Studies on the Biosynthesis of Taxol: Total Synthesis of Taxa-4(20),11(12)-diene and Taxa-4(5),11(12)-diene. The First Committed Biosynthetic Intermediate

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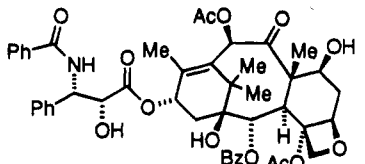
The total synthesis of taxa-4(20),11(12)-diene and taxa-4(5),11(12)-diene is described.

Introduction

The scientific community has recently put great emphasis on the elucidation of the mechanism of action, biosynthesis, semisynthesis, and total synthesis of the potent and commercially significant anticancer drug taxol (**1**) along with several biologically active analogues.[1] Chemists and biologists alike have been drawn to taxol due to its promising spectrum of antineoplastic activity, its unique mechanism of action, and the synthetic challenge that the complex and densely functionalized ring system poses.

Taxol was first isolated from the bark of the pacific yew, *Taxus brevifolia*.[2] Unfortunately the pacific yew is slow growing and is primarily found in environmentally sensitive areas of the Pacific Northwest and stripping the tree of its bark kills the yew. It takes three trees to obtain ~10 kg of bark from which up to 1 g of pure taxol can be isolated.[1c] The recent approval by the FDA of taxol (paclitaxel) for the treatment of advanced ovarian cancer[1a] has created a severe supply and demand problem. Alternative means of taxol production are therefore being vigorously pursued.



1, TAXOL

To date, totally synthetic methods have fallen short as an alternative source for taxol production. This is due to the highly complex nature of the taxol structure which mandates lengthy and expensive synthetic routes. A method which shows promise is the semisynthesis of taxol from 10-deacetylbaccatin III which can be isolated from the needles, a renewable source, of the European yew, *Taxus baccata*.[1b,c] In order to produce large quantities of taxol or a pharmacophoric equivalent by semisynthetic or perhaps, by genetically engineered biosynthetic methods, it is significant to gain a better understanding of the detailed biosynthetic pathways[3-5] in *T. brevifolia* and other related taxol-producing species.

In 1966 Lythgoe and co-workers proposed a biosynthetic pathway (Scheme 1) in which the tricyclic carbon framework of the taxoids was envisioned to arise by the sequential intramolecular cyclizations of the double bonds of geranylgeranyl pyrophosphate (**2**) via cation **3** to 1(*S*)-verticillene (**4**) and then to taxa-4(20),11(12)-diene (**6**) via cation **5**.[6] The elaboration of taxol from this simple diterpene skeleton would then involve a series of nine two-electron enzymatic oxidations, acylations, and attachment of the side chain to produce taxol.

Very recently, Croteau and associates[7] have isolated the C-ring double bond isomer, taxa-4(5),11(12)-diene (**7**), from yew bark extract and have elegantly demonstrated that this substance (and not **6**) is the primary product of a diterpenoid cyclase present in a cell-free preparation from sapling yew stems utilizing [1-^{3}H]-geranylgeranyl pyrophosphate as a substrate. These workers further demonstrated that ^{3}H-labeled-**7**, when incubated with yew stem sections, was converted in significant radiochemical yield to taxol, 10-deacetyl baccatin III, and several other highly functionalized taxanes. Based on these important findings, it would appear that the putative cation species **5** suffers β-H elimination to furnish **7** and not **6** as originally proposed by Lythgoe.[6]

Due to the very low yield of natural **7** that can be obtained from current yew harvest (an extract from 750 kg of *T. brevifolia* bark powder yielded[7] 1 mg of 85% pure **7**) and the remaining uncertainty as to the possible role of **6** in the biosynthesis of the taxoids,[8] access to these isotopically labeled tricyclic diterpenes is deemed highly desirable, since these substances can potentially serve as useful probes for establishing the initial sequence of hydroxylation reactions of this tricyclic core and the further elaborations to taxol. As part of a program aimed at manipulating taxoid biosynthesis at the genetic level, the slow steps in the biosynthetic pathway will need to be elucidated. Since geranylgeranyl pyrophosphate serves as a starting material for many other biosynthetic

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(1) For reviews see: (a) Georg, G. I.; Ali, S. M.; Zygmunt, J.; Jayasinghe, L. R. *Exp. Opin. Ther. Pat.* **1994**, *4*, 109. (b) Boa, A. N.; Jenkins, P. R.; Lawerence, N. J. *Contemp. Org. Synth.* **1994**, 47. (c) Nicolaou, K. C.; Dai,W-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15. (d) Guenard, D.; Gueritte-Voegelein, F.; Potier, P. *Acc. Chem. Res.* **1993**, *26*, 160. (e) Kingston, D. G. *Pharmacol. Ther.* **1991**, *52*, 1. (f) Swindell, C. S. *Org. Prep. Proc. Int.* **1991**, *23*, 465. (g) Rowinsky, E. K.; Cazenave, L. A.; Donehower, R. C. *J. Nat. Cancer Inst.* **1990**, *82*, 1247. (h) Floss, H. G.; Mocek, U. In *Taxol: Science and Applications*, Suffness, M., Ed.; CRC Press: Boca Raton, FL, 1995.

(2) Wani, M. C.; Tayler, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.

(3) Han, K.-H.; Fleming, P.; Walker, K.; Loper, M.; Chilton, W. S.; Mocek, U.; Gordon, M. P.; Floss, H. G. *Plant Sci.* **1994**, *95*, 187.

(4) (a) Stierle, A.; Strobel. G.; Stierle, D. *Science* **1993**, *260*, 214. (b) Strobel, G. A.; Stierle, A.; Van Kuijk, F. J. G. M. *Plant Sci.* **1992**, *84*, 65.

(5) (a) Fleming, P. E.; Knaggs, A. R.; He, X.-G.; Mocek, U.; Floss, H. G. *J. Am. Chem. Soc.* **1994**, *116*, 4137. (b) Fleming, P. E.; Mocek, U.; Floss, H. G. *J. Am. Chem. Soc.* **1993**, *115*, 805.

(6) (a) Harrison, J. W.; Scrowston, R. M.; Lythgoe, B. *J. Chem. Soc. (C)* **1966**, 1933; see also: (b) Gueritte-Voegelein, F.; Guenard, D.; Potier, P. *J. Nat. Prod.* **1987**, *50*, 9.

(7) Koepp, A. E.; Hezari, M.; Zajicek, J.; Vogel, B. S.; LaFever, R. E.; Lewis, N. G.; Croteau, R. *J. Biol. Chem.* **1995**, *270*, 8686.

(8) It is mechanistically possible that both **6** and **7** are formed and/or that initially formed **6** suffers a subsequent isomerization to **7**; these possibilities are presently being investigated.

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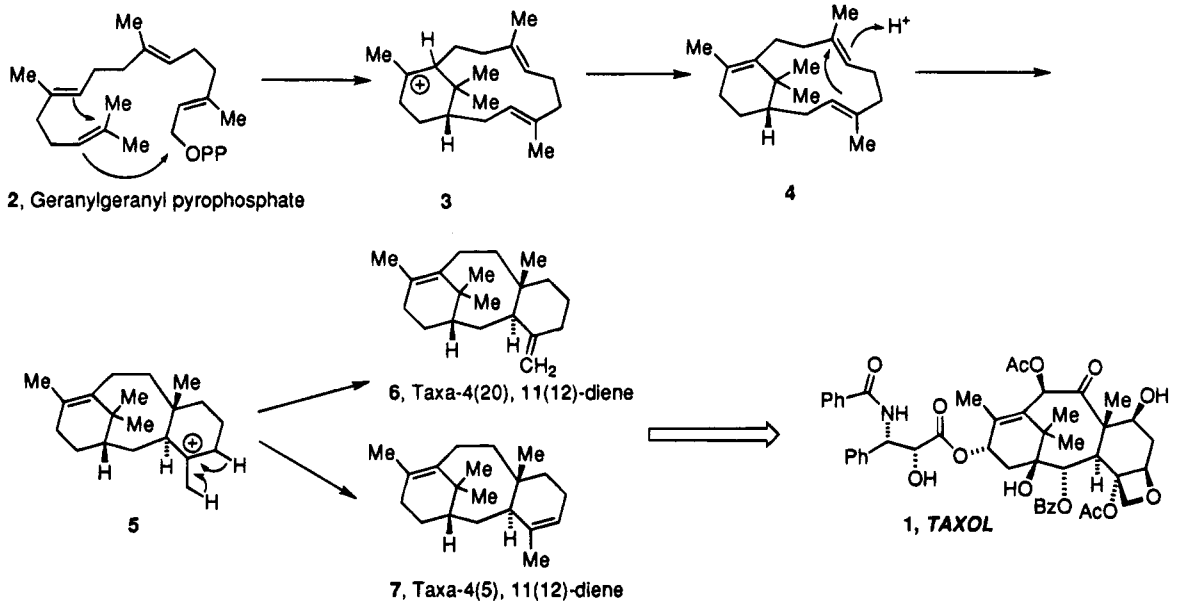
Scheme 1



pathways,[9] the diterpenoid cyclase step may be rate-limiting in the secondary metabolic flux to taxol.[7] As a first step toward targeting the slow steps in the biosynthesis of taxol, we have undertaken the synthesis of the first committed biosynthetic intermediate in taxol biosynthesis which, as reported by Croteau and associates,[7] is compound **7**. Reported herein are preparatively useful syntheses of (±)-taxa-4(20),11(12)-diene (**6**) and (±)-taxa-4(5),11(12)-diene (**7**) that are readily amenable to the incorporation of isotopic labels.

Results and Discussion

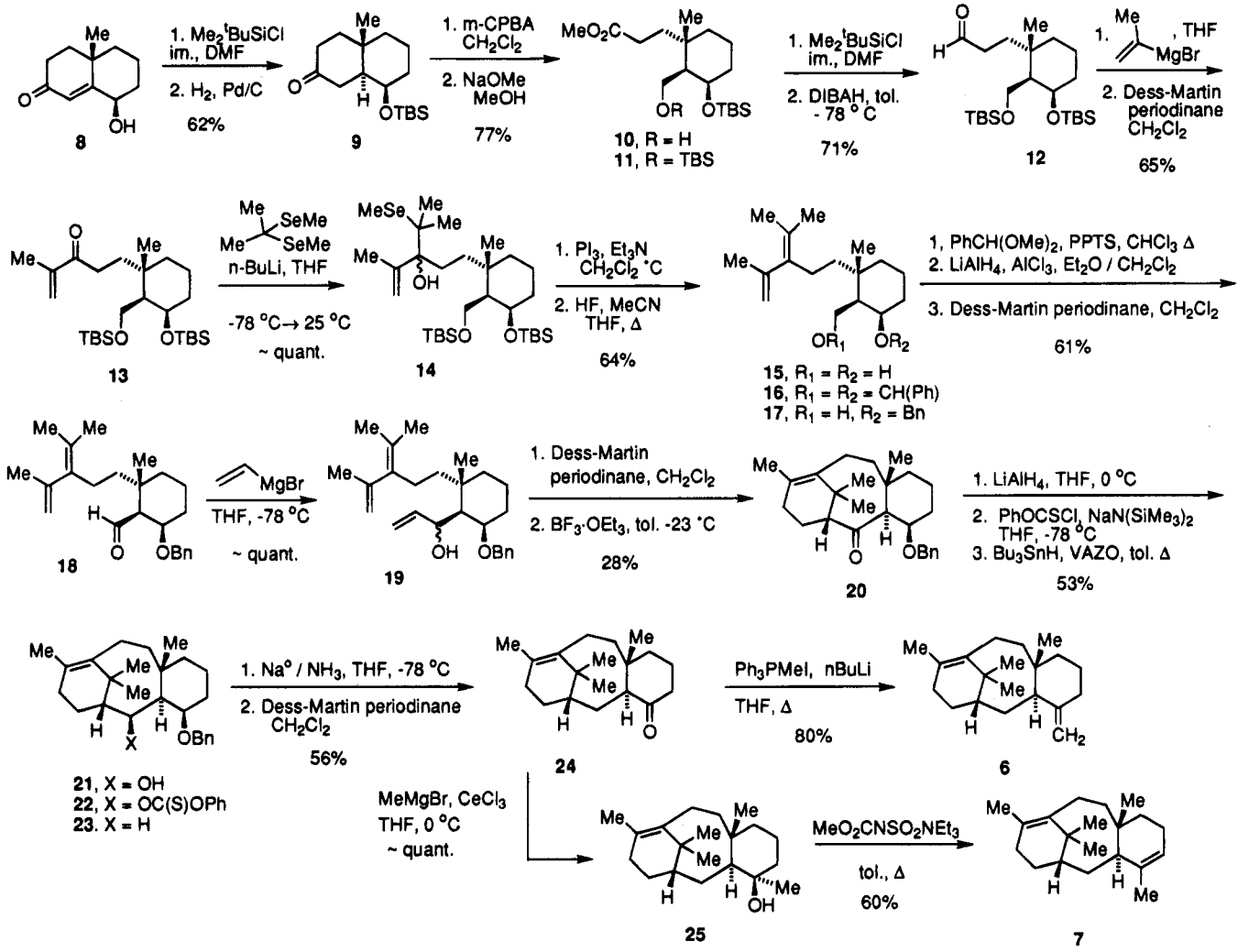
Despite the intensive efforts in the past several years by many groups[1c,10] to achieve the total synthesis of natural taxoids, it was somewhat surprising to discover that there were no reports concerning the successful construction of the simple C_{20} core framework first proposed by Lythgoe (taxa-4(20)-11,12-diene (**6**)). Our objectives were to identify a route that would (1) quickly yield the desired twenty-carbon framework with the correct relative stereochemistry; (2) produce gram quantities; and (3) permit the convenient and economical installation of stable and/or radioisotopes in the very final stage of the synthesis. After considering several alternatives, we decided to adapt a route originally devised by Shea and Davis[11a-g] that relied on the use of an intramolecular Diels–Alder cyclization reaction forming the A/B-ring system with an aromatic C-ring. This strategy was concurrently explored by Jenkins and co-workers[11h-j] to access a model A/B/(saturated) C-ring system containing the C-19 methyl group with the correct relative stereochemistry, but without functionality in the C-ring. Conscripting this approach for the synthesis of the taxadienes **6** and **7** required installing a functional group in the C-ring at C-4 for the ultimate installation of the C-20 carbon atom and the 4(20)- or 4(5)-double bonds. The route described below closely parallels the Jenkins synthesis,[11h] the important difference being the early introduction of a hydroxyl group in the C-ring precursor that will ultimately become the functionalized C-4 carbon of the taxadienes.

Scheme 2 outlines the synthesis of taxa-4(20),11(12)-diene (**6**). The starting bicyclic enone **8** is easily prepared by the large scale condensation of 2-methylcyclohexanone with methylvinyl ketone under acidic conditions to produce the Robinson annulation product in 60% yield.[12] Conversion to the dienol acetate[13] followed by m-CPBA

(9) For leading references, see: (a) Herbert, B. A. *The Biosynthesis of Secondary Metabolites*; Chapman and Hall: London, **1981**. (b) Nakanishi, K.; Goto, T.; Ito, S.; Nozoe, S. *Natural Products Chemistry*; Kodansha, Ltd.: Tokyo, 1974; Vol. I. (c) *Recent Advances in Phytochemistry Vol. 24: Biochemistry of the Mevalonic Acid Pathway to Terpenoids*; Towers, G. H. N., Stafford, H. A., Eds.; Plenum Press: New York, 1990. (d) Luckner, M. *Secondary Metabolism in Microorganisms, Plants and Animals*; Springer-Verlag: Berlin, 1990.

(10) For some leading references on the total synthesis of taxol and synthetic approaches, see: (a) Holton. R. A.; Juo, R. R.; Kim, H. B.; Williams, A. D.; Harusawa, S.; Lowenthal, R. E.; Yogai, S., *J. Am.Chem.Soc.* **1988**, *110*, 6558. (b) Wender, P. A.; Mucciaro, T. P. *J. Am. Chem. Soc.* **1992**, *114*, 5878. (c) Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E.A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624. (d) Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634. (e) Nicolaou, K. C.; Yang, Z.; Liu, J.-J.; Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *J. Am. Chem. Soc.* **1995**, *117*, 645. (f) Nicolaou, K. C.; Ueno, H.; Liu, J.-J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.* **1995**, *117*, 653 (and references cited therein). (g) Nicolaou, K. C.; Yang, Z.; Liu, J.-J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Cliaborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630. (h) Holton, R. A.; Somoza, C.; Kim, H.-B.; Liang, F.; Biediger, J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597. (i) *Idem. Ibid.* **1994**, *116*, 1599. (j) Blechert, S.; Kleine-Klausing, A. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 412. (k) Berkowitz, W. F.; Amarasekara, A. S. *Tetrahedron Lett.* **1985**, *26*, 3663. (l) Horiguchi, Y.; Furukawa, T.; Kuwajima, I. *J. Am. Chem. Soc.* **1989** *111*, 8277. (m) Hitchcock, S. A.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 4843. (n) Lu, Y.-F.; Fallis, A. G. *Tetrahedron Lett.* **1993**, *34*, 3367. (n) Ohtsuka, Y.; Oishi, T. *Chem. Pharm. Bull.* **1991**, *39*, 1359. (o) Wang, Z.; Warder, S. E.; Perrier, H.; Grimm, E. L.; Berstein, M. A.; Ball, R. G. *J. Org. Chem.* **1993**, *58*, 2931. (p) Sakan, K.; Smith, D. A.; Babirad, S. A.; Fronczek, F. R.; Houk, K. N. *J. Org. Chem.* **1991**, *56*, 2311. (q) Paquette, L. A.; Zhao, M. *J. Am. Chem. Soc.* **1993**, *115*, 354. (r) Winkler, J. D.; Kim, H. S.; Kim, S. *Tetrahedron Lett.* **1995**, *36*, 687. (s) Kojima, T.; Inouye, Y.; Kakisawa, H. *Chem. Lett.* **1985**, 323. (t) Swindell, C. S.; Patel, B. P. *J. Org. Chem.* **1990**, *55*, 3. (u) Martin, S. F.; White, J. B.; Wagner, R. *J. Org. Chem.* **1982**, *47*, 3190. (v) Funk, R. L.; Daily, W. J.; Parvez, M. *J. Org. Chem.* **1988**, *53*, 4141. (w) Yadov, J. S.; Ravishankar, R. *Tetrahedron Lett.* **1991**, *32*, 2629; a 9(10)-dehydro version of **6** has been reported, see: (x) Kende, A. S.; Johnson, S.; Sanfilippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc.* **1986**, *108*, 3513. (y) Masters, J. J.; Jung, D. K.; Danishefsky, S. J.; Snyder, L. B.; Park, T. K.; Isaacs, R. C. A.; Alaimo, C. A.; Young, W. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 452.

Scheme 2

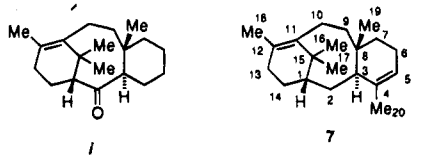


oxidation[14,15] yields alcohol **8** (obtained as a separable 4.5:1 mixture with the corresponding alcohol epimer). Installation of the hydroxyl group in the decalone system at this point provides a C-4 functional group for the ultimate introduction of the C-20 carbon atom of the taxadiene system. Protection of alcohol **8** as a TBS ether[16] followed by hydrogenation[17] produced **9** as a single diastereomer in 62% overall yield from **8**. The bicyclic ring system was demonstrated to be *trans*-fused by ^{1}H NMR NOE experiments. Subjecting **9** to Baeyer–Villiger conditions[18] provided the corresponding lactones (86%, 1:2 ratio of desired:undesired regioisomers, respectively) which were opened using sodium methoxide to furnish ester **10** (90% in a 1:2 ratio of desired:undesired regioisomers, respectively). Despite the poor regioselectivity of this reaction, it was possible to isolate a preparatively useful amount of the desired isomer **10** in a convenient manner.

Compound **10** was then protected as the corresponding *tert*-butyldimethylsilyl ether followed by DIBAH[11h] reduction to form aldehyde **12** in 71% overall yield from compound **10**.

Addition of 2-propenyl magnesium bromide[11h] to aldehyde **12** yielded the corresponding allylic alcohol as a single diastereomer which was subsequently oxidized using the Dess–Martin periodinane reagent[19] to produce enone **13** in 65% yield. Reaction of 2,2-bis(methylseleno)-propane[20] with n-BuLi furnished the lithio seleno species

(11) The taxane model system reported by Jenkins and Bonnert (ref 11h) culminated in the synthesis of the tricyclic compound *i* shown below; taxol numbering is used for this structure and the taxadienes **6** and **7** reported in this paper:



i 7

(a) Shea, K. J.; Davis, P. D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 419. (b) Shea, K. J.; Davis, P. D. *Angew. Chem. Suppl.* **1983**, *22*, 564. (c) Shea, K. J.; Gilman, J. W.; Haffner, C. D.; Dougherty, T. K. *J. Am. Chem. Soc.* **1986**, *108*, 4953. (d) Jackson, R. W.; Higby, R. G.; Shea, K. J. *Tetrahedron Lett.* **1992**, *33*, 4695. (e) Shea, K. J.; Haffner, C. D. *Tetrahedron Lett.* **1988**, *29*, 1367. (f) Shea, K. J.; Sakata, S. T. *Tetrahedron Lett.* **1992**, *33*, 4261. (g) Jackson, R. W.; Higby, R. G.; Gilman, J. W.; Shea, K. J. *Tetrahedron* **1992**, *48*, 7013. (h) Bonnert, R. V.; Jenkins, P. R. *J. Chem. Soc. Perkin Trans. 1* **1989**, 413. (i) Brown, P. A.; Jenkins, P. R. *J. Chem. Soc. Perkin Trans. 1* **1986**, 1303 (j) Brown, P. A.; Jenkins, P. R.; Fawcett, J.; Russell, D. R. *J. Chem. Soc. Perkin Trans. 1* **1984**, 253.

(12) Heathcock, C. H.; Ellis, J. E. *Tetrahedron Lett.* **1971**, *52*, 4995.

(13) Julia, S.; Rasseur, M. J. *Bull. Soc. Chim. Fr.* **1962**, 374.

(14) Wege, P. M.; Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 3144.

(15) Holland, H. L.; Auret, B. J. *Can. J. Chem.* **1975**, *53*, 2041.

(16) Corey, E. J.; Vankateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(17) Beeson, C.; Dix, T. A. *J. Org. Chem.* **1992**, *57*, 4386.

(18) DeBoer, A.; Ellwanger, R. E. *J. Org. Chem.* **1974**, *39*, 77.

(19) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

which added to compound **13** chemoselectively to form **14** as a ~4:1 mixture of diastereomers in essentially quantitative yield.[11h] Elimination[21] followed by removal of the silyl ethers with HF in acetonitrile[11h] produced diol **15** in 64% yield. Diol **15** was condensed with benzaldehyde dimethyl acetal to afford benzylidine acetal **16** as a 3:1 mixture of diastereomers in 88% yield.[22,23] Interestingly, attempts to protect the diol system of **15** with benzaldehyde in the presence of a Lewis acid led to the hetero Diels–Alder cyclization of the diene system with benzaldehyde. The use of the benzaldehyde dimethyl acetal obviated this problem. The acetal mixture was reduced using $LiAlH_4/AlCl_3$[24] to produce an inseparable mixture of alcohol **17** and the corresponding regioisomer (~quant.) in a 4:1 ratio, respectively. This mixture was subsequently oxidized with Dess–Martin periodinane[19] to furnish a separable mixture of the desired aldehyde **18** and the undesired ketone in a 2.3:1 ratio, respectively, in 69% yield.

Addition of vinylmagnesium bromide[11h] to aldehyde **18** furnished allylic alcohol **19** as a 5.4:1 mixture of diastereomers in essentially quantitative yield. This mixture was oxidized with Dess–Martin periodinane[19] and then subjected to Lewis acid-catalyzed intramolecular [4 + 2] cycloaddition (BF_3–OEt_2 for 48 h) to produce the Diels–Alder product **20** in 28% yield.[11h] The relative stereochemistry of **20** was evident from ^1H NMR NOE experiments and was finally corroborated through a single crystal X-ray analysis of the subsequent transformation product **24**. Stereoselective reduction of ketone **20** furnished alcohol **21** which is believed to possess the β-relative stereochemistry, since the top face of **21** is blocked by both C-16 and C-19 (taxane numbering) methyl groups thus forcing $LiAlH_4$ to attack from the bottom face. Compound **21** was sequentially converted into xanthate ester **22** followed by deoxygenation with tri-*n*-butyltin hydride in hot toluene to afford **23** in 53% yield overall yield from **20**. Dissolving metal reduction of the benzyl ether of compound **23** followed by Dess–Martin periodinane oxidation[19] produced ketone **24** in 56% yield. The structure and relative stereochemistry of **24** was firmly established by single crystal X-ray analysis (Figure 1).[25]

Ketone **24** served as the key intermediate for the final elaborations to both taxa-4(20),11(12)-diene (**6**) and taxa-4(5),11(12)-diene (**7**). The exomethylene group of **6** was conveniently installed utilizing methylenetriphenylphosphorane in hot THF[26] to furnish (±)-**6** in 80% yield. To demonstrate the usefulness of compound **24** for accessing isotopically labeled forms of taxa-4(20),11(12)-diene (**6**), the ^{13}C-labeled substance[27] was prepared by utilizing [^{13}C-methyl]triphenylphosphonium iodide (99% atom ^{13}C)

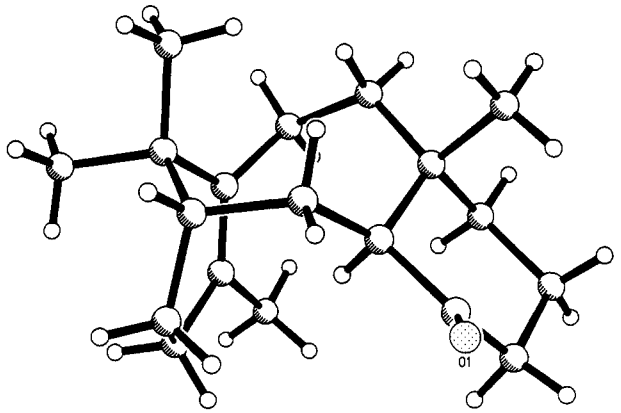


Figure 1. X-ray stereostructure of compound **24**. Spheres are of fixed, arbitrary radius.

and generating the ylide as above with n-BuLi, and olefinating ketone **24** in exactly the same manner.[25]

The natural product **7** was prepared by condensing ketone **24** with methylmagnesium bromide in the presence of $CeCl_3$[28] in THF at 0 °C to give a single stereoisomeric tertiary alcohol (**25**) which is presumed to have the indicated α-stereochemistry.[10a] Dehydration of **25** with the Burgess reagent gave an approximately 1:1 mixture of taxa-4(20),11(12)-diene (**6**) and taxa-4(5),11-(12)-diene (**7**) in 60% combined yield. Comparison of synthetic **7** with an authentic, natural sample by capillary GC, EI-mass spec, ^1H NMR and ^{13}C NMR firmly established the identity of this substance.[7,29] The authentication of the structure of synthetic **7** also serves to corroborate and secure the structural assignment very recently made for the natural product isolated from Pacific Yew bark.[7]

Discussion

The proposed cyclization of 1(*S*)-verticillene (**4**) via cation **5** (Scheme 1), constitutes a reasonable mechanistic pathway for the formation of taxa-4(5),11(12)-diene (**7**).[1,6] We attempted to generate cation **5** in an effort to examine the intrinsic tendency of this species to suffer β-H elimination forming **6** and/or **7**. In addition, it was initially hoped that we could also effect the isomerization of **6** → **7**. Thus, treatment of taxa-4(20),11(12)-diene (**6**) under the following conditions gave either no reaction or decomposition: dry HCl in ether at 0 °C dec; HCl/H_2O in ether at 0 °C dec; H_2SO_4 in H_2O/ethanol at 0 °C dec; BF_3–Et_2O in ether at 0 °C dec; $Pd(Cl)_2$ in toluene at reflux (no reaction); $RhH(CO)(P(Ph)_3)_3$ toluene at reflux (no reaction). In every case, we could not detect any evidence for the production of compound **7**. Additional experiments aimed at effecting the generation of cation **5** and monitoring the reactivity of this species are in progress.

The intermediacy of the Lythgoe structure **6**[6] in the biosynthesis of the taxoids presently remains, at best, uncertain and, based on the very recent work of Croteau and associates,[7] seems unlikely. The present synthesis

(20) 2,2-Bis(phenylseleno)propane was used by Jenkins and Bonnert (ref 11h) for a similar transformation. It was found that this reagent would add to ketone **13** in the presence of t-BuLi in ether in high yield; however, attempts to effect the elimination of this adduct to compound **15** proved unsuccessful (only decomposition was observed). The sterically less demanding 2,2-bis(methylselno)propane was found to be more effective: Krief, A.; Cravador, A. *C. R. Acad. Sci. Paris Ser. C.* **1979**, 267.

(21) Krief, A.; Halazy, S. *J. Chem. Soc. Chem. Commun.* **1979**, 1136.

(22) Bartlett, P. A.; Akerfeldt, K. *Carbohydr. Res.* **1986**, *158*, 137.

(23) Ferro, V.; Molerino, M.; Stick, R. V.; Tilbrook, G.; Mattew, D. *Aust. J. Chem.* **1988**, *41*, 813.

(24) Mori, Y.; Morishima, N. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2061.

(25) (a) See supporting information. (b) X-ray data for the crystallographic analysis of compound **24** has been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

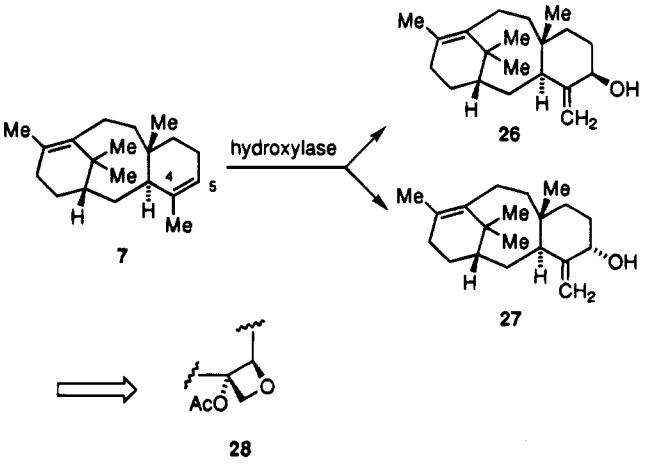
(26) Leopold, E. J. *Org. Synth.* **1985**, *64*, 164.

(27) The results of attempted biosynthetic incorporation experiments with ^{13}C-labeled **6** will be the subject of a separate paper.

(28) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

(29) Authentication of the synthetic material by comparison to natural **7** by capillary GC and EI-mass spec analysis was kindly carried out by Professor Rodney Croteau of the Institute of Biological Chemistry, Washington State University.

Scheme 3



of this substance in ^{13}C-labeled form and the ready adaptability of this route to provide [20-^{3}H]- and/or [20-^{14}C]-labeled-**6** provides convenient access to tools that can furnish a very definitive answer to this question; these studies are currently being pursued.[27]

The route to taxa-4(5),11(12)-diene (**7**) from ketone **24** reported herein, establishes a convenient route to synthesize [20-^{3}H]- and/or [20-^{14}C]-labeled **7** which will be useful probes to determine the sequence of hydroxylation reactions from **7** into the taxoid manifold. The synthesis of these radiolabeled biosynthetic intermediates and their utilization in biosynthetic studies with *T. brevifolia* are currently being pursued in these laboratories.

Finally, taxa-4(20),11(12)-diene (**6**) is ideally suited to serve as a starting material to prepare the C-5 allylic alcohol (**26** or **27**, Scheme 3) which has been suggested as the first oxidation product from taxa-4(5),11(12)-diene (**7**)[7] or from taxa-4(20),11(12)-diene (**6**)[1h] on the pathway to taxol. The C-4,C-5 acetoxy oxetane system (**28**) present in taxol can be envisioned[1h] to arise from either epimer (**26** or **27**), and the elucidation of the stereochemistry of this substance will certainly prove insightful as to the possible mechanisms for elaboration of the C/D-ring system. These and related issues concerning the early stages of taxol biosynthesis are being pursued in these laboratories and will be reported on in due course.

Summary

The total synthesis of the first committed biosynthetic intermediate involved in taxol biosynthesis (taxa-4(5),-11(12)-diene (**7**)) has been achieved. In addition, taxa-4(20),11(12)-diene (**6**), first proposed by Lythgoe[6] to constitute the direct cyclization product of geranylgeranyl pyrophosphate to the taxoid ring system, has been synthesized.

Experimental Section

General Information. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC 300 spectrometer. Chemical shifts are reported in parts per million with $CHCl_3$ as the internal standard. Infrared spectra were recorded on a Perkin-Elmer 1600 Series FTIR and are reported as λ_{max} in cm^{-1}. Melting points were determined in open-ended capillary tubes on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ, and are accurate to within the calculated values by ±0.4%. High-resolution mass spectra were carried out by UCR Mass Spectrometry Facility, Department of Chemistry, University of California at Irvine, Irvine, CA. Thin layer chromatography (TLC) was performed on 0.25-mm E. Merck precoated silica gel glass plates. Visualization on TLC was achieved with ultraviolet light, an I_2 developing chamber, and/or heating of TLC plates submerged in a 5% solution of phosphomolybdic acid in 95% ethanol. Reagents and solvents were commercial grades and were used as supplied unless otherwise stated and with the following exceptions. Tetrahydrofuran, toluene, and diethyl ether were freshly distilled from sodium benzophenone ketyl. Dichloromethane was freshly distilled from CaH_2. DMF was dried over 3-Å molecular sieves. All moisture sensitive reactions were carried out in glassware that was flame dried under high vacuum (0.5–2.0 mmHg) and then purged with N_2. The term "concentrated" refers to the removal of volatile solvents using an aspirated rotary evaporator.

Decalone 9. To a 3 M solution of **8**[12–15] (38 g, 0.21 mol) in DMF under argon was added imidazole (46 g, 0.66 mol) and *tert*-butyldimethylsilyl chloride[16] (100 g, 0.66 mol). The mixture was allowed to stir for 18 h at 35 °C. The crude reaction mixture was poured into a separatory funnel followed by H_2O (500 mL) and Et_2O (500 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 500 mL). The organic layer was washed once with H_2O (250 mL), saturated aqueous NH_4Cl solution (250 mL), and brine (250 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude oil was purified by column chromatography (32:1 hexanes/EtOAc) to give 46.5 g (75%) of the corresponding silyl ether as a yellow oil. This material was directly used for the next step.[17] IR (neat) 2928, 2856, 1680 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.7 (s, 1H), 4.22 (dd, J = 2.6, 2.6 Hz, 1 Hz), 2.55 (ddd, J = 17, 14.7, 5.3 Hz, 1H), 2.33 (ddd, J = 17.1, 3.5, 3.5 Hz, 1H), 2.05 (apparent ddq, J = 14, 4.8, 2.7 Hz, 1H), 1.9–1.72 (m, 2H), 1.72–1.55 (m, 2H), 1.55–1.39 (m, 2H), 1.35 (s, 3H), 1.25 (ddd, J = 13.5, 13.5, 3.4 Hz, 1H), 0.82 (s, 9H), 0.0 (s, 3H), −0.5 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.9, 167.7, 125.6, 73.1, 41.5, 39.7, 35.6, 34.9, 34.3, 25.6, 24.1, 17.9, 16.3, −4.7, −5.1. Anal. Calcd for $C_{17}H_{30}O_2Si$: C, 69.34; H, 10.27. Found: C, 69.23; H, 10.31.

To a 0.3 M solution of the silyl ether obtained above (103 g, 0.35 mol) in anhydrous MeOH under argon was added Pd/C (43 g, 0.02 mol) followed by bubbling H_2(g) through the solution for 3 min. The solution was allowed to stir for 2 days under a hydrogen balloon. The mixture was concentrated, taken up in EtOAc (3 × 500 mL), and filtered through a plug of silica gel. The silica gel was washed with EtOAc (200 mL). The organic layer was concentrated and purified by column chromatography (32:1, 16:1 hexanes/EtOAc) to give 85 g (83%) of **9** as a colorless oil. IR (neat) 2946, 1715 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.7 (ddd, J = 2.6, 2.6, 2.6 Hz, 1H), 2.67 (dd, J = 14.6, 14.6 Hz, 1H), 2.46 (ddd, J = 15.7, 13.8, 6.7 Hz, 1H), 2.26 (dddd, J = 15.6, 4.6, 2.1, 2.1 Hz, 1H), 2.0 (ddd, J = 15, 3.4, 2.3 Hz, 1H), 1.87 (apparent ddq, J = 14.2, 4.5, 3.3 Hz, 1H), 1.78–1.68 (m, 1H), 1.6–1.3 (m, 6H), 1.2 (s, 3H), 1.07 (ddd, J = 13.4, 13.4, 3.4 Hz, 1H), 0.85 (s, 9H), 0.0 (s, 3H), −0.05 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 212.9, 70.9, 47.4, 42.9, 42.3, 40.3, 38.2, 33.8, 33.1, 25.7, 18.5, 17.9, 16.7, −4.7, −5.2. Anal. Calcd for $C_{17}H_{32}O_2Si$: C, 68.86; H, 10.87. Found: C, 68.76; H, 10.67.

Methyl Ester 10. To a 0.3 M solution of m-CPBA (87.5 g, 0.25 mol) in CH_2Cl_2 at 25 °C was added a 0.2 M solution of **9** (50 g, 0.17 mol) in CH_2Cl_2, and the resulting mixture was allowed to stir for 18 h. $Na_2S_2O_3$ (45 g, 0.29 mol) was added to a 1 M solution of $NaHCO_3$ (32.7 g, 0.39 mol), and this solution was slowly added to the reaction mixture and allowed to stir for 1 h. The layers were separated, and the aqueous layer was extracted once with Et_2O (1 L). The organic layers were combined, washed twice with saturated aqueous $NaHCO_3$ (1 L), dried over Na_2SO_4, and concentrated to give 45.3 g (86%) of lactones A and B (A, the faster eluting regioisomer: R_f 0.37, 4:1 hexanes/EtOAc; B, the slower eluting regioisomer: R_f 0.32, 4:1 hexanes/EtOAc) as an oil. The crude mixture was not separated at this stage and was used directly for the next transformation. Analytical samples of each could be separated at this stage for characterization: **Lactone regioisomer A**: IR (neat) 2930, 2856, 1736 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.35 (dd, J = 13.2, 8.2 Hz, 1H), 4.0 (d, J = 2.7 Hz, 1H), 3.87 (d, J = 13.2 Hz, 1H), 2.76 (ddd, J = 14.8, 11.6, 3.8 Hz, 1H),

2.45 (ddd, J = 14.6, 5.2, 3.5 Hz, 1H), 1.9–1.6 (m, 2H), 1.5–1.3 (m, 6H), 1.15 (s, 3H), 1.2–1.0 (m, 1H), 0.85 (s, 9H), 0.01 (s, 3H), –0.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.9, 71.9, 70.2, 50.1, 40.8, 39.9, 34.9, 33.9, 30.0, 25.7, 25.6, 19.4, 17.8, 16.4, –4.4, –5.4. Anal. Calcd for $C_{17}H_{32}O_3Si$: C, 65.33; H, 10.32. Found: C, 65.72; H, 10.50. **Lactone B**: IR (neat) 2930, 2857, 1733 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.35 (dd, J = 13.2, 11.2 Hz, 1H), 4.05 (ddd, J = 13.3, 5.4, 1.9 Hz, 1H) 3.86 (d, J = 2.8 Hz, 1H), 2.89 (dd, J = 14.6, 11.3 Hz, 1H), 2.2 (d, J = 14.6 Hz, 1H), 1.8–1.3 (m, 7H), 1.15 (s, 3H), 1.3–1.05 (m, 2H), 0.85 (s, 9H), 0.0 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.6, 73.2, 64.7, 46.1, 44.8, 41.2, 36.7, 35.2, 34.0, 25.7, 19.3, 17.9, 16.1, –4.4, –5.2.

To a 0.45 M solution of the lactones obtained above (A and B) (110 g, 0.35 mol) in MeOH at 0 °C was added sodium methoxide (47.6 g, 0.88 mol); the mixture was allowed to stir for 1 h. Concentrated HCl was then added dropwise until a pH of 3 was reached. H_2O (500 mL) and EtOAc (500 mL) were added, and the aqueous layer was extracted with EtOAc (3 × 250 mL). The organic layer was washed once with saturated aqueous $NaHCO_3$ solution (250 mL), once with brine (250 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude oil was purified by column chromatography (4:1, 2:1 hexanes/EtOAc) to give 33.8 g (28%) of **10** (R_f 0.5, 2:1 hexanes/EtOAc) and 54.2 g (62%) of the corresponding undesired regioisomer (R_f 0.33, 2:1 hexanes/EtOAc) as pale yellow oils. **10**: IR (neat) 3466, 2931, 2857, 1740 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.2 (ddd, J = 7.3, 3.6, 3.6 Hz, 1H), 3.9 (dd, J = 10.5, 10.5 Hz, 1H), 3.7 (dd, J = 10.5, 3.5 Hz, 1H), 3.62 (s, 3H), 2.24 (dd, J = 9.8, 8 Hz, 2H), 1.8–1.45 (m, 7 H), 1.25–1.1 (m, 3H), 0.9 (s, 3H), 0.85 (s, 9H), 0.02 (s, 3H), –0.02 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.6, 69.9, 60.3, 51.6, 48.3, 35.5, 35.4, 35.2, 31.4, 28.5, 25.7, 23.8, 18.4, 17.9, –4.6, –5.2. Anal. Calcd for $C_{18}H_{36}O_4Si$: C, 62.74; H, 10.53. Found: C, 62.88; H, 10.69. Data for the undesired regioisomer: IR (neat) 3358, 2933, 2857, 1738 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.95 (ddd, J = 6, 3, 3 Hz, 1H), 3.69 (dd, J = 7.5, 7.5 Hz, 2H), 3.62 (s, 3H), 2.55 (dd, J = 16.5, 8.4 Hz, 1H), 2.3 (dd, 16.5, 4.2 Hz, 1H), 1.85 (ddd, J = 7.6, 3.6, 3.6 Hz, 1H), 1.75–1.6 (m, 1H), 1.55 (dd, J = 7.5, 7.5 Hz, 2H), 1.48–1.2 (m, 6H), 0.98 (s, 3H), 0.85 (s, 9H), 0.0 (s, 3H), –0.02 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.8, 69.0, 58.9, 51.4, 44.4, 44.1, 36.3, 35.5, 32.8, 30.4, 25.8, 22.8, 18.0, 17.4, –4.5, –5.4.

Bis-Silyl Ether 11. To a 3 M solution of **10** (13 g, 37.8 mmol) in DMF was added imidazole (7.8 g, 113 mmol) and *tert*-butyldimethylsilyl chloride (17 g, 113 mmol); the mixture was allowed to stir for 14 h at 35 °C. The crude reaction mixture was poured into H_2O (100 mL) and extracted with Et_2O (3 × 100 mL). The organic layer was washed once with H_2O (100 mL), once with saturated NH_4Cl solution (100 mL), and once with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated. The oil was purified by column chromatography (32:1 hexanes/EtOAc) to give 12.3 g (71%) of **11** as a pale yellow oil. IR (neat) 2916, 1745 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.17–4.1 (m, 1H), 3.7–3.65 (m, 2H), 3.6 (s, 3H), 2.3–2.15 (m, 2H), 1.8–1.55 (m, 4H), 1.4–1.1 (m, 5H), 0.95 (s,-3H), 0.86 (s, 9H), 0.84 (s, 9H), 0.01 (s, 3H), –0.01 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.8, 67.5, 60.1, 51.4, 49.9, 37.6, 37.0, 34.8, 33.6, 28.6, 25.9, 25.8, 22.1, 18.1, 17.0, –4.6, –5.1, –5.3, –5.4. Anal. Calcd for $C_{24}H_{52}O_4Si_2$: C, 62.83; H, 10.98. Found: C, 63.02; H, 10.89.

Aldehyde 12. To a 0.07 M solution of **11** (12.5 g, 27.3 mmol) in toluene at –78 °C was added a 1.5 M solution of DIBAH (18.2 mL, 27.3 mmol); the mixture was allowed to stir for 1 h. The resulting mixture was quenched with 1 M HCl (200 mL) and extracted with Et_2O (3 × 150 mL). The organic layer was washed twice with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated to give 11.7 g (100%) of **12** as a colorless oil and was directly used for the next step without further purification. IR (neat) 2930, 2856, 1729 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.75 (t, J = 1.9 Hz, 1H), 4.09–4.18 (m, 1H), 3.7–3.6 (m, 2H), 2.4–2.3 (m, 2H), 1.8–1.5 (m, 4H), 1.4–1.1 (m, 5H), 1.0 (s, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.03 (s, 3H), 0.01 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.9, 67.6, 60.3, 50.0, 38.6, 37.3, 34.7, 34.5, 33.6, 25.9, 25.8, 22.1, 18.2, 18.0, 16.9, –4.6, –5.1, –5.3, –5.4. Anal. Calcd for $C_{23}H_{48}O_3Si_2$: C, 64.44; H, 11.29. Found: C, 64.59; H, 11.16.

Enone 13. To a 0.4 M solution of magnesium (960 mg, 40 mmol) in THF was added a catalytic amount of iodine and freshly distilled 2-bromopropene (3.3 mL, 36.4 mmol) slowly with concurrent heating. The resulting solution was refluxed for 0.5 h and cooled to 0 °C. To this solution was added a 0.36 M solution of **12** (13 g, 30.3 mmol) in THF dropwise. The reaction mixture was allowed to stir for 2 h at 0 °C, quenched with saturated NH_4Cl solution (100 mL), and extracted with Et_2O (3 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4, and concentrated. The crude oil was purified by column chromatography (32:1 hexanes/EtOAc) to give 9.95 g (71%) of the corresponding allylic alcohol as a single diastereomer (pale yellow oil). This material was directly used for the next oxidation step. IR (neat) 3349, 2930, 2856 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.93–4.88 (m, 1H), 4.83–4.78 (m, 1H), 4.18–4.1 (m, 1H), 3.95 (dd, J = 6.3, 6.3 Hz, 1H), 3.69–3.62 (m, 2H), 1.8–1.6 (m, 1H), 1.7 (s, 3H), 1.55–1.4 (m, 3H), 1.4-1.1 (m, 8H), 0.95 (s, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.8, 115.5, 111.3, 77.7, 77.3, 67.5, 60.1, 50.3, 38.8, 37.6, 34.9, 33.9, 28.8, 26.3, 26.1, 22.8, 18.5, 18.3, 17.7, 17.6, –4.3, –4.8, –4.9, –5.0. Anal. Calcd for $C_{26}H_{54}O_3Si_2$: C, 66.32; H, 11.56. Found: C, 66.50; H, 11.64.

To a 0.1 M solution of the allylic alcohol onbtained above (19.9 g, 42.34 mmol) in CH_2Cl_2 at 25 °C was added Dess–Martin periodinane reagent (35.9 g, 84.7 mmol); the resulting mixture was allowed to stir for 16 h. $Na_2S_2O_3 \cdot 5H_2O$ (31.5 g, 1127 mmol) was added to a 1 M solution of $NaHCO_3$ (8.2 g, 97.4 mmol); this solution and Et_2O (100 mL) were added to the reaction mixture and allowed to stir for 30 min. Saturated aqueous $NaHCO_3$ solution (200 mL) was added, and the mixture was extracted with Et_2O (3 × 100 mL). The organic layer was washed twice with saturated aqueous $NaHCO_3$ solution (100 mL), dried over Na_2SO_4, and concentrated. The crude oil was passed through a plug of silica gel (8:1 hexanes/EtOAc) to give 18 g (91%) of **13** as a clear, colorless oil. IR (neat) 2930, 2857, 1682 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.95–5.9 (m, 1H), 5.73–5.7 (m, 1H), 4.2–4.1 (m, 1H), 3.7–3.6 (m, 2H), 2.6 (dd, J = 8.6, 8.6 Hz, 2H), 1.85 (dd, J = 1.2, 0.74 Hz, 3H), 1.8–1.5 (m, 4H), 1.4–1.15 (m, 5H), 0.98 (s, 3H), 0.88 (s, 9H), 0.85 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.7, 144.6, 124.1, 67.4, 59.9, 50.2, 37.2, 34.9, 33.6, 31.8, 29.7, 25.9, 25.85, 25.81, 22.2, 18.2, 18.1, 17.8, 17.1, –4.6, –5.1, –5.2, –5.3. Anal. Calcd for $C_{26}H_{52}O_3Si_2$: C, 66.60; H, 11.18. Found: C, 66.63; H, 11.05.

Methylselenide Adduct 14. To a 0.23 M solution of 2,2-bis(methylseleno)propane[20] (3.5 g, 15.3 mmol) in THF at –78 °C was added a 1.6 M solution of n-BuLi (9.5 mL, 15.3 mmol); the resulting mixture was allowed to stir for 1 h. To this solution was added a 0.35 M solution of **13** (7.14 g, 15.3 mmol) in THF dropwise, and the resulting solution was allowed to stir for 18 h as the temperature rose to 25 °C. The reaction was quenched by the addition of H_2O (100 mL) and was subsequently extracted with Et_2O (3 × 100 mL). The organic layer washed twice with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated to give 9.2 g of **14** (100%) as a ≈4:1 mixture of diastereomers (pale yellow oil). The crude oil was directly used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.05 (s, 1H), 4.89 (m, 1H), 4.15 (s, 1H), 3.72 (m, 1H), 3.61 (m, 2H), 2.0 (s, 3H), 1.78 (s, 3H), 1.48 (s, 3H), 1.40 (s, 3H), 0.9 (s, 3H), 0.85 (s, 18H), 0.0 (s, 12H).

Diene Diol 15. To a 0.14 M solution of phosphorus triiodide (13.1 g, 37.7 mmol) in CH_2Cl_2 at 0 °C was added a solution of triethylamine (15.6 mL, 111 mmol) and **14** (9.2 g, 15.3 mmol) in CH_2Cl_2 (64 mL) dropwise. The resulting solution was allowed to stir for 1 h and then filtered through a plug of silica gel. The silica gel was washed twice with Et_2O (100 mL), and the organic layer was washed once with 1 M HCl (100 mL) and once with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude oil was passed through a plug of silica gel (32:1 hexanes/EtOAc) to give 5.4 g (71%) of the corresponding diene as a pale yellow oil. This substance was directly utilized for the next step without further purification. An analytical sample was prepared by column chromatography

(silica gel, hexanes). IR (neat) 2929, 2856, 1463 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.9–4.83 (m, 1H), 4.51 (d, J = 2.6 Hz, 1H), 4.15 (br s, 1H), 3.7–3.6 (m, 2H), 1.98 (dd, J = 17.4, 8.1 Hz, 2H), 1.72 (s, 3H), 1.55 (s, 6H), 1.4–1.2 (m, 9H), 0.95 (s, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.9, 137.1, 124.3, 112.7, 67.2, 59.5, 49.9, 41.3, 37.2, 34.9, 33.7, 29.7, 26.0, 25.9, 24.9, 22.9, 21.7, 19.5, 18.2, 18.1, −4.6, −5.1, −5.2, −5.3. Anal. Calcd for $C_{29}H_{58}O_2Si_2$: C, 70.38; H, 11.81. Found: C, 70.57; H, 11.63.

To a 0.05 M solution of the diene obtained above (5.8 g, 11.7 mmol) in THF/CH_3CN (1:1) was added 48% HF (2.3 mL, 117 mmol), and the mixture was brought to reflux temperature for 40 min. The mixture was cooled to 25 °C, and H_2O (100 mL) followed by solid $NaHCO_3$ were added until a pH of 3 was reached. The resulting solution was extracted 3× with $CHCl_3$ (150 mL) and the organic layer dried over Na_2SO_4 and concentrated. The crude oil was purified by column chromatography (2:1 hexanes/EtOAc) to give 2.8 g (90%) of **15** as a white solid (mp 94.6–95.0 °C). IR (neat) 3300, 2926, 2870, 1631, 1445 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.88 (sextet, J = 1.4 Hz, 1H), 4.5 (dd, J = 2.8, 0.8 Hz, 1H), 4.18 (ddd, J = 7.7, 3.9, 3.9 Hz, 1H), 3.95 (dd, J = 11, 9 Hz, 1H), 3.77 (dd, J = 11, 3.9 Hz, 1H), 3.6 (s, 2H, D_2O exch.), 2.05–1.88 (m, 2H), 1.72 (dd, J = 1 Hz, 3H), 1.72–1.59 (m, 4H), 1.62 (s, 6H), 1.45–1.31 (m, 2H), 1.2–1.1 (m, 3H), 0.95 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.5, 136.6, 124.6, 112.9, 69.6, 60.7, 47.2, 38.8, 35.6, 35.1, 31.2, 24.7, 24.4, 22.7, 21.7, 19.4, 18.7. Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.63; H, 11.36. Found: C, 76.47; H, 11.42.

Benzylidene Acetal 16. To a 0.2 M solution of **15** (9.8 g, 36.8 mmol) in $CHCl_3$ was added PPTS (1.9 g, 7.4 mmol) and benzaldehyde dimethyl acetal (7.7 mL, 51.6 mmol). The mixture was refluxed with concurrent azeotropic removal of MeOH using a Dean–Stark trap for 1 h (Note: replenish lost $CHCl_3$ during azeotropic removal of MeOH). The mixture was cooled to room temperature, saturated aqueous $NaHCO_3$ solution (100 mL) was added, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated. The excess benzaldehyde dimethyl acetal was removed by Kugelrohr distillation of the oil at 100 °C under 18 mm of pressure to give 11.5 g (88%) of **16** as a 3:1 mixture of diastereomers (pale yellow oil). R_f 0.66 (8:1 hexanes/EtOAc): Major isomer: IR (neat) 3070, 3021, 2931, 2861, 1630, 1455 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.55–7.45 (m, 2H), 7.4–7.25 (m, 3H), 5.5 (s, 1H), 4.92–4.88 (m, 1H), 4.55 (d, J = 2.7 Hz, 1H), 4.4 (d, J = 12 Hz, 1H), 4.15–4.05 (m, 1H), 3.93 (dd, J = 12, 3.8 Hz, 1H), 2.1–1.79 (m, 4H), 1.75 (s, 3H), 1.67 (s, 3H), 1.66 (s, 3H), 1.58–1.38 (m, 4H), 1.3 (s, 3H), 1.3–1.12 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.6, 139.1, 136.8, 128.8, 128.3, 126.5, 124.7, 112.9, 102.1, 76.3, 67.7, 41.7, 40.8, 37.2, 34.8, 32.0, 24.7, 23.7, 22.7, 21.7, 19.4, 17.3. Anal. Calcd for $C_{24}H_{34}O_2$: C, 81.31; H, 9.67. Found: C, 81.54; H, 9.73. R_f 0.61 (8:1 hexanes/EtOAc): IR (neat) 3070, 3033, 2922, 2868, 1452, 1387 cm^{-1}. Minor isomer: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.5–7.4 (m, 2H), 7.4–7.3 (m, 3H), 5.8 (s, 1H), 4.92–4.88 (m, 1H), 4.53 (d, J = 2.7 Hz, 1H), 4.35 (ddd, J = 12.6, 5, 5 Hz, 1H), 4.06 (d, 2.8 Hz, 1H), 4.03 (s, 1H), 2.35–2.15 (m, 2H), 2.1–1.88 (complex, 2H), 1.75–1.65 (m, 2H), 1.72 (s, 3H), 1.65 (s, 6H), 1.55–1.35 (m, 2H), 1.35–1.1 (m, 3H), 0.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.5, 138.9, 136.5, 128.7, 128.3, 126.1, 124.9, 113.1, 93.8, 72.4, 64.5, 40.7, 36.4, 35.4, 33.2, 24.7, 24.3, 23.8, 22.8, 21.7, 19.9, 19.5. Anal. Calcd for $C_{24}H_{34}O_2$: C, 81.31; H, 9.67. Found: C, 81.49; H, 9.44.

Aldehyde 18. To a 0.12 M solution of **16** (11.5 g, 32.5 mmol) in CH_2Cl_2/Et_2O (1:1) at 0 °C was added $LiAlH_4$ (2.6 g, 64.9 mol); the resulting mixture was allowed to stir for 5 min. To this solution was slowly added a 4 M solution of $AlCl_3$ (17.3 g, 129.8 mmol) in Et_2O. After the addition was complete, the ice bath was removed, and the solution was allowed to stir for 30 min as the temperature rose to 25 °C. EtOAc (50 mL) was added dropwise followed by H_2O (200 mL). The mixture was extracted with Et_2O (3 × 150 mL) the organic layer washed twice with H_2O (100 mL), dried over anhydrous Na_2SO_4, and concentrated to yield 11.5 g (100%) of a 4:1 mixture of alcohols **17** and the undesired regioisomer as a pale yellow crude oil; this material was used directly as a mixture without further purification. The crude product was dissolved in CH_2Cl_2 (320 mL), and to this solution was added Dess–Martin periodinane reagent (27.4 g, 64.7 mmol); the resulting mixture was allowed to stir for 4.5 h. $Na_2S_2O_3 \cdot 5H_2O$ (24.1 g, 97 mmol) was added to a 1 M solution of $NaHCO_3$ (6.3 g, 74.4 mol); this solution and Et_2O (100 mL) were added to the reaction mixture and allowed to stir for 30 min. Saturated aqueous $NaHCO_3$ solution (150 mL) was added, and the mixture was extracted with Et_2O (3 × 200 mL), and the organic layer was washed twice with saturated aqueous $NaHCO_3$ solution (150 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude oil was purified by column chromatography (silica gel, 64:1, 32:1 hexanes/EtOAc) to give 5.52 g (48%) of **18** and 2.4 g (21%) of the corresponding regioisomeric ketone oxidation product both as pale yellow oils. **18**: IR (neat) 3069, 3027, 2932, 2858, 1720 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.98 (d, J = 4.7 Hz, 1H), 7.4–7.2 (m, 5H), 4.89 (sextet, J = 1.4 Hz, 1H), 4.51 (dd, J = 2.7, 0.8 Hz, 1H), 4.49 (s, 2H), 3.88 (ddd, J = 8.7, 4.3, 4.3 Hz, 1H), 2.45 (dd, J = 4.7, 4.7 Hz, 1H), 2.05–1.75 (m, 5H), 1.73 (dd, J = 0.9, 0.9 Hz, 3H), 1.65 (s, 3H), 1.55 (s, 3H), 1.55–1.5 (m, 2H), 1.42 (dd, J = 11.8, 5.5 Hz, 1H), 1.37 (dd, 10.3, 6.8 Hz, 1H), 1.24 (ddd, J = 13.8, 10.3, 7.3 Hz, 1H), 1.05 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.7, 146.3, 138.4, 136.1, 128.3, 127.4, 127.3, 125.0, 113.2, 75.5, 70.3, 58.4, 38.4, 36.2, 35.3, 28.5, 24.5, 24.3, 22.7, 21.7, 19.4, 18.9. Anal. Calcd for $C_{24}H_{34}O_2$: C, 81.30; H, 9.67. Found: C, 81.24; H, 9.67.

Allylic Alcohol 19. To a 0.1 M solution of **18** (5.5 g, 15.6 mmol) in THF at −78 °C was added a 0.45 M solution of vinylmagnesium bromide (69 mL, 31.2 mmol) in THF dropwise; the resulting mixture was allowed to stir for 1 h. The reaction was quenched with 1 M HCl (100 mL) and extracted with Et_2O (3 × 100 mL). The organic layer was washed twice with brine (75 mL), dried over anhydrous Na_2SO_4, and concentrated to give 5.9 g (100%) of **19** as a 5.4:1 mixture of diastereomers (pale brown oil). The crude oil was taken on directly for the next step without additional purification. Analytical samples of these diastereomers were isolated by column chromatography (silica gel, 128:1; 64:1 hexanes/EtOAc) to give clear colorless oils. Major isomer: R_f 0.54 (8:1 hexanes/EtOAc): IR (neat) 3461, 3069, 2910, 1630 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.4–7.25 (m, 5H), 5.85 (ddd, J = 17, 10.4, 3.9 Hz, 1H), 5.35 (ddd, J = 17, 2, 2 Hz, 1H), 5.13 (ddd, J = 10.3, 2, 2 Hz, 1H), 4.91–4.88 (m, 1H), 4.6–4.52 (m, 3H), 4.45 (d, J = 8.2 Hz, 1H), 4.3 (1/2 ABq, J = 11.3 Hz, 1H), 4.18–4.11 (m, 1H), 2.2–2.09 (m, 1H), 2.02 (dd, J = 12.4, 4.8 Hz, 1H), 1.92 (dd, J = 12.5, 5.4 Hz, 1H), 1.88–1.71 (m, 1H), 1.74 (dd, J = 1.3, 1.3 Hz, 3H), 1.65 (s, 6H), 1.5–1.38 (m, 6H), 1.3 (s, 3H), 1.15 (dddd, J = 14.2, 12.7, 3.9, 3.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.4, 142.6, 137.9, 136.7, 128.5, 127.7, 127.5, 124.7, 113.5, 113.1, 76.6, 71.7, 70.4, 49.3, 41.4, 38.3, 36.1, 28.6, 24.8, 23.6, 22.8, 21.7, 19.5, 16.9. Anal. Calcd for $C_{26}H_{38}O_2$: C, 81.61; H, 10.02. Found: C, 81.8; H, 10.18. Minor isomer: R_f 0.37 (8:1 hexanes/EtOAc): IR (neat) 3429, 3069, 2921, 2868, 1630 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.4–7.2 (m, 5H), 6.1 (ddd, J = 17.1, 10.3, 6.7 Hz, 1H), 5.18 (ddd, J = 17.2, 1.6, 1.6 Hz, 1H), 5.02 (ddd, J = 10.3, 1.4, 1.4 Hz, 1H), 4.9–4.85 (m, 1H), 4.58 (1/2 ABq, J = 11.7 Hz, 1H), 4.53–4.47 (m, 2H), 4.28 (1/2 ABq, J = 11.7 Hz, 1H), 3.85 (ddd, J = 6.3, 3.3, 3.3 Hz, 1H), 2.58 (s, 1H, D_2O exch.), 2.1–1.9 (m, 3H), 1.72 (s, 3H), 1.73–1.65 (m, 1H), 1.63 (s, 6H), 1.5–1.25 (m, 7H), 1.15 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.9, 142.1, 138.9, 137.1, 128.3, 127.3, 127.0, 124.4, 114.0, 112.8, 78.2, 74.9, 70.6, 50.9, 41.7, 37.6, 36.5, 28.3, 25.1, 23.7, 22.8, 21.7, 19.5, 17.7. Anal. Calcd for $C_{26}H_{38}O_2$: C, 81.61; H, 10.02. Found: C, 81.38; H, 9.86.

Diels–Alder Adduct 20. To a 0.1 M solution of **19** (5.9 g, 15.6 mmol) in CH_2Cl_2 was added Dess–Martin periodinane reagent (11.1 g, 26.1 mmol); the resulting mixture was allowed to stir for 12 h. $Na_2S_2O_3 \cdot 5H_2O$ (11.6 g, 46.8 mmol) was added to a 1 M solution of $NaHCO_3$ (3 g, 35.9 mol); this solution with Et_2O (50 mL) was added to the reaction mixture and allowed to stir for 30 min. Saturated aqueous $NaHCO_3$ solution (75 mL) was added, and the mixture was extracted with Et_2O (3 × 50 mL). The organic layer was washed twice with saturated aqueous $NaHCO_3$ (50 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude oil was purified by column chroma-

tography (silica gel 32:1 hexanes/EtOAc) to give 4.2 g (91%) of the keto-diene product as a clear colorless oil. This material was directly used for the subsequent intramolecular Diels–Alder cycloaddition reaction. IR (neat) 3048, 3027, 2932, 2868, 1694, 1673 cm $^{-1}$. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.2 (m, 5H), 6.41 (dd, J = 17.4, 10.4 Hz, 1H), 6.12 (dd, J = 17.4, 1.2 Hz, 1H), 5.64 (dd, J = 10.4, 1.2 Hz, 1H), 4.9–4.87 (m, 1H), 4.54 (1/2 ABq, J = 12.4 Hz, 1H), 4.51 (dd, J = 2.7, 0.73 Hz, 1H), 4.44 (1/2 ABq, J = 12.4 Hz, 1H), 3.77 (ddd, J = 10.8, 5.1, 5.1 Hz, 1H), 3.34 (d, J = 5.2 Hz, 1H), 2.1–1.75 (m, 5H), 1.75–1.6 (m, 1H), 1.7 (s, 3H), 1.62 (s, 3H), 1.6 (s, 3H), 1.45–1.15 (m, 4H), 0.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.9, 146.5, 139.9, 138.9, 136.4, 128.2, 127.3, 127.1, 126.4, 124.9, 113.2, 76.6, 70.3, 54.0, 37.3, 37.0, 32.0, 26.5, 25.1, 24.9, 22.8, 21.7, 19.7, 19.5. Anal. Calcd for $C_{26}H_{36}O_2$: C, 82.05; H, 9.54. Found: C, 82.08; H, 9.63.

To a 0.15 M solution of the keto-diene obtained above (321 mg, 0.84 mmol) in toluene at −78 °C was added $BF_3{\cdot}OEt_2$ (0.21 mL, 1.68 mmol); the resulting solution was allowed to stand at −23 °C for 48 h. Saturated aqueous $NaHCO_3$ solution (10 mL) was added, and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated. The crude oil was purified by column chromatography (silica gel, 64:1 hexanes/EtOAc) to give 99 mg (31%) of **20** as an oil which solidifies under vacuum (mp 75.7–77.0 °C). [It was found that scaling this reaction above 500 mg of the ketodiene, resulted in moderately lower yields as a result of the reaction not going to completion; the product and starting material are inseparable. A total of approximately 2 gm of compound **20** have thus far been obtained by setting up the Diels–Alder cyclization reactions in parallel at roughly 300 mg reaction scales.] IR (neat) 3016, 2911, 2868, 1683, 1456 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45–7.34 (m, 2H), 7.34–7.15 (m, 3H), 4.6 (1/2 ABq, J = 12.1 Hz, 1H), 4.4 (1/2 ABq, J = 12.1 Hz, 1H), 3.55 (d, J = 2.5 Hz, 1H), 3.25 (d, J = 2.1 Hz, 1H), 2.81 (dt, J = 13.2, 5.6 Hz, 1H), 2.6–2.45 (m, 1H), 2.42 (d, J = 8.7 Hz, 1H), 2.19–2.02 (m, 1H), 2.02–1.6 (m, 8H), 1.8 (s, 3H), 1.5–1.38 (m, 1H), 1.28–1.1 (m, 2H), 1.25 (s, 3H), 1.2 (s, 3H), 1.1 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 214.9, 139.4, 137.6, 130.4, 128.0, 127.1, 126.9, 76.5, 71.8, 62.9, 51.2, 40.8, 38.9, 38.4, 38.3, 29.9, 29.8, 28.9, 25.7, 25.3, 25.2, 22.1, 18.6, 17.7. Anal. Calcd for $C_{26}H_{36}O_2$: C, 82.05; H, 9.54. Found: C, 82.02; H, 9.43.

Alcohol 21. To a 0.07 M solution of **20** (1.3 g, 3.4 mmol) in THF at 0 °C was added $LiAlH_4$ (136 mg, 3.4 mmol); the resulting mixture was allowed to stir for 45 min at 0 °C. The mixture was quenched with 1 M HCl (25 mL) and extracted with Et_2O (3 × 25 mL). The organic layer was washed once with brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated to give 1.3 g (100%) of **21** as a single diastereomer (clear colorless oil). The crude product was directly used for the next step without additional purification. An analytical sample was prepared by column chromatography (silica gel, 64:1 hexanes/EtOAc). IR (neat) 3586, 3006, 2928, 1454 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.2 (m, 5H), 4.63 (1/2 ABq, J = 11.7 Hz, 1H), 4.23 (1/2 ABq, J = 11.7 Hz, 1H), 3.85 (d, J = 3.1 Hz, 1H), 3.4 (d, J = 2.6 Hz, 1H), 2.73 (apparent dt, J = 13.5, 5 Hz, 1H), 2.57 (apparent dt, J = 14.5, 4.7 Hz, 1H), 2.38–2.21 (m, 1H), 2.28 (d, J = 3.2 Hz, 1H), 2.2–1.98 (m, 4H), 1.93 (dd, J = 8.9, 3 Hz, 1H), 1.85–1.6 (m, 3H), 1.65 (s, 3H), 1.55 (s, 3H), 1.45–1.35 (m, 1H), 1.28 (s, 3H), 1.28–0.98 (m, 4H), 1.0 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.1, 138.5, 128.3, 127.8, 127.3, 127.2, 88.4, 86.6, 71.8, 49.5, 43.3, 41.9, 41.3, 38.6, 38.0, 32.7, 29.0, 28.4, 28.3, 26.1, 25.2, 23.9, 21.4, 18.2. Anal. Calcd for $C_{26}H_{38}O_2$: C, 81.63; H, 10.01. Found: C, 81.82; H, 10.12.

Xanthate Ester 22. To a 0.06 M solution of **21** (1.3 g, 3.4 mmol) in THF at −78 °C was added phenyl chlorothionoformate (2.3 mL, 16.9 mmol) followed by a 1 M solution of sodium bis(trimethylsilyl)amide (3.7 mL, 3.7 mmol); the resulting solution was allowed to stir for 10 min. The ice bath was removed, and the mixture was allowed to sir for 18 h. EtOAc (50 mL) was added, and the solution was washed once with H_2O (50 mL) and once with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude oil was purified by column chromatography (silica gel, 128:1; 64:1; 32:1 hexanes/EtOAc) to give 1.7 g, (100%) of **22** as a yellow solid (mp 153.1–153.8 °C). IR (neat) 3004, 2925, 1485, 1450, 1283, 1190 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.4–7.2 (m, 8H), 6.8–6.7 (m, 2H), 5.52 (d, J = 3.7 Hz, 1H), 4.53 (1/2 ABq, J = 11.1 Hz, 1H), 4.33 (1/2 ABq, J = 11.1 Hz, 1H), 3.49 (d, J = 2.7 Hz, 1H), 2.84 (apparent dt, J = 13.5, 5.2 Hz, 1H), 2.68 (d, J = 2.7 Hz, 1H), 2.6 (dd, J = 13.7, 5.2 Hz, 1H), 2.5–2.38 (m, 1H), 2.35 (dd, J = 9.1, 3.7 Hz, 1H), 2.3–2.12 (m, 2H), 2.08 (br d, J = 15.9 Hz, 1H), 1.9–1.7 (m, 3H), 1.71 (s, 3H), 1.51 (s, 3H), 1.5–1.1 (m, 5H), 1.3 (s, 3H), 1.05 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.5, 153.5, 139.5, 138.2, 129.2, 128.8, 128.0, 127.4, 126.8, 126.1, 122.3, 96.8, 85.1, 72.1, 46.1, 42.1, 41.1, 38.5, 38.4, 32.2, 28.9, 28.8, 27.3, 25.9, 25.2, 22.2, 21.6,18.0.

Benzyl Ether 23. To a 0.03 M solution of **22** (1.76 g, 3.4 mmol) in toluene was added VAZO (348 mg, 1.0 mmol) followed by tributyltin hydride (4.6 mL, 16.9 mmol), and the resulting mixture was heated to reflux temperature for 2 h. The mixture was then concentrated and the oil chromatographed (silica gel, 128:1, 64:1, 32:1 hexanes/EtOAc) to give 660 mg (53%) of **23** as a clear colorless oil. IR (neat) 3008, 2925, 1455 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.2 (m, 5H), 4.58 (1/2 ABq, J = 12.2 Hz, 1H), 4.24 (1/2AB q, J = 12.2 Hz, 1H), 3.32 (ddd, J = 2.8, 2.8, 2.8 Hz, 1H), 2.7 (apparent dt, J = 13, 3.6 Hz, 1H), 2.4–2.28 (m, 1H), 2.2–2.15 (m, 1H), 2.1–1.6 (m, 6H), 1.65 (s, 3H), 1.4–1.1 (m, 5H), 1.3 (s, 3H), 1.05–0.9 (m, 4H), 1.0 (s, 3H), 0.95 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.0, 138.5, 129.5, 128.1, 126.8, 126.7, 83.9, 71.7, 43.5, 41.1, 39.5, 39.3, 38.6, 37.9, 32.3, 31.0, 30.2, 29.2, 25.5, 25.3, 24.9, 23.2, 21.8, 17.9. Anal. Calcd for $C_{26}H_{38}O$: C, 85.19; H, 10.45. Found: C, 85.03; H, 10.48.

Ketone 24. To a 0.07 M solution of **23** (660 mg, 1.8 mmol) in THF at −78 °C was added NH_3 (25 mL). Na was added until the blue color of the solution persisted, and the mixture was allowed to stir for 1 h. The mixture was quenched with saturated aqueous NH_4Cl solution (10 mL) and warmed to 25 °C. H_2O (20 mL) and Et_2O (20 mL) were added, and the reaction mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed once with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude oil was purified by column chromatography (silica gel, 32:1; 16:1, hexanes/EtOAc) to give 419 mg (84%) of the corresponding secondary alcohol product as a clear colorless oil which solidifies under vacuum (mp 110.5–111 °C). This material was directly used for the next step. IR (neat) 3368, 2926, 1456 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.7 (br s, 1H), 2.7 (apparent dt, J = 13.3, 3.8 Hz, 1H), 2.42–2.28 (m, 1H), 2.17 (ddd, J = 5.4, 2.7, 2.7 Hz, 1H), 2.13–1.55 (m, 8H), 1.65 (s, 3H), 1.48–1.35 (m, 3H), 1.32 (s, 3H), 1.28 (dd, J = 4.7, 2.5 Hz, 1H), 1.25–1.15 (m, 3H), 1.02–0.92 (m, 1H), 1.0 (s, 3H), 0.95 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.2, 129.6, 76.3, 43.5, 41.2, 39.4, 38.9, 38.4, 37.8, 34.2, 32.0, 30.9, 30.1, 25.5, 24.9, 23.1, 21.8, 17.5. Anal. Calcd for $C_{19}H_{32}O$: C, 82.55; H, 11.67. Found: C, 82.47; H, 11.72.

To a 0.1 M solution of the alcohol obtained above (274 mg, 0.99 mmol) in CH_2Cl_2 was added Dess–Martin periodinane reagent (842 mg, 1.98 mmol); the resulting mixture was allowed to stir for 1 h. $Na_2S_2O_3{\cdot}5H_2O$ (0.7 g, 2.97 mmol) was added to a 1 M solution of $NaHCO_3$ (0.19 g, 2.28 mmol); this solution with Et_2O (15 mL) was added to the reaction mixture, and the resulting mixture was allowed to stir for 30 min. Saturated aqueous $NaHCO_3$ solution (20 mL) was added, and the mixture was extracted with Et_2O (3 × 20 mL). The organic layer was washed twice with saturated aqueous $NaHCO_3$ solution (20 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude oil was purified by column chromatography (silica gel, 32:1 hexanes EtOAc) to give 181 mg (67%) of **24** as a white solid (mp 97.7–100 °C). Crystals of this substance were collected and a single, large crystal was subjected to single crystal X-ray diffraction (see supporting information and Figure 1). IR (neat) 2927, 1711, 1457 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.06 (d, J = 6H, 1H), 2.85 (apparent dt, J = 13.7, 5.3 Hz, 1H), 2.4–1.8 (m, 10H), 1.8–1.7 (m, 2H), 1.78 (s, 3H), 1.45–1.2 (m, 3H), 1.3 (s, 3H), 1.12 (ddd, J = 15, 10, 4.9 Hz, 1H), 1.0 (s, 3H), 0.95–0.79 (m, 1H), 0.62 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 213.5, 137.5, 130.1, 77.2, 51.4, 42.7, 42.4, 40.8, 39.5, 39.3, 36.8, 30.6, 29.9, 25.3, 24.7, 24.1, 23.4, 22.7,

22.2, 21.9. Anal. Calcd for $C_{19}H_{30}O$: C, 83.14; H, 11.03. Found: C, 82.89; H, 11.17.

Taxa-4(20),11(12)-diene (6). To a 0.04 M solution of methyltriphenylphosphonium iodide (59 mg, 0.15 mmol) in THF at 25 °C was added a 1.6 M solution of n-BuLi (0.09 mL, 0.15 mmol) in hexanes, and the resulting mixture was heated to reflux temperature for 1 h. To this solution was added a 0.02 M solution of **24** (20 mg, 0.073 mmol) in THF, and the resulting mixture was heated to reflux temperature for 18.5 h. The reaction was cooled to 25 °C and saturated aqueous NH_4Cl solution (10 mL) followed by hexanes (10 mL) were added. The phases were separated, and the aqueous layer was extracted twice with hexanes (10 mL). The combined organic extracts were washed once with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude oil was purified by preparative TLC (silica gel, hexanes) to give 16 mg (80%) of **6** as a clear colorless oil. IR (neat) 2929, 1644, 1458, 1376, 880 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.7 (dd, J = 2.9, 1.4 Hz, 1H), 4.48 (d, J = 1.1 Hz, 1H), 2.83–2.7 (m, 1H), 2.59 (br s, 1H), 2.4–2.2 (m, 2H), 2.15–1.75 (m, 6H), 1.75–1.69 (m, 1H), 1.73 (s, 3H), 1.65–1.5 (m, 4H), 1.3–1.1 (m, 3H), 1.3 (s, 3H), 1.0 (s, 3H), 0.6 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.8, 137.9, 129.7, 105.2, 43.7, 42.7, 40.3, 40.2, 39.4, 38.4, 38.0, 30.8, 30.2, 28.9, 25.5, 24.8, 24.1, 22.9, 22.8, 22.0. Anal. Calcd for $C_{20}H_{32}$: C, 88.16; H, 11.84. Found: C, 88.40; H, 11.88.

[20-^{13}C]-Taxa-4(20),11(12)-diene (6). To a 0.07 M solution of [^{13}C-methyl]triphenylphosphonium iodide (115 mg, 0.285 mmol, Aldrich 99% ^{13}C) in THF at 25 °C was added a 1.4 M solution of n-BuLi (0.2 mL, 0.285 mmol) in hexanes, and the resulting mixture was heated to reflux temperature for 1 h. To this solution was added a 0.04 M solution of **24** (39 mg, 0.142 mmol) in THF, and the resulting mixture was heated to reflux temperature for 18.5 h. The reaction was worked up as described above for **6**. The crude oil was purified by preparative TLC (silica gel, hexanes) to give 27 mg (70%) of [20-^{13}C]-**6** as a clear colorless oil. IR (neat) 2928, 1620, 1457, 1376, 872 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.7 (dd, J = 154, 1.3 Hz, 1H), 4.5 (d, J = 154 Hz, 1H), 2.76 (m, 1H), 2.6 (br s, 1H), 2.4–2.2 (m, 2H), 2.1–1.7 (m, 6H), 1.75–1.69 (m, 1H), 1.75 (s, 3H), 1.65–1.5 (m, 4H), 1.3 (s, 3H), 1.3–1.1 (m, 3H), 1.1 (s, 3H), 0.6 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.7 (d, J = 80 Hz), 137.9, 129.7, 105.2, 43.7, 42.6, 40.24, 40.21, 39.4, 38.37 (d, J = 2.8 Hz), 38.0, 30.8, 30.2, 28.87 (d, J = 3.6 Hz), 25.5, 24.8, 24.12 (d, J = 2.6 Hz), 22.9, 22.7, 22.0.

Alcohol 25. To a 0.02 M solution of **24** (28 mg, 0.102 mmol) in THF was added anhydrous $CeCl_3$ (252 mg, 1.02 mmol); the resulting mixture was allowed to stir for 2 h. This solution was cooled to 0 °C and a 3.1 M solution of MeMgBr (0.33 mL, 1.02 mmol) was added dropwise. The reaction mixture was allowed to stir for 30 min at 0 °C. The reaction was quenched with saturated ammonium chloride solution (10 mL). The layers were separated, and the aqueous layer was extracted twice with Et_2O (10 mL). The organic layer was washed once with brine solution (20 mL), dried over anhydrous Na_2SO_4, and concentrated to give 28 mg (93%) of **25** as a pale yellow oil. The crude, oily product was directly used for the next step without further purification. An analytical sample was prepared by column chromatography (silica gel, 32:1, hexanes/EtOAc). IR (neat) 3477, 2931, 1461, 1371 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.68 (apparent dt, J = 14.76, 6.74 Hz, 1H), 2.35–2.19 (m, 1H), 2.12–1.95 (m, 3H), 1.89 (dd, J = 5.38, 2.56 Hz, 1H), 1.8 (ddd, J = 13.23, 3.75, 3.75 Hz, 1H), 1.75–1.55 (m, 7H), 1.62 (s, 3H), 1.55–1.21 (m, 4H), 1.32 (s, 3H), 1.2–1.1 (m, 1H), 1.18 (s, 3H), 1.0 (s, 3H), 0.95 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.2, 128.8, 74.1, 43.5, 42.9, 41.4, 41.3, 39.4, 39.0, 38.9, 32.1, 31.7, 29.7, 26.8, 25.5, 24.8, 24.4, 22.2, 21.4, 19.0. HRMS Calcd for $C_{20}H_{34}O$: 290.2609, found: 290.2610.

Taxa-4(20),11(12)-diene (6) and Taxa-4(5),11(12)-diene (7). To a 0.02 M solution of **25** (28 mg, 0.097 mmol) in toluene at reflux temperature was added Burgess reagent ($MeO_2CNSO_2NEt_3$) (46 mg, 0.193 mmol), and the resulting mixture was allowed to stir at reflux temperature for 10 min. The mixture was cooled to 25 °C and diluted with EtOAc (15 mL). The organic layer was washed once with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude oil was purified by preparative TLC (silica gel, hexanes) to give 8 mg (R_f = 0.59, 30.5%) of **6** and 8 mg (R_f = 0.51, 30.5%) of **7**. Data for **7**: IR (neat) 2941, 1449, 1374 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.27 (m, 1H), 2.6 (ddd, J = 14.8, 10.0, 5.2 Hz, 1H), 2.5 (brs, 1H), 2.38–2.21 (m, 1H), 2.2–1.95 (m, 3H), 1.95–1.55 (m, 8H), 1.69 (s, 3H), 1.68 (s, 3H), 1.4 (ddd, J = 14.8, 5.5, 5.5 Hz, 1H), 1.31 (s, 3H), 1.18 (dd, J = 12.7, 6.0 Hz, 1H), 1.0 (s, 3H), 0.8 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.5, 137.7, 129.5, 121.1, 44.3, 41.4, 39.8, 39.0, 38.5, 37.3, 30.7, 29.8, 28.4, 26.3, 24.5, 23.9, 23.2, 22.6, 21.6, 21.5. This substance was found to be identical to an authentic, natural sample by ^1H NMR, ^{13}C NMR, EI-mass spec, and capillary GC.[7,29]

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Supporting Information Available: ^1H and ^{13}C NMR spectra of the ^{13}C-labeled taxa-4(20),11(12)-diene (**6**), taxa-4(5),11(12)-diene (**7**), and taxa-4(20),11(12)-diene (**6**) (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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