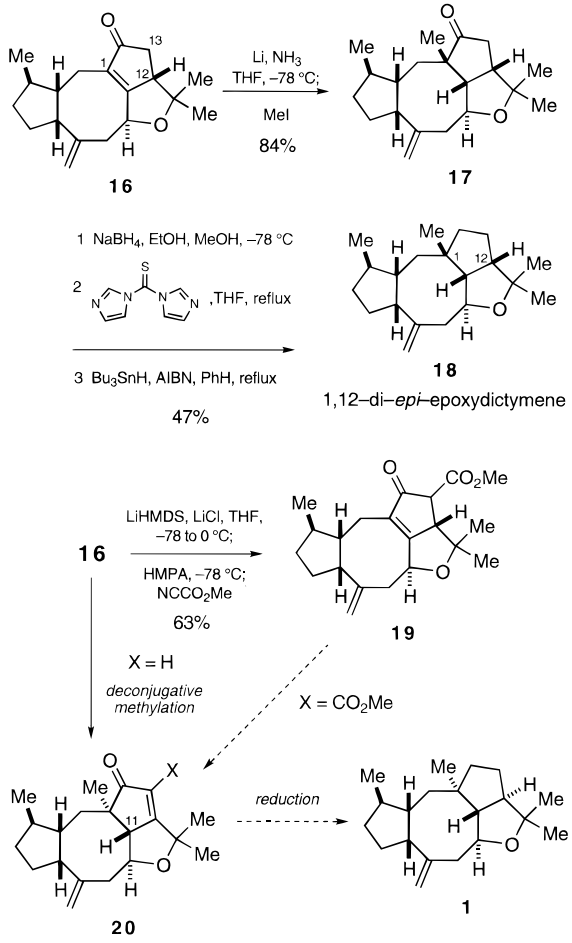
Scheme 9



It was difficult to imagine an expedient route to epoxydictymene involving reductively alkylated ketone **17**, but this undesired product did serve a purpose. Reduction of the carbonyl to methylene by a three-step process provided a tetracyclic product epimeric to epoxydictymene at C1 and C12. Di-*epi*-epoxydictymene **18** was useful in gaining familiarity with the physical properties and chromatographic behavior of these systems. Since an authentic sample of the natural material was not available, the technical knowledge gleaned from **18** facilitated later isolation and purification of epoxydictymene.

Another strategy seeking simultaneous solution to two remaining tasks was next explored (Scheme 9). The general plan was to methylate at C1 while preserving the overall oxidation state of the system. While the enolate formed in dissolving metal reduction of enone **16** was alkylated exclusively from the top face (as drawn), model building and molecular modeling were consistent with the notion that the dienolate derived from enone **16** (by γ-deprotonation at C12) would exhibit the opposite facial selectivity, from the bottom face of the molecule. Following this deconjugative alkylation, isomerization of the olefin into conjugation with ketone would lead to enone **20**, with the configuration of C11 predicted to favor the desired stereochemistry based on examination of molecular models. Further speculation proposed that reduction of **20** would favor construction of the *trans*-fused 5−5, in contrast to the reduction of enone **16**. Unfortunately, all conditions explored (*e.g.*, KH, THF; MeI) for the first transformation (deconjugative methylation) were unsuccessful, affording either products of alkylation at C13 or decomposition, and thus this expedient solution could not be investigated further. In order to promote alkylation at C1 rather than C14, compound **19** was

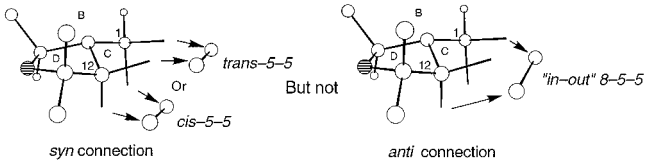
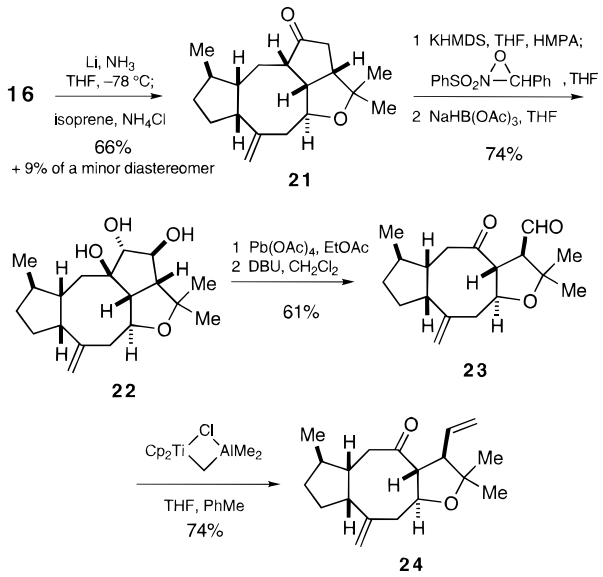


Figure 3. The predicted spatial relationship of C1 and C12 in epoxydictymene's ABD ring system (abbreviated for clarity), and two modes (*syn* and *anti*) of connecting them.

Scheme 10

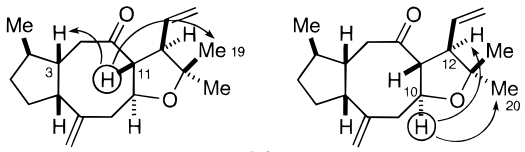


prepared by carboxymethylation of an enolate derived from the enone, following the procedure of Mander.[35] The aim was to generate a dianion derived from **19**, with the most reactive position being C1. Again, deconjugative methylation was elusive.

The results of the reductive and deconjugative methylation studies suggested that alkylation at C1 with the desired facial preference could be achieved only after inversion of the configuration at C12. This inference was supported by molecular modeling. As summarized in Figure 3, connecting C1 and C12 in a *syn* manner with two carbon atoms results in a ring system that is considerably less strained than that obtained by bridging these two positions in an *anti* manner. Despite the strained *trans*-5−5 system that one of the *syn* connection modes yields, plastic models of the "in−out"[36,37] 8−5−5 system suggest that the *anti* connection is much more tenuous.

Ring-Opening/Reclosure Strategy: Radical and Anionic Cyclizations. Since all attempts at inverting the configuration of C12 with all rings of the tetracyclic skeleton intact were unsuccessful, we next considered an approach that opened the C ring and interconverted functional groups in such a way to allow reclosure of this ring with the correct configurations at all sites. This series of experiments began with Pauson−Khand product **16** (Scheme 10). Although reductive methylation of this enone installed the C1 methyl with the incorrect configuration (Scheme 9), this process did afford the correct configuration at C11, the 8−5−5 fusion carbon. Thus, Li/NH_3 reduction of this enone, followed by an isoprene/NH_4Cl quench, gave ketone **21** in good yield. Omission of the isoprene step

(35) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.
(36) Isolation and structure of ingenol, which contains an "inside−outside" bridged ring system: Zechmeister, K.; Brandl, F.; Hoppe, W.; Hecker, E.; Opferkuch, H. J.; Adolf, W. *Tetrahedron Lett.* **1970**, *11*, 4075.
(37) For a review on the "inside−outside" bridged ring system: Alder, R. W. *Acc. Chem. Res.* **1983**, *16*, 321.



24

Figure 4. Some of the cross peaks observed in a phase-sensitive NOESY experiment performed on **24**, enabling assignment of stereochemistry at C11 and C12. The identity of each resonance was first established with a DQF COSY experiment.

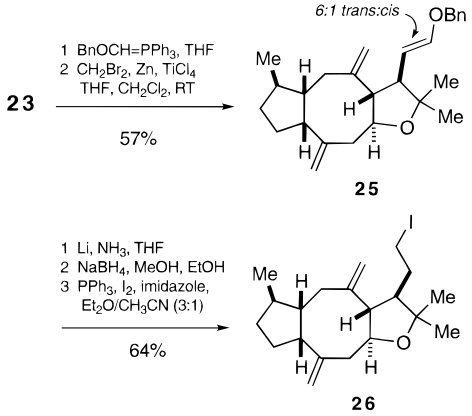
produced significant amounts of overreduction to the secondary alcohol. Separation of C12 diastereomers produced in the Pauson−Khand reaction was more efficient after the reduction of these two enones to the ketones (minor diastereomer not shown).

Opening of this ring and epimerization at C12 were effected with a three-step sequence that began with double α-hydroxylation and reduction of this keto diol with $NaHB(OAc)_3$ to give triol **22**. The stereochemical arrangement shown is based on hydroxylation from the less-hindered (top) face of the ketone followed by directed reduction of the carbonyl.[38] Oxidative excision of C14 with lead tetraacetate gave a compound whose C12 configuration could be inverted when subjected to DBU in dichloromethane, giving keto aldehyde **22** as a 3:1 mixture of diastereomers (minor diastereomer not shown). One recycling of this minor diastereomer with DBU gave a 61% overall yield of **23**. Exclusion of oxygen (three freeze−pump−thaw cycles) was required in this reaction for maximal yield.

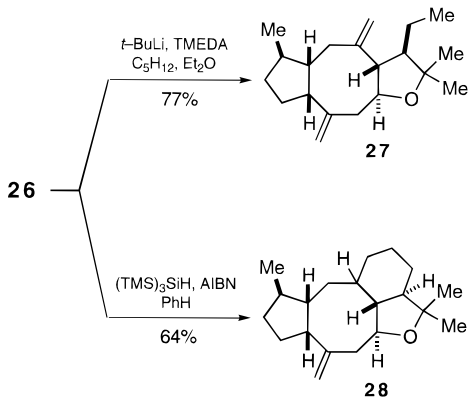
Support for the stereochemical assignment of the major diastereomer of **23** was provided by a combination of DQF COSY and phase-sensitive NOESY NMR experiments of a closely related derivative (Figure 4). Keto diene **24**, prepared by treatment of **23** with Tebbe's methylenation reagent (Scheme 10), exhibited strong cross peaks in its NOESY spectrum between the C3 and C11 protons, consistent with the assignment shown for C11. Further, there was also a strong cross peak between the C11 proton and those attached to only one of the diastereotopic methyl groups (C19). The proton at C10 showed strong cross peaks to the proton at C12 at those attached to the *other* diastereotopic methyl (C20). Taken together, these data are most consistent with the stereochemical assignments made at C11 and C12 for compound **24** and therefore its precursor, keto aldehyde **23**. Noteworthy was that the Tebbe reagent reacted only with the aldehyde carbonyl in **23**. This difference in reactivity of the two carbonyl groups of **23** was exploited in subsequent strategies and was critical to the completion of the synthesis of the natural product.

On the basis of results of studies of the cyclization of 5-hexenyllithium to (cyclopentyl)methyllithium,[39] Bailey and co-workers reported an elegant method for the synthesis of *trans*-bicyclo[3.3.0]octanes.[40,41] A suitable substrate for this transformation in the context of the synthesis of epoxydictymene was prepared from keto aldehyde **23** in five steps by the sequence shown in Scheme 11. Selective Wittig olefination of the aldehyde with the phosphorane derived from benzyl bromomethyl ether provided a compound whose ketone, while resistant to methylenation by the Tebbe reagent, was smoothly olefinated with the reagent system of Lombardo (Zn, CH_2Br_2, $TiCl_4$) to give **25** as a 6:1 mixture of olefin isomers, favoring

Scheme 11



Scheme 12



the *trans*. Reductive debenzylation of this mixture afforded an aldehyde which was immediately reduced with $NaBH_4$ to the primary alcohol. The desired iodide **26** was obtained from this alcohol in a single step.

Although the Bailey protocol for anionic cyclization of 5-hexenyl iodides was successful in our hands on simpler systems, exposure of iodide **26** to these conditions resulted in the exclusive formation of protodehalogenation product **27**. No cyclized material could be detected in the reaction mixture (Scheme 12). Since another method commonly used in the synthesis of five-membered rings is the 5-*exo*-*trig* cyclization of the hexenyl radical,[42] iodide **26** was also subjected to such conditions. In contrast to the metal−halogen exchange conditions, cyclization did occur upon addition of a solution of tris(trimethylsilyl)silane[43,44] and AIBN to a refluxing benzene solution of the iodide. However, NMR analysis (^1H, ^{13}C, DEPT 90, DEPT 135) of the reaction product revealed that the product did not exhibit the appearance of the methyl singlet characteristic of epoxydictymene and was most consistent with the product of 6-*endo* cyclization, 5−8−6−5 tetracycle **28**. In retrospect, this result is not surprising since 6-*endo* products are often favored over the 5-*exo* products in radical cyclizations of 5-alkyl-5-hexenyl iodides.[42]

The 6-*endo* cyclization of iodide **26** prompted examination of another substrate in which cyclization could occur only at the desired C1. Iodide **30** was thus prepared by means of a six-step sequence whose key transformation was lithium di-

(38) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

(39) Bailey, W. F.; Patricia, J. J.; DelGobbo, V. C.; Jarret, R. M.; Okarma, P. J. *J. Org. Chem.* **1985**, *50*, 2000.

(40) Bailey, W. F.; Khanolkar, A. D. *Tetrahedron Lett.* **1990**, *31*, 5993.

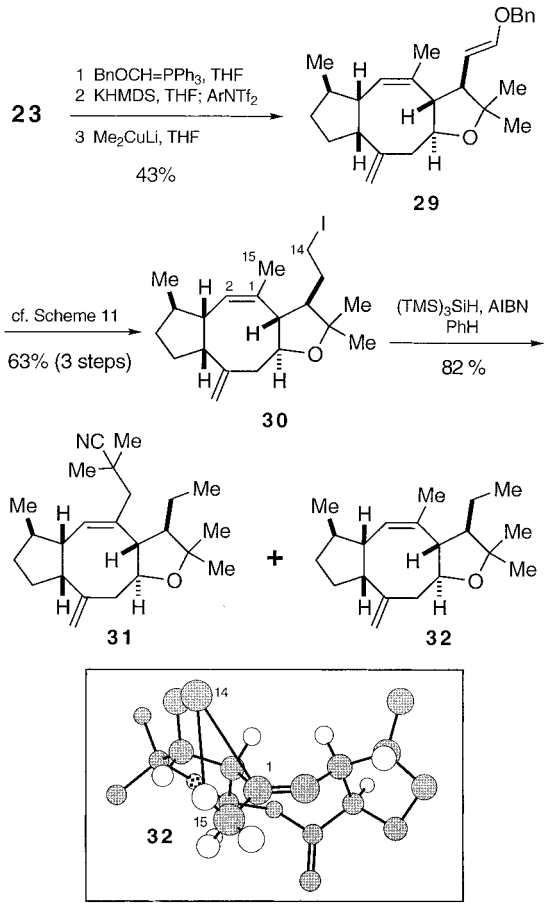
(41) Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K. V. *J. Am. Chem. Soc.* **1992**, *114*, 8053.

(42) Review: Curran, D. P. *Radical Cyclization and Sequential Radical Reactions*; Curran, D. P., Ed.; Pergamon Press: New York, 1991; Vol. 4.2, pp 779−831.

(43) Chatgilialoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* **1988**, *53*, 3642.

(44) Kulicke, K. J.; Giese, B. *Synlett* **1990**, 91.

Scheme 13



methylcuprate displacement of a vinyltriflate[45] at C1 (Scheme 13). Modeling of this compound predicted that C2 would be much more distant than C1 and therefore inaccessible to an approaching carbon centered radical at C14. Indeed, generation of this radical under the conditions used in the previous case (Scheme 12) confirmed that C2 was not the preferred site of attack. However, cyclization was not detected in this experiment either. A major product (**31**) appeared to be the result of generation of a radical at C14, a 1,6 transfer of one of the hydrogens at C15 to C14, and trapping of the allylic radical by a species generated in the fragmentation of the radical initiator AIBN. Thus, C15 was again the most accessible site to the approaching C14 radical. In fact, the second-lowest energy conformation (within 0.3 kcal of the global mininum, Macromodel, Monte Carlo, MM2) of **32**, seen in trace amounts in the crude reaction mixture, predicted that the the distance between C14 and a proton attached to C15 was approximately equal to that between C14 and C1.

Adjustment of the electronic characteristics of the C1−C15 olefin in **26** in order to bias cyclization in favor of a 5-*exo* mode rather than a 6-*endo* mode was next investigated. Attachment of a cyano group to C15 was attractive, for it provided the desired electronic bias for both radical[46] and anionic cyclizations. Further, the cyano group could be removed following cyclization in a single reductive step.[47] Preparation of the requisite acrylonitrile was accomplished in 5 steps from keto aldehyde **23** (Scheme 14).

Wittig olefination of the aldehyde was again the first step (*cf.* Schemes 11 and 13), but the phosphorane of choice in this

(45) Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47.
(46) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753.
(47) Ohsawa, T.; Kobayashi, T.; Mizuguchi, Y.; Saitoh, T.; Oishi, T. *Tetrahedron Lett.* **1985**, *26*, 6103.

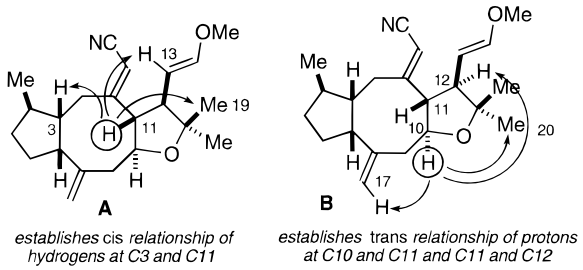
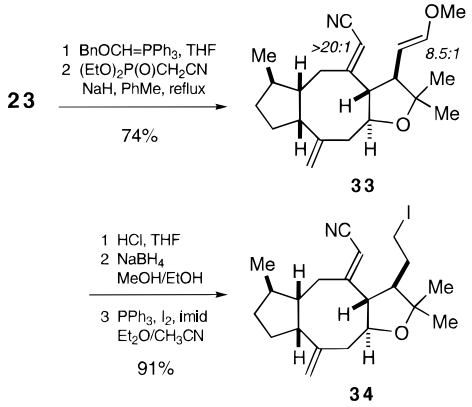
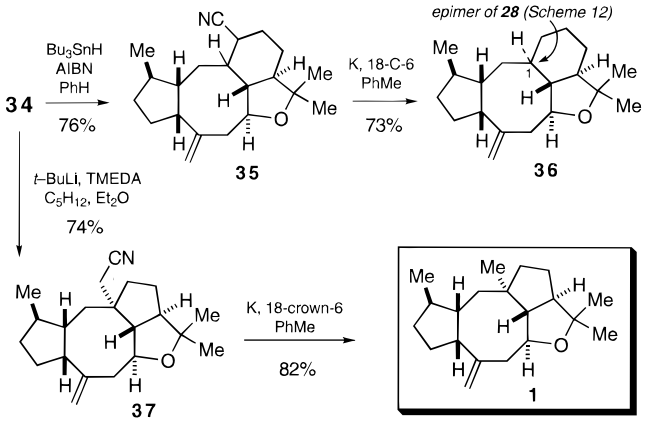


Figure 5. NOE DIFF experiments of the major isomer of **32**: (A) Irradiation of the C11 proton resulted in enhancement of the C3, C13, and C19 protons. (B) Irradiation of the C10 resonance enhanced the C12 and C20 protons, and one of the C17 protons. These data are most consistent with stereochemical assignment shown.

Scheme 14



Scheme 15



case was that derived from chloromethyl methyl ether, as selective reduction of a benzyl enol ether in the presence of the acrylonitrile and the exocyclic olefin was unlikely. Wadsworth−Emmons olefination of the C1 ketone with diethyl (cyanomethyl)phosphonate under forcing conditions (toluene, reflux, 24 h), afforded **33** in 74% overall yield as an 8.5:1 mixture of olefin isomers (enol ether), favoring the *trans*. Only one configuration of the acrylonitrile could be detected.

Due to the harshness of the Wadsworth−Emmons conditions, the major isomer of **33** was examined with NOE DIFF experiments to confirm that epimerization at C11 had not occurred. These NMR experiments, summarized in Figure 5, exhibited NOE behavior analogous to that seen previously on a similar system (**24**, Figure 4). Acid-catalyzed hydrolysis of the enol ether liberated an aldehyde that was converted with two reactions into the cyclization substrate, iodide **34**.

Scheme 15 illustrates the two cyclizations that were accomplished with **34**. Despite the cyano group, radical cyclization conditions still effected a 6-*endo* cyclization, in the same

maner as that observed in the case lacking the cyano group (Scheme 12). Reductive decyanation[47] of cyclization product **35** produced 5−8−6−5 system **36**. Surprisingly, this compound was not identical to **28**. ^{1}H, ^{13}C, DEPT 90, and DEPT 135 NMR experiments supported the connectivity shown, and since epimerization at any site is unlikely in the three steps (**33** to **34**, Scheme 14) following stereochemical assignment, **36** is most likely epimeric to **28** at C1. The factors governing this divergent stereoinduction are unclear.

While the electronic influence of the cyano group was not sufficient to favor the strained *trans*-5−5 in a radical cyclization, it proved sufficient in an anionic cyclization. Metal−halogen exchange of iodide **34** effected a cyclization in 74% yield. As the ^{1}H and ^{13}C NMR spectra of this compound were nearly identical to those reported for epoxydictymene (except for the differences expected for substitution of CN for H), the structure shown for **37** having the complete 5−8−5−5 skeleton of epoxydictymene was assigned to this material.

Final confirmation that this cyclization had occurred in the desired 5-*exo* mode was realized by completion of the synthesis of epoxydictymene. Reductive decyanation[47] of **37** provided synthetic (+)-epoxydictymene (**1**), whose spectral and physical properties were identical in every respect with those reported for the natural material (^{1}H and ^{13}C NMR, HRMS, IR, $[\alpha]_D$).[1]

The Lewis acid-promoted Nicholas reaction and subsequent intramolecular Pauson−Khand reaction successfully assembled three of the four rings of epoxydictymene, and an anionic conjugate addition provided a means to construct the fourth. These efficient transformations of dicobalthexacarbonyl clusters with a bridging alkyne ligand await further use in the synthesis of complex carbocyclic ring systems.

Experimental Section

Unless otherwise noted, all reactions were performed in oven-dried or flame-dried glassware, sealed with a rubber septum or a ground-glass stopper, under an atmosphere of dry nitrogen. Nitrogen was bubbled through concentrated sulfuric acid, then passed over a tower of KOH/Drierite ($CaSO_4$), and supplied through a glass manifold. Solvents and reagents were transferred via oven-dried syringes, under a positive N_2 pressure.

Dicobalt octacarbonyl was exclusively purchased from Strem Chemicals, as other suppliers' stock of this reagent was consistently contaminated with oxidation byproducts. Ether, hexanes, and THF were distilled from a deep blue or purple solution over benzophenone ketyl. Dichloromethane (CH_2Cl_2), acetonitrile, and TMSCl were distilled from CaH_2. All other reagents were used as supplied by commercial manufacturers without any further purification unless specifically noted.

Thin layer chromatography (TLC) was performed on analytical (0.25 mm) silica gel 60 plates coated with a 254 nm fluorescent indicator from E. Merck. Compounds were visualized using a Mineralight ultraviolet lamp (254 nm), or by staining with a *p*-anisaldehyde (in EtOH) or a cerium ammonium molybdate (aqueous) stock solution.

Semipreparative scale HPLC was performed at 380 psi on a Septec Novaprep 5000 instrument using an ultraviolet detector, and a gradient of HPLC-grade hexanes and *tert*-butyl methyl ether through a silica 100 A column (51 × 250 mm).

1(*S*)-(Hydroxymethyl)-2(*R*)-[3-(trimethylsilyl)isopropenyl]-5(*R*)-methylcyclopentane (5). A solution of sublimed potassium *tert*-butoxide (6.73 g, 60.0 mmol) in dry hexane (30 mL) was cooled under an argon atmosphere to −20 °C, and neat **9b**[15] (3.08 g, 20.0 mmol) was added dropwise. After 5 min of vigorous stirring, a solution of *n*-BuLi (33.3 mL, 1.8 M, 60.0 mmol) was added dropwise. The reaction was allowed to warm to 0 °C over 30 min, during which time the heterogeneous mixture became pale yellow and then deep orange. After 1.5 h at 0 °C nearly all solids had dissolved, but there was no change in overall color. The reaction was cooled to −78 °C and treated with freshly distilled TMSCl (6.52 g, 7.6 mL, 60.0 mmoL), dropwise, in a manner such that the reaction temperature did not exceed −60 °C. The resulting mixture was allowed to warm slowly to 0 °C over 1 h, during which time a white precipitate had formed and the mixture had paled to light yellow. Quenched with saturated $NaHCO_3$ (30 mL) and diluted with ether (300 mL), the mixture showed no residual color. The organics were then separated from the heavily salted aqueous layer and washed with water (25 mL) and brine (3 × 20 mL). The ethereal solution was dried ($MgSO_4$), filtered, and carefully concentrated *in vacuo*.

The resulting yellow oil was dissolved in MeOH (24.0 mL), and treated with K_2CO_3 (2.76 g, 20.0 mmol). After 15 min TLC analysis indicated complete hydrolysis of the silyl ether. The solution was diluted with ether (200 mL), washed with pH 7.00 buffer (10 mL). The aqueous layer was extracted with ether (50 mL). The combined organics solutions were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Semipreparative HPLC (4:1 hexanes/methyl *tert*-butyl ether) produced 2.15 g (50%) of **5** as a colorless oil, along with 1.10 g (36%) of the starting alcohol **9b** (R_f = 0.4 in 4:1 hexane/EtOAc): $[\alpha]^{23}_D$ −73.5° (*c* 0.0264, $CHCl_3$); IR (film) 3327, 3082, 2951, 2868 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (s, 1H), 4.64 (s,1H), 3.48 (br m, 1H), 3.36 (br m, 1H), 2.43 (overlapping dd, $J_1 = J_2 = 7.8$, $J_3 = 10.3$, 1H), 1.92−1.50 (m, 7H), 1.07 (m, 1H), 1.01 (d, J = 6.4, 3H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 106.8, 64.1, 50.6, 48.5, 36.1, 33.5, 29.5, 28.3, 21.7, −1.4; HRMS (EI) *m/z* calcd for M^+ 226.1573, found 226.1752.

2-Ethynyl-4,4-dimethyl-1,3-dioxane (11). A mixture of propiolaldehyde diethyl acetal (39 mmol, 5 g, 5.6 mL), 3-methyl-1,3-butanediol (58.5 mmol, 6.1 g, 5.4 mL), and *p*-toluenesulfonic acid (1.95 mmol, 371 mg) in benzene (120 mL) was heated at reflux under an atmosphere of nitrogen for 4 h. The resulting pale yellow solution was allowed to cool to room temperature and diluted with 120 mL of ether. The mixture was washed with saturated $NaHCO_3$ (25 mL) and brine (3 × 20 mL). The aqueous layers were combined and extracted with ether (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and carefully concentrated *in vacuo* (note: **11** is volatile) to give a yellow, pungent oil. Silica gel chromatography of this residue (1:2 pentane/CH_2Cl_2) gave 4.6 g (33 mmoL, 84%) of pure **11** as a clear oil. Kügelrohr distillation (200 °C; 1 atm) provided analytically pure **11** (3.6 g, 26 mmoL; 66%; R_f = 0.24 in 1:2 pentane/CH_2Cl_2): IR (thin film/NaCl) 3266, 2131, 1738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (d, J = 1.3 Hz, 1H), 3.95 (ddd, J = 11.8, 5.5, 1.7 Hz, 1H), 3.85 (apparent dt, J = 12, 2.8 Hz, 1H), 2.49 (d, J = 1.3 Hz, 1H), 1.89 (apparent dt, J = 12, 5.5 Hz, 1H), 1.30 (obscured m, 1H), 1.28 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.45, 79.53, 72.90, 72.36, 63.14, 35.35, 31.15, 21.37.

1-Ethoxy-1-(2-methyl-3-buten-2-oxy)-2-propyne (10). To a solution of propioaldehyde diethyl acetal (2.56 g, 2.9 mL, 20.0 mmol) in CH_2Cl_2 (200 mL) at −78 °C was added bromodimethylborane (4.83 g, 3.9 mL, 40.0 mmol) dropwise, and the resulting solution was allowed to warm to −40 °C over the course of 2 h. Diisopropylethylamine (6.46 g, 8.7 mL, 50.0 mmol) was added, followed by 2-methyl-3-buten-2-ol (5.17 g, 6.3 mL, 60.0 mL). The solution was allowed to warm to 0 °C over 2 h, stirred at this temperature for an additional 2 h, and poured into a mixture of THF (100 mL) and saturated aqueous $NaHCO_3$ (100 mL). After addition of 200 mL ether, the mixture separated into two layers, and the organic layer was washed in succession with 25 mL each of saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl. The combined aqueous layers were extracted with 50 mL ether. The combined organic solutions were dried ($MgSO_4$), filtered, and concentrated *in vacuo* (**10** is volatile.). The crude product mixture was purified by silica gel chromatography (20:1 pentane/ether) to give **10** (1.8 g, 54%, R_f = 0.52 in 10:1 hexane/ethyl acetate) as a clear oil: IR (film) 3943, 3299, 2980, 2934, 2890, 2122 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (dd, J = 10.7, 17.6, 1H), 5.31 (d, J = 1.7, 1H), 5.20 (d, J = 17.6, 1H), 5.15 (d, J = 10.7, 1H), 3.69 (overlapping dq, J = 2.1, 7.1, 2H), 2.49 (d, J = 1.7, 1H), 1.35 (s, 3H), 1.32 (s, 3H), 1.19 (t, J = 7.1, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 114.7, 87.0, 80.5, 77.7, 72.7, 58.9, 27.6, 26.0, 15.1; HRMS (EI) *m/z* calcd for $[M + NH_4]^+$ 186.1494, found 186.1489.

1(*S*)-[4-Ethoxy-4-(2-methyl-3-buten-2-oxy)butyn-1-yl]-2(*R*)-[3-(trimethylsilyl)isopropenyl]-5(*R*)-methylcyclopentane (14). A mixture of allysilane **9b** (113 mg, 0.50 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (133 mg, 0.65 mmol) in CH_2Cl_2 (8 mL) was cooled to

−30 °C and treated, dropwise, with trifluoromethanesulfonic anhydride (155 mg, 0.093 mL, 0.55 mmol). The reaction was warmed to −10 °C and stirred for 10 min. Gradually, a white solid precipitated. The cloudy suspension was diluted with dry hexanes to triturate any salts remaining in solution, and the mixture was concentrated *in vacuo* with particular care to avoid bumping. The nonvolatile residue was resuspended in hexanes and filtered through a glass frit, resulting in a clear solution of the desired triflate.

Acetal **10** (168 mg, 0.189 mL, 1.0 mmol) in dry THF (20 mL) was cooled to −78 °C and treated dropwise with a 1.9 M solution of *n*-BuLi (0.79 mL, 1.5 mmol). HMPA (3.58 mmol, 0.35 mL, 2.0 mmol) was added, and the mixture was stirred 1 h, warmed to −35 °C, and kept at this temperature for 30 min. In the meantime, the triflate solution described above was concentrated *in vacuo*, dissolved in THF (6 mL), and added dropwise via cannula to the acetylide solution at −35 °C. This solution was allowed to warm to room temperature over 1 h. The progress of the coupling reaction was monitored by TLC analysis, as the spot corresponding to the nonpolar triflate (or a decomposition product thereof) slowly transformed to a more polar, lower R_f spot that was distinct from the starting acetal **10**. When TLC revealed no further progress (after 40 min at room temperature), the reaction was quenched with 1:1 saturated $NaHCO_3/H_2O$ (5 mL) and diluted with ether (20 mL). The organic layer was washed with brine (3 × 5 mL), and the combined aqueous layers were extracted with ether (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. SGC of the crude oil (20:1 hexanes/EtOAc) gave 156 mg (82%) of pure **14** (R_f = 0.47 in 10:1 hexane/EtOAc) (single diastereomer): IR (film) 2953, 2869, 2238 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.87 (dd, J = 10.7, 17.6, 1H), 5.30 (s, 1H), 5.18 (d, J = 17.6, 1H), 5.11 (d, J = 10.7, 1H), 4.57 (s, 1H), 4.52 (s, 1H), 3.65 (overlapping dq, J = 2.0, 7.1, 2H), 2.43 (m, 1H), 2.08−1.77 (m, 5H), 1.61−1.54 (m, 2H), 1.58 (d, J = 13.4, 1H), 1.39 (d, J = 13.4, 1H), 1.33 (s, 3H), 1.30 (s, 3H), 1.17 (t, J = 7.1, 3H), 1.10 (m, 1H), 1.03 (d, J = 6.7, 3H), −0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 143.2, 114.2, 107.5, 87.6, 85.7, 77.2, 58.5, 48.9, 46.9, 38.1, 32.9, 28.1, 27.7, 27.5, 26.0, 22.6, 20.4, 15.2, −1.3; HRMS (EI) *m/z* calcd for M^+ 376.2798, found 376.2812.

[3(*S*)-(1,1-Dimethylpropenoxy)-5-methylene-9(*R*)-methyl-(6*R*,-10*S*)-bicyclo[6.3.0]undecyne]dicobalt Hexacarbonyl Complex (3) (From 14). To a solution of **14** (1.56 g, 2.35 mmol) in ether (235 mL) at −78 °C was added with trimethylsilyl trifluoromethanesulfonate (580 mg, 0.63 mL, 2.60 mmol. The deep red solution was allowed to stir at this temperature for 15 min and poured into a mixture of saturated $NaHCO_3$ (100 mL) and ether (200 mL). The organic layer was washed with saturated NaCl (100 mL), dried ($MgSO_4$), filtered through silica, and concentrated *in vacuo* giving 1.26 g (98%) of a red oil. ^1H NMR analysis of this crude product revealed a 10:1 mixture of desired **3** to ethyl ether **15**, each as a single diastereomer. This material was used in subsequent Pauson−Khand reactions without further purification: IR (film) 2953, 2870, 2087, 2047 (vs), 2022 (vs) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.97 (dd, J = 8.8, 14.2, 1H), 5.20 (br d, J = 14.2, 1H), 5.16 (br d, J = 8.8, 1H), 5.04 (br s, 1H), 4.98 (br s, 1H), 4.62 (dd, J = 3.6, 9.0, 1H), 2.79 (br dd, J = 1.7, 9.0, 1H), 2.68 (obscured, 1H), 2.66 (obscured, 1H), 2.54 (m, 1H), 1.96 (dd, $J_1 = J_2$ = 10.1, 1H), 1.85 (m, 1H), 1.76 (m, 1H), 1.68−1.50 (m, 5H), 1.36 (s, 3H), 1.34 (s, 3H), 1.06 (d, J = 6.3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 146.6, 144.3, 114.0, 111.9, 76.3, 75.5, 50.4, 49.6, 45.9, 42.9, 42.8, 33.9, 30.0, 26.3, 26.1, 20.9, 20.7; MS (CI) *m/z* calcd for $[M + NH_4]^+$ 562, found 562.

1,11-Dehydro-1-desmethyl-12-*epi*-14-oxoepoxydictymene (16) (Thermal Pauson−Khand). A solution of **14** (1.1 g, 2.0 mmol) in acetonitrile (200 mL) was brought rapidly to reflux under an atmosphere of air and heated at that temperature for 15 min. The solution was cooled to room temperature and filtered through layered Celite (top, 5 g) and silica gel (bottom, 5 g), eluting with ethyl acetate. A bluish solid was retained by the Celite. Evaporation *in vacuo* of the clear solution afforded a yellow oil which was purified by silica gel chromatography (4:1 hexanes/EtOAc) to give 486 mg (85%) of enone **16** as a 5:1 mixture of diasteromers at C12 (^1H NMR analysis) that were more efficiently separated after subsequent dissolving metal reduction. A pure sample of the major diastereomer was prepared by the NMO-promoted Pauson−Khand[10] (see Supporting Information) and subsequent recrystallization: R_f = 0.37 in 4:1 hexane/EtOAc; $[\alpha]^{23}_D$ +85° (*c* 0.020, $CHCl_3$); IR (film) 3490, 2939, 2861, 1707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.15 (br s, 1H), 4.94 (br s, 1H), 4.32 (m, 1H), 2.95 (m, 1H), 2.81 (dd, J = 5.9, 11.3, 1H), 2.58−2.52 (m, 2H), 2.30 (m, 1H), 2.09 (dd, $J_1 = J_2$ = 11.3, 1H), 2.07−1.92 (m, 3H), 1.75−1.50 (m, 4H), 1.44−1.36 (m, 2H), 1.42 (s, 3H), 1.01 (obscured m, 1H), 1.00 (d, J = 6.3, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1, 182.9, 149.1, 135.7, 116.3, 81.6, 76.3, 52.2, 52.1, 48.3, 46.7, 38.4, 37.7, 34.2, 33.1, 27.5, 22.6, 19.9, 18.3; HRMS (FAB) *m/z* calcd for M^+ 286.1927, found 286.1922.

1,11-Dehydro-1-desmethyl-12-*epi*-14-oxoepoxydictymene (16) (NMO-Promoted Pauson−Khand). A solution of cobalt complex **14** (30 mg, 55 mmol) in CH_2Cl_2 (10 mL) was treated with a single portion of solid *N*-methylmorpholine *N*-oxide (39 mg, 0.33 mmol) at room temperature. After 12 h a purple precipitate had formed and TLC analysis indicated consumption of all starting material. The mixture was passed through a small plug of silica gel and the filtrate was concentrated *in vacuo*. The resulting yellow oil was purified by SGC (3:1 hexane/ether) to give 11 mg (38 mmol, 70%) of a solid, shown to be an 11:1 mixture of the diastereomeric enones **16** and **2** by spectral analysis.

1-Desmethyl-14-oxo-1,12-di-*epi*-epoxydictymene (21). Ammonia (15 mL) was distilled from sodium into a dry three-necked flask equipped with a dry ice condenser, a three-way stopcock, and a rubber septum. Lithium (14 mg, 2.0 mmol) was added and the mixture was stirred at −78 °C until the deep blue color was uniformly dispersed. The mixture was treated with a THF solution of **16** (110 mg, 0.38 mmol in 6 mL of THF) dropwise, via cannula. After 15 min at −78 °C, the reaction was quenched by addition of 1.5 mL of isoprene, at which point the solution lost its blue color, turning light brown at first, and then into a clear pink. Saturated ammonium chloride (8 mL) was added with caution; the mixture was diluted with ether (35 mL) and then allowed to warm to room temperature. The clear solution was stirred for 4 h at room temperature, open to air inside a fume hood, until excess ammonia had evaporated. The remaining biphasic mixture was poured into a separatory funnel containing 6 mL of 6 N HCl and 30 mL of ether. The layers were separated, and the organic layer was washed with saturated NH_4Cl (10 mL) and then saturated $NaHCO_3$ (2 × 10 mL). The aqueous layer was washed with two portions of ether (20 mL each). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a yellow oil. SGC (4:1 hexane/EtOAc) gave three major fractions. The least polar fraction contained 10 mg (35 mmol, 9%) of the minor diastereomer (not shown in figure); a highly crystalline solid (R_f = 0.41 in 4:1 hexane/EtOAc). A second, more polar fraction gave 65 mg (0.22 mmol, 60%) of the major diastereomer **21**, also as a crystalline solid (R_f = 0.36 in 4:1 hexane/EtOAc). Finally, the most polar fraction contained a mixture of **21** and starting materials **18** (12 mg, ∼11%). This fraction could be purified with a second SGC purification, giving an additional 6% of the major diastereomer: IR (thin film/NaCl) 2957, 2930, 1738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.99 (s, 1H), 4.70 (s, 1H), 3.59 (apparent dt, J = 10.3, 3.9 Hz, 1H), 3.14 (dd, J = 9.5, 7.9 Hz, 1H), 2.75 (dd, J = 12, 3.9 Hz, 1H), 2.74 (m, 1H), 2.57 (m, 1H), 2.38 (apparent t, J = 10.4 Hz, 1H), 2.22 (dd, J = 19.2, 10.4 Hz, 1H), 2.1−1.98 (m, 3H), 1.88 (m, 1H), 1.62−1.54 (m, 2H), 1.32 (s, 3H), 1.22 (s, 3H), 1.20 (m, 1H), 1.06 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.78, 150.02, 114.93, 81.20, 80.17, 53.02, 52.37, 50.29, 49.44, 49.28, 47.62, 38.54, 38.45, 33.57, 32.79, 30.37, 26.31, 24.86, 18.34; HRMS (FAB/NaI) *m/z* calcd for $C_{19}H_{28}O_2Na$ 311.1987, found 311.1986; $[\alpha]_D^{20}$ +105.5° (*c* 0.015, $CHCl_3$).

1-Desmethyl-1,13,14-trihydroxy-1,12-di-*epi*-epoxydictymene (22). A solution of KHMDS in toluene (740 mL of a 0.54 M solution, 0.4 mmol) was diluted with THF (2.5 mL), cooled to −78 °C, and treated with a solution of ketone **21** (29 mg, 0.1 mmol) in 500 mL of THF (rapid addition via cannula). HMPA (TOXIC!, 0.5 mL) was added after 5 min to the pale yellow solution, and the mixture was stirred at −78 °C for 2 h. A solution of the oxaziridine of Davis (130 mg, 0.5 mmol) in 1 mL of THF was then added via syringe and the solution was stirred at −78 °C for an additional 20 min. The reaction was quenched at −78 °C with saturated $NaHCO_3$ (1 mL), then diluted with EtOAc, and allowed to warm to room temperature. The layers were separated, and the organic layer was washed with brine (2 × 5 mL)

and dried over $MgSO_4$. Concentration *in vacuo* gave a crude oil (HMPA contaminated) that was dissolved in THF (3 mL), and treated with $Na(AcO)_3BH$ (64 mg, 0.3 mmol). After 5 h the reaction was quenched by addition of excess MeOH (2 mL) and a few drops of 1 N NaOH. The mixture was concentrated *in vacuo*, and the resulting thick oil was passed through a short (5 cm long) plug of silica gel with 9:1 EtOAc/MeOH to remove any salts. A thick gel had formed after concentration of the filtrate *in vacuo*. The residue was purified by SGC (3% then 5% then 10% MeOH in chloroform) to give 23 mg (0.071 mmol, 71%) of the desired triol **22** (R_f = 0.16 in 1:3 hexane/EtOAc) along with 3 mg (9.3 mmol, 9%) of a minor diastereomer. These could be combined for use in the next reaction: IR (thin film/NaCl) 3372, 2951, 2868 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.03 (s, 1H), 4.74 (s, 1H), 4.10 (dd, J = 7.3, 4.5 Hz, 1H), 3.86 (s, 1H), 3.83 (apparent dt, J = 9.7, 4.5 Hz, 1H), 2.76−2.68 (overlapping m, 3H), 2.43 (d, J = 11.2 Hz, 1H), 2.05−1.95 (m, 1H), 2.02 (s, 1H), 1.96−1.90 (m, 1H), 1.89 (s, 1H), 1.85 (d, J = 3.8 Hz, 1H), 1.7−1.64 (overlapping m, 4H), 1.33 (overlapping s, 6H), 1.23 (m, 1H), 0.96 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.00, 114.48, 89.67, 82.36, 81.05, 80.98, 79.36, 62.33, 60.41, 49.24, 47.30, 45.50, 38.65, 33.40, 32.93, 32.59, 31.67, 24.91, 18.43; HRMS (FAB/NaI) *m/z* calcd for $C_{19}H_{30}O_4Na$ 345.2042, found 345.2039; $[\alpha]_D^{20}$ −4.5° (*c* 0.009, $CHCl_3$).

Keto Aldehyde 23. Triol **22** (72 mg, 0.226 mmol) was dissolved in dry EtOAc (11 mL) and treated with solid $Pb(OAc)_4$ (201 mg, 0.453 mmol) in one portion, at room temperature. After 5 min the canary yellow mixture was poured over a plug of silica gel (5 cm long), and eluted with EtOAc. The filtrate was concentrated *in vacuo* to give a clear, colorless oil. This was dissolved in CH_2Cl_2 (11 mL), and after three freeze−pump−thaw cycles (argon), treated with DBU (0.100 mL, 0.68 mmol). The mixture was stirred at room temperature, under an atmosphere of argon, for 24 h, diluted with EtOAc (25 mL), washed with HCl (1 N, 5 mL), water (5 mL), and saturated NaCl (5 mL). The organic solution was dried (Na_2SO_4), filtered, concentrated *in vacuo*, and purified by SGC (4:1 hexane/EtOAc) gave 32.1 mg (49%) of pure **23**, along with 4 mg (12.9 mg, 20%) of a minor diastereomer (not shown) (R_f = 0.29 in 4:1 hexane/EtOAc). This minor component was resubjected to the above conditions for further equilibration toward **23**. Following this step, a total of 40 mg (61%) of pure **23** (colorless oil) and 4 mg (6%) of the minor diastereomer were obtained: $[\alpha]^{23}_D$ +15° (*c* 0.003, $CHCl_3$); IR (film) 2951, 2868, 1720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.62 (br s, 1H), 4.96 (br s, 1H), 4.94 (br s, 1H), 3.66 (ddd, J_1 = 4.3, J_2 = J_3 = 9.7, 1H), 3.61 (dd, J_1 = J_2 = 9.7, 1H), 3.52 (d, J = 9.7, 1H), 2.85 (dd, J = 4.0,12.1, 1H), 2.75 (m, 1H), 2.41 (m, 1H), 2.36 (dd, J_1 = J_2 = 11.7, 1H), 2.15 (dd, J = 3.5, 12, 1H), 2.0 (p obs dd, J_1 = J_2 = 12, 1H), 2.0−1.9 (m, 1H), 1.8−1.64 (m, 4H), 1.54 (s, 3H), 1.21 (s, 3H), 1.17 (m, 1H), 1.10 (d, J = 7.0, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 198.8, 144.0, 116.1, 82.4, 80.2, 64.3, 53.6, 49.2, 46.6, 43.7, 42.4, 40.9, 32.4, 29.7, 28.9, 26.5, 21.8; HRMS (FAB) *m/z* calcd for $[M + Na]^+$ 313.1780, found 313.1796.

Keto Diene 24. A solution of the keto aldehyde **23** (4 mg, 0.014 mmol) in THF (1 mL) was treated with the Tebbe reagent[48] (0.050 mL of a 0.4 M solution in toluene, 0.020 mmol) at −40 °C. After a total of 1 h of stirring at −40 °C, the reaction was warmed to −25 °C and quenched with one drop of 15% aqueous NaOH. The mixture was diluted with ether and allowed to warm to room temperature. After an additional hour of stirring, the mixture was pale yellow in color. This was passed through a plug of silica gel, concentrated *in vacuo*, and purified by SGC (8:1 hexane/EtOAc), affording 3 mg (74%) of **24**: IR (thin film/NaCl) 2928, 2866, 1701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.58 (m, 1H), 5.01 (s, 1H), 4.99 (d, J = 4.9 Hz, 1H), 4.92 (overlapping s, 2H), 3.64 (apparent dt, J = 10.6, 4.4 Hz, 1H), 3.22 (apparent t, J = 10.8 Hz, 1H), 3.13 (dd, J = 10.8, 8.3 Hz, 1H), 2.85 (dd, J = 12.3, 4.4 Hz, 1H), 2.69 (m, 1H), 2.37 (overlapping m, 2H), 2.08 (d, J = 14.8 Hz, 1H), 1.94 (overlapping m, 2H), 1.74−1.64 (overlapping m, 3H), 1.30 (s, 3H), 1.17−1.10 (m, 1H), 1.10 (s, 3H), 1.09 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.83, 143.67, 135.09, 117.53, 115.99, 83.71, 82.65, 58.93, 56.54, 49.54, 48.00, 43.54, 42.58, 40.94, 32.37, 28.69, 28.33, 26.16, 22.26; HRMS (FAB/NaI) *m/z* calcd for $C_{19}H_{28}O_2Na$ 311.1987, found 311.1981.

(48) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611.

Acrylonitrile 33. To a solution of (methoxymethyl)triphenylphosphonium chloride (360 mg, 1.05 mmol) in THF (8.6 mL) at −78 °C was added a solution of KHMDS in THF (0.6 M, 1.09 mL, 0.655 mmol). The resulting yellow solution was stirred at this temperature for 30 min, and a solution of keto aldehyde **23** (38 mg, 0.131 mmol) in THF (4.5 mL) was added. This mixture was stirred at this temperature for 30 min, warmed to room temperature, and stirred at room temperature 1.5 h. Hexanes (15 mL) were added, and the mixture was filtered through a plug of Celite. The yellow oil afforded upon evaporation of the filtrate was purified by silica gel chromatography (4:1 hexanes/EtOAc), giving the desired methyl enol ether (35 mg, 83%) as an 8.5:1 mixture of olefin isomers. This material (25 mg, 0.0786 mmol) was added to a premixed solution of NaH (32 mg, 60% suspension, 0.786 mmol) and diethyl (cyanomethyl)phosphonate (278 mg, 1.57 mmol, 0.254 mL) in toluene (16 mL). This solution was heated at reflux for 48 h, cooled to room temperature and diluted with water (10 mL) and EtOAc (10 mL). The organic phase was washed with water (3 × 5 mL) and saturated NaCl (5 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by SGC (4:1 hexanes/EtOAc) afforded **33** (24.8 mg, 93%) as a clear oil as an 8.5:1 mixture of olefin isomers (see above). Data for major olefin isomer: IR (film) 2953, 2868, 2215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.21 (d, J = 12.6, 1H), 5.05 (s, 1H), 4.88 (s, 1H), 4.87 (s, 1H), 4.44 (dd, J = 9.8, 12.6, 1H), 3.62 (ddd, J_1 = 4.4, J_2 = J_3 = 10.3, 1H), 2.81 (dd, J = 4.4, 12.3, 1H), 2.63 (dd, J = 10.7, 11.2, 1H), 2.63 (obscured m, 1H), 2.53 (dd, J = 12.3, 16.0, 1H), 2.36−2.32 (m, 2H), 2.02−1.90 (m, 4H), 1.85−1.67 (m, 4H), 1.24 (s, 3H), 1.16 (m, 2H), 1.11 (s, 3H), 1.05 (d, J = 6.8, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 149.4, 145.3, 117.1, 114.8, 99.4, 94.9, 85.0, 82.2, 56.4, 54.5, 53.3, 48.6, 46.1, 43.9, 40.0, 37.7, 32.1, 28.8, 27.9, 25.5, 21.4; HRMS (FAB) *m/z* calcd for $[M + Na]^+$ 364.2253, found 364.2269.

Iodoacrylonitrile 34. To a solution of **33** (23.0 mg, 0.0674 mmol) in THF (6.9 mL) was added aqueous 1 N HCl (6.9 mL), and this solution was stirred at room temperature for 36 h. The pale yellow solution was diluted with water (10 mL) and EtOAc (10 mL), and the organic phase was washed with saturated NaCl (3 mL). After extraction of the aqueous phase with EtOAc (10 mL), the combined organics were dried ($MgSO_4$), filtered, and concentrated *in vacuo*, giving 25 mg (100%) of an aldehyde that was immediately dissolved in MeOH/EtOH (1.7 mL, 5.1 mL), cooled to −78 °C, and treated with sodium borohydride (26 mg, 0.674 mmol). After this mixture was stirred at this temperature for 1 h, water (5 mL) and EtOAc (15 mL) were added, and the aqueous layer was extracted with EtOAc (10 mL). The combined organic solutions were dried (Na_2SO_4), filtered, concentrated *in vacuo*, and purified by silica gel chromatography (1:2 hexanes/EtOAc) to give the desired primary alcohol (21 mg, 95%) as a clear oil: $[\alpha]^{23}_D$ +250° (*c* 0.0043, $CHCl_3$); IR (film) 3447, 2947, 2215, 1613, 1369, 1053, 897 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.15 (d, J = 2.4, 1H), 4.89 (s, 1H), 4.81 (br s, 1H), 3.55 (obscured m, 1H), 3.54 (t, J = 6.9, 2H), 2.80 (dd, J = 4.7,12.3, 1H), 2.76 (dd, J = 12.5, 16.4, 1H), 2.56 (m, 1H), 2.48 (dd, J = 9.6, 11.1, 1H), 2.30−2.00 (m, 5H), 1.85 (ddd, J_1 = 1.0, J_2 = J_3 = 12.3, 1H), 1.85−1.70 (m, 3H), 1.63 (dddd, J_1 = 6.7, J_2 = J_3 = 6.9, J_4 = 7.0, 1H), 1.53 (dddd, J_1 = J_2 = 6.9, J_3 = J_4 = 7.2, 1H),1.33 (s, 3H), 1.30−1.15 (m, 2H), 1.15 (s, 3H), 1.07 (d, J = 7.0, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 144.1, 117.1, 114.5, 94.5, 87.0, 81.8, 60.9, 54.0, 50.5, 48.8, 43.8, 41.9, 40.1, 38.7, 32.5, 31.6, 29.4, 27.8, 25.2, 22.6; HRMS (FAB) *m/z* calcd for $[M + Na]^+$ 352.2252, found 352.2259.

To a solution of this alcohol (18.6 mg, 0.0565 mmol) in ether (3.3 mL) and acetonitrile (1.1 mL) at room temperature were added in the order listed triphenylphosphine (44.5 mg, 0.170 mmol), imidazole (11.5 mg, 0.170 mmol), and iodine (43.0 mg, 0.170 mmol). The yellow solution exothermed slightly, and a white precipitate developed over 5 min. The mixture was diluted with ether (15 mL), filtered through a short (5 cm) plug of celite, washed with saturated sodium hydrogen carbonate (5 mL) and saturated NaCl (5 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting yellow oil was purified by silica gel chromatography (10:1 hexanes/EtOAc) to give **34** (24.1 mg, 94%) as a clear oil.

15-Cyanoepoxydictymene (37). A frozen ether (0.9 mL) solution of **34** (6.2 mg, 0.014 mmol) was degassed under high vacuum and then cooled to −78 °C under argon. Stirring of the ethereal solution

was initiated with a magnetic stirring bar, and solution of *t*-BuLi in pentane (0.031 mmol, 1.5 M, 0.021 mL) was then added. The solution turned yellow immediately. After the mixture was stirred at this temperature for 15 min, the stirring bar was stopped, and the solution was warmed to room temperature and held at this temperature for 30 min. Water (0.1 mL) was added, and the mixture was diluted with ether (5 mL). The organic phase was washed with saturated NaCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a yellow oil that was purified with silica gel chromatography (10:1 to 4:1 hexanes/EtOAc) to give **37** (3.1 mg, 74%) as a clear oil: $[\alpha]^{23}_D$ +68° (*c* 0.0020, $CHCl_3$); IR (film) 2948, 2867, 2243 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.00 (s, 1H), 4.87 (s, 1H), 3.52 (ddd, $J_1 = 6.8$, $J_2 = J_3 = 9.8$, 1H), 2.84 (dd, $J = 6.7$,11.8, 1H), 2.65 (ddd, $J = 6.6$, 9.8, 12.1, 1H), 2.45 (d, $J = 16.3$, 1H), 2.33 (ddd, $J = 7.5$, 11.1, 13.7, 1H), 2.25 (d, $J = 16.3$, 1H), 2.15 (m, 1H), 2.02 (ddd, $J_1 = 3.1$, $J_2 = J_3 = 12.4$, 1H), 1.79 (m, 1H), 1.70 (dd, $J = 10.3$, 11.1, 1H), 1.60−1.20 (m, 9H), 1.25 (s, 3H), 1.17 (s, 3H), 1.07 (m, 1H), 1.01 (d, $J = 6.5$, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 119.0, 115.4, 78.0, 74.1, 59.3, 57.6, 50.9, 48.0, 43.9, 43.3, 41.8, 39.2, 39.0, 34.6, 34.0, 29.2, 26.7, 24.1, 20.3, 19.3; HRMS (EI) *m/z* calcd for M^+ 313.2406, found 313.2407.

(+)-Epoxydictymene 1. To a suspension of potassium metal (2.6 mg, 0.064 mmol) in toluene (0.4 mL) at room temperature was added a solution of 18-crown-6 (6.8 mg, 0.026 mmol) in toluene (0.1 mL). To this mixture was added a solution of **35** (4.0 mg, 0.013 mmol) in toluene (0.5 mL), and the heterogenous mixture was stirred at room temperature for 2 h. During this time a fine white powder appeared, and the liquid phase became pale yellow. The mixture was quenched with *i*-PrOH (0.1 mL) and transferred into a mixture of water and EtOAc (1 mL of each). The organic layer was washed with saturated NaCl, dried ($MgSO_4$), and filtered through a short (2 cm × 0.5 cm) plug of silica gel. The silica gel was washed with 1:1 hexanes/EtOAc. Evaporation of the combined filtrates yielded an oil that was purified by silica gel chromatography (20:1 hexanes/EtOAc), giving **1** (2.5 mg, 73%) as an oil. **Synthetic 1:** $[\alpha]^{23}_D$ +70° (*c* 0.0015, hexane); IR (film) 2948, 2869, 1634, 1456, 1138, 999, 893 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.95 (s, 1H), 4.79 (s, 1H), 3.54 (ddd, $J_1 = 6.7$, $J_2 = J_3 = 9.9$, 1H), 2.82 (dd, $J = 6.6$, 11.6, 1H), 2.63 (ddd, $J_1 = 6.7$, $J_2 = J_3 = 11.5$, 1H), 2.45 (ddd, $J = 7.8$, 11.2, 13.6, 1H), 2.00 (dd, $J = 10.3$, 13.7, 1H), 1.94 (ddd, $J_1 = 4.0$, $J_2 = J_3 = 12.5$, 1H), 1.75−1.60 (m, 4H), 1.60−1.40 (m, 3H), 1.40−1.16 (m, 4H), 1.24 (s, 3H), 1.15 (s, 3H), 1.02 (p obscured, 1H), 0.98 (d, $J = 6.5$, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 114.5, 78.0, 74.8, 59.6, 57.5, 51.0, 48.4, 44.2, 43.9, 43.3, 41.5, 36.7, 34.7, 34.2, 29.3, 24.4, 24.1, 20.3, 19.2; HRMS (EI) *m/z* calcd for M^+ 288.2455, found 288.2453. **Reported for natural product:**[1] $[\alpha]^{23}_D$ +72.1° (*c* 0.9, hexane); IR (film) 1630, 1140, 999, 893 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.98 (s, 1H), 4.77 (s, 1H), 3.57 (dt, $J = 7$, 10, 1H), 2.82 (dd, $J = 7$, 12, 1H), 2.64 (ddd, $J = 7$, 10, 12, 1H), 2.48 (ddd, $J = 7$, 11, 14, 1H), 2.03 (dd, $J = 10$, 14, 1H), 1.26 (s, 3H), 1.17 (s, 3H), 1.01 (d, $J = 7$, 3H), 0.89 (s, 3H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 145.8, 114.1, 77.7, 74.6, 59.5, 57.4, 50.8, 48.3, 44.1, 43.8, 43.2, 41.4, 36.6, 34.6, 34.1, 29.2, 24.3, 24.0, 20.2, 19.1; HRMS (EI) *m/z* calcd for M^+ 288.2455, found 288.2495.

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Supporting Information Available: Experimental procedures and complete physical and spectral data for compounds **3**, **12**, **13**, **17**−**19**, **25**−**31**, and **35**−**36** (14 pages total). See any current masthead page for ordering and Internet access instructions.

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