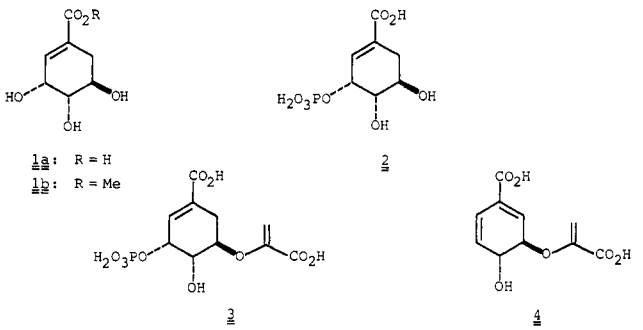
Total Synthesis of (±)-Methyl Shikimate and (±)-3-Phosphoshikimic Acid

Paul A. Bartlett* and Loretta A. McQuaid

Contribution from the Department of Chemistry, University of California, Berkeley, California 94720. *Received March 14, 1984*

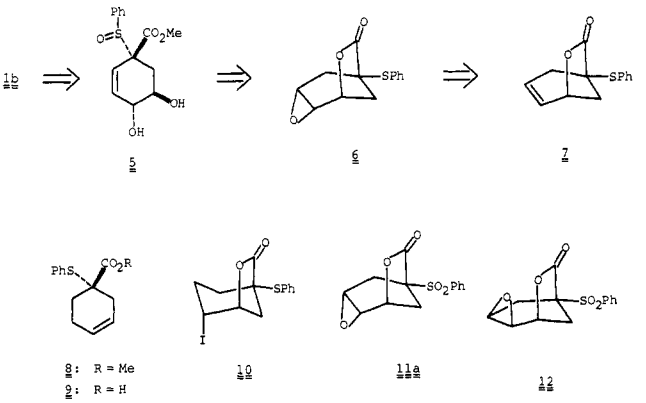
Abstract: A synthesis of methyl shikimate (**1b**) which proceeds in >50% yield has been developed from 3-cyclohexene-1-carboxylic acid via the iodo lactone (**19**) and epoxides **11b** and **14b**. This route also provides access to a protected derivative of methyl shikimate (**22**) which is suitable for conversion to 3-phosphoshikimic acid (**2**), thus enabling the first total synthesis of this intermediate in the shikimate–chorismate pathway. An alternative method for introduction of the allylic phosphate moiety via a novel palladium-catalyzed allylic phosphate transposition (**33** → **34**) was also demonstrated.

The shikimate/chorismate pathway occupies a crucial position in the chemistry of plants and microorganisms. The biosynthetic traffic along this route has many destinations, including the aromatic amino acids, lignins, essential cofactors such as folic acid and the isoprenoid quinones, and a host of secondary metabolites.[1,2] Shikimic acid (**1a**) is biosynthesized from D-glucose and subsequently converted to chorismic acid (**4**) through the intermediates shikimate 3-phosphate (**2**) and 5-enolpyruvylshikimate 3-phosphate (**3**). Because of the importance of this pathway, synthetic routes to these compounds and an understanding of their chemistry are of continuing interest.



Interest in shikimic acid as a target for total synthesis has remained high since the first route was reported by Smissman[3] and Raphael.[4] At least seven total syntheses of this material have been described,[3-9] as well as a number of partial syntheses.[10-15]

Scheme I



In contrast, synthetic work on the phosphate and enolpyruvyl derivatives **2**–**4** has been limited. There has been no report of the chemical synthesis of the phosphates **2** and **3**, and only recently have syntheses of chorismic acid (**4**) been completed by McGowan and Berchtold[16] and by Ganem and co-workers.[17]

Any synthesis of shikimic acid could in principle serve as a basis for preparation of derivatives **2** and **3**, provided that a means of differentiating the three hydroxyl groups were available. However, with the exception of recent synthetic work,[7-9,18] the classical routes to shikimic acid do not provide an opportunity for selective introduction or protection of the cis vicinal hydroxyls. A route to shikimic acid which addresses this question therefore appeared to us to be a valuable goal. We describe here a new total synthesis of racemic shikimic acid (**1**), the first synthesis of shikimic acid 3-phosphate (**2**), and a novel method for the introduction of an allylic phosphate via allylic rearrangement.

Total Synthesis of (±)-Shikimic Acid

We initially envisaged constructing shikimic acid by the route depicted in Scheme I. The key elements to our plan were the control of relative stereochemistry via iodolactonization (**9** → **10**) and sterically controlled epoxidation processes (**7** → **6**) and the introduction of the allylic alcohol moiety via a Mislow–Evans rearrangement (**5** → **1b**).

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(2) Ganem, B. *Tetrahedron* **1978**, *34*, 3353.
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(8) Coblens, K. E.; Muralidharan, U. B.; Ganem, B. *J. Org. Chem.* **1982**, *47*, 5040.
(9) Professor William R. Roush (personal communication) has completed a synthesis of shikimic acid related to ours.
(10) Fischer, H. O. L.; Dangschat, G. *Naturwissenshaften* **1938**, *26*, 562; Dangschat, G. Fischer, H. O. L. *Biochim. Biophys. Acta* **1950**, *4*, 199.
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(12) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1973**, *95*, 7821.
(13) Cleophax, J.; Mercier, D.; Gero, S. D. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 652.
(14) Bestmann, H. J.; Heid, H. A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 336.
(15) Yoshikawa, M.; Ikeda, Y.; Kayakiri, H.; Kitagawa, I. *Heterocycles* **1982**, *17*, 209. **Note Added in Proof**: Since submission of our manuscript, we have become aware of three additional syntheses of shikimic acid: Fleet, G. W. J.; Shing, T. K. M.; Warr, S. M. *J. Chem. Soc. Perkin Trans. 1* **1984**, 905. Campbell, M. M.; Kaye, A. D.; Sainsbury, M.; Yavarzadeh, R. *Tetrahedron Lett.* **1984**, *25*, 1629. Rajapaksa, D.; Keay, B. A.; Rodrigo, R. *Can. J. Chem.* **1984**, *62*, 826.
(16) McGowan, D. A.; Berchtold, G. A. *J. Am. Chem. Soc.* **1982**, *104*, 1153, 7036; Hoare, J. H.; Policastro, P. P.; Berchtold, G. A. *Ibid.* **1983**, *105*, 6264.
(17) Ganem, B.; Ikota, N.; Muralidharan, V. B.; Wade, W. S.; Young, S. D.; Yukimoto, Y. *J. Am. Chem. Soc.* **1982**, *104*, 6787.
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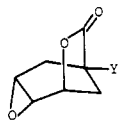
The α-phenylthio ester **8** is obtained in good yield from methyl 3-cyclohexene-1-carboxylate,[19] and converted to the iodo lactone **10** by saponification and treatment with aqueous KI_3.[20] Elimination of HI from **10** using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing tetrahydrofuran then provides the olefinic lactone **7** in 62% overall yield from methyl 3-cyclohexene-1-carboxylate. We were not able to functionalize the double bond of **7** with preservation of the sulfide oxidation level, although a number of methods for halohydrin formation and singlet oxygen oxidation were explored. Peracid oxidation produces first the sulfone of **7** and finally, under vigorous conditions, the epoxide **11a** in 85% yield. The stereoselectivity of the epoxidation reaction is high, leading to only 3% of the isomeric epoxide **12**.

When we were forced to abandom our plans for the Mislow–Evans rearrangement, we considered introduction of the allylic alcohol moiety via epoxides **15a** and **15b**. We envisaged that



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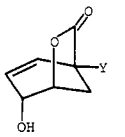

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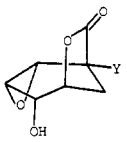

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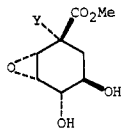

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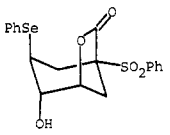

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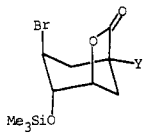


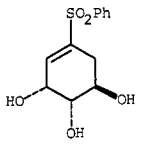
17

a: Y = SO_2Ph **b**: Y = H

methanolysis of the sulfonyl lactone **14a** followed by reductive elimination would generate the 1,2-double bond and unveil the 3-hydroxyl group simultaneously. Alternatively, base-induced elimination of the unsubstituted analogue **15b** would lead to the shikimate system as well: Ganem's recent synthesis of **1** in fact proceeds via epoxy lactone **14b**.[8] The sulfone route was attractive in view of our desire to prepare the shikimate derivatives **2** and **3**, since the sulfonyl epoxide **15a** would not be subject to premature elimination, as we feared could be a problem with the unsubstituted analogue **15b**.

With the sulfonyl epoxide **11a** in hand, we developed two methods for its isomerization to the allylic alcohol **13a**. A modification of the Sharpless procedure[21] involving ring opening with diisobutylaluminum phenylselenide to give **16**,[22] followed by oxidation with ozone and elimination in the presence of diethylamine,[23] affords the allylic alcohol **13a** in 56% overall yield after extensive optimization. A significantly more efficient procedure involves triphenylphosphine-catalyzed[24] epoxide opening with trimethylsilyl bromide followed by elimination of the trimethylsilyl bromohydrin **17a** with DBU.[25] Aqueous workup gives the desired alcohol **13a** in up to 95% yield from the epoxide.

The allylic alcohol **13a** is quite resistant to epoxidation, as Holbert and Ganem found for a closely related system.[26] However, using unbuffered trifluoroperoxyacetic acid as they recommend, the epoxy alcohol **14a** can be obtained as a single isomer in 91% yield. Structure **14a** incorporates all three hydroxyl groups in a manner which in principle allows them to be uncovered and protected selectively. To provide the parent methyl shikimate, the lactone is cleaved with K_2CO_3 in methanol to give the hydroxy ester **15a** in equilibrium with a small amount of the starting lactone. Attempts to drive this ring opening to completion by aqueous hydrolysis lead instead to trihydroxy sulfone **18**. Finally,



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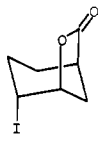

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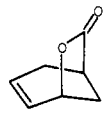

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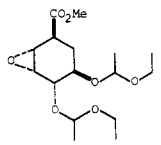
the sulfonyl epoxide moiety of **15a** is subjected to reductive elimination with aluminum amalgam in wet THF to provide methyl shikimate. This final step proved to be discouragingly capricious and could not be accomplished reproducibly or in better than 50% yield with any of a variety of reducing agents[27] or protected derivatives of diol **15a**.

We turned therefore to the unsubstituted lactone series **11b** → **15b**. The known lactone **20** was prepared in 84% yield by iodocyclization of 3-cyclohexene-1-carboxylic acid and DBU-induced elimination of the product **19**.[31] Of a variety of peracids investigated for the formation of epoxide **11b**, 3,5-dinitroperoxybenzoic acid[32] proved to be the most efficient, affording the exo and endo isomers in yields of 81% and 6%, respectively.[33] Isomerization of **11b** to the allylic alcohol **13b** and conversion to the epoxy alcohol **14b** are accomplished as described for the sulfonyl series, using trimethylsilyl bromide/DBU and 3,5-dinitroperoxybenzoic acid, providing the desired product in 75–85% yield for the two steps. Methanolysis of the epoxy lactone **14b** with K_2CO_3 in anhydrous methanol at room temperature provides racemic methyl shikimate, mp 176–177 °C, in 98% yield. This represents an overall yield from 3-cyclohexene-1-carboxylic acid of >50%. During the course of our continuing work on this project, Ganem and his co-workers reported their synthesis of shikimic acid, which intersects with our route at lactone **14b**. They report that hydrolysis of the lactone with NaOH in methanol affords shikimic acid directly in 90% yield.

Total Synthesis of (±)-3-Phosphoshikimic Acid

To prepare the 3-isomer of phosphoshikimic acid selectively from lactone **14b** requires that the epoxy diol **15b** be isolated and protected before elimination of the epoxide occurs. Isolation of this material can in fact be accomplished reproducibly in 89–91% yield if methanolysis of **14b** is allowed to proceed for only 5 min at 0 °C (K_2CO_3). The small amount of methyl shikimate that is isolated as a byproduct is readily removed by column chromatography. The hydroxyl groups are protected under nonbasic conditions by forming the bis(ethoxyethyl ether) **21** with ethyl



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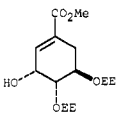

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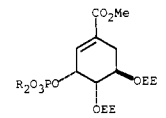
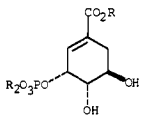


23a: R = Me
23b: R = $pNO_2PhCH_2CH_2$
23c: anion

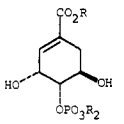
(19) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.
(20) Van Tamelen, E. E.; Sharma, M. *J. Am. Chem. Soc.* **1954**, *76*, 2135.
(21) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697. Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 1689.
(22) Bartlett, P. A.; Chouinard, P. M. *J. Org. Chem.* **1983**, *48*, 3854.
(23) Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22.
(24) Andrews, G. C.; Cranford, T. C.; Contillo, L. G., Jr. *Tetrahedron Lett.* **1981**, *3803*.
(25) Detty, M. R.; Siedler, M. D. *J. Org. Chem.* **1981**, *46*, 1283.
(26) Holbert, G. W.; Ganem, B. *J. Am. Chem. Soc.* **1978**, *100*, 351.
(27) Among those conditions explored were Al(Hg) in a variety of solvents, Na(Hg) in aqueous THF[28] or in the presence of Na_2HPO_4,[29] Zn dust in aqueous NH_4Cl or acetic acid, and Zn(Ag) couple.[30]
(28) Kocienski, P. J.; Tideswell, J. *Synth. Commun.* **1979**, *9*, 411. Kocienski, P. J. *Tetrahedron Lett.* **1979**, 441.
(29) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.
(30) Clark, R.; Heathcock, C. H. *J. Org. Chem.* **1972**, *38*, 3658.
(31) (a) Grewe, R.; Heinke, A.; Somner, C. *Chem. Ber.* **1956**, *89*, 1978. (b) Kato, M.; Kageyama, M.; Tanaka, R.; Kuwahara, K.; Yoshikoshi, A. *J. Org. Chem.* **1975**, *40*, 1932. (c) Trost, B. M.; Timko, J. M.; Stanton, J. L. *J. Chem. Soc., Chem. Commun.* **1978**, 436.
(32) Rastetter, W. H.; Richard, T. J.; Lewis, M. D. *J. Org. Chem.* **1978**, *43*, 3163.
(33) A similar sequence has been pursued by Stork and Logusch starting with the 1-methyl analogue: Stork, G.; Logusch, E. W. *Tetrahedron Lett.* **1979**, 3361.

vinyl ether and pyridinium *p*-toluenesulfonate.[34] The epoxide moiety is unaffected by the protection procedure, but is readily opened up with K_2CO_3 in methanol at room temperature to give the selectively protected shikimate derivative **22** in 98% overall yield from the epoxy diol **15b**.

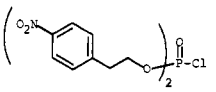
The free hydroxyl group of **22** can be transformed to the dimethyl phosphate **23a** with dimethyl phosphorochloridate in pyridine. However, we were not able to effect selective cleavage of the phosphate methyl esters. Treatment with trimethylsilyl bromide[35] leads to premature cleavage of the acetal protecting groups, even in the presence of isobutylene as HBr scavenger. These protecting groups must remain in place until the phosphate methyl esters are cleaved, as demonstrated by isolation of a mixture of the 3- and 4-(dimethyl phosphate) isomers **24** and **25a** on



24: R = Me
2: R = H



25a: R = Me
25b: R = H



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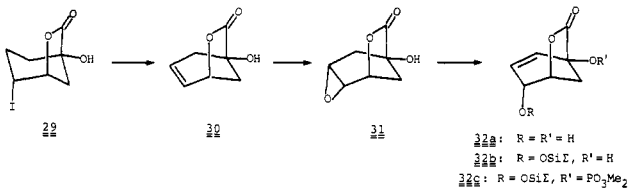
treatment of **23a** with a trace of *p*-toluenesulfonic acid in methanol. This vicinal isomerization is precedented in the chemistry of 3-phosphoshikimate itself, which Weiss and Mingioli showed equilibrates with the 4-phospho isomer **25b** in hot acetic acid.[36] Cleavage of the acetal protecting groups by trimethylsilyl bromide can be prevented by using pyridine as solvent; however, under these conditions it appears that the *allylic* phosphate bond is cleaved in competition with the methyl esters.[35]

Introduction and deprotection of the phosphate moiety under basic conditions are accomplished by using bis(*p*-nitrophenylethyl) phosphorochloridate (**26**) as described by Uhlmann and Pfleiderer.[37] Phosphorylation of **22** with **26** and 4-(dimethylamino)-pyridine (DMAP) in pyridine leads to the fully protected phosphate **23b** in 81% yield. Deprotection of the phosphate, without cleavage of the acetals, occurs on treatment of **23b** with DBU in either chloroform or pyridine. The resulting salt **23c** is not isolated but extracted directly into 2 N NaOH for hydrolysis of the carboxyl ester. Acidification of this solution with a cation exchange resin (Dowex 50W-X8, H^+ form) to pH 2.3 for 1 h in turn effects cleavage of the acetal protecting groups. ^1H NMR analysis (250 MHz) of this material in comparison with an authentic mixture of the 3- and 4-phospho isomers[36] indicates that no significant isomerization has taken place under these hydrolysis conditions. Finally, purification of the crude product by ion exchange chromatography affords the sodium salt of 3-phosphoshikimic acid **2** in 89% overall yield from the fully protected compound **23b**. The ^{13}C and ^{31}P NMR spectra of our synthetic material were fully in accord with the assigned structure. Moreover, an authentic sample of the tris(cyclohexylammonium) salt of **2**[38] was converted to the sodium salt and shown to be identical with our racemic product by 250-MHz ^1H NMR spectroscopy.

Alternative Route to a Derivative of 3-Phosphoshikimic Acid

The recent success reported by Overman[39,40] and others[41,42] in mercury- and palladium-catalyzed rearrangements of allylic esters

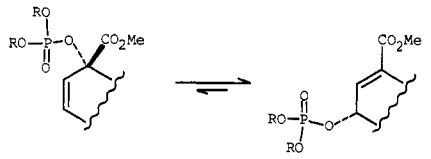
Scheme II



29 **30** **31**

32a: R = R' = H
32b: R = OSiΣ, R' = H
32c: R = OSiΣ, R' = PO_3Me_2

suggested that a shorter route to the allylic phosphate moiety of **2** was potentially available. We anticipated that the equilibrium between allylic phosphate isomers **27** and **28** would favor the latter

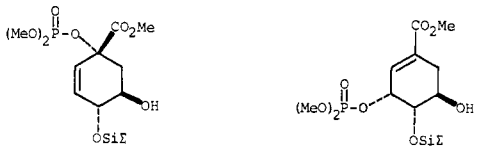


27 **28**

for steric as well as electronic reasons. The sequence depicted in Scheme II was therefore attractive as an alternative approach to 3-phosphoshikimate derivatives.

The appropriate substrates are available by a sequence analogous to those described above, starting with 1-hydroxy-3-cyclohexene-1-carboxylic acid.[43] The conversion of this material to lactone **30** in 16% yield was reported some time ago by Wolinsky et al. in connection with their synthesis of quinic acid.[43] We were able to obtain this water-soluble lactone in 71% yield by cyclization with iodine and elimination with DBU, avoiding the use of an aqueous workup in the latter reaction. Isolation and purification of the epoxide **31** are also complicated by its solubility behavior; the best procedure we developed for its preparation employs *m*-chloroperoxybenzoic acid as oxidant and direct chromatographic purification of the product, to give **31** in 63% yield. None of the endo isomer has been detected. Isomerization of the epoxide moiety to allylic diol **32a** proceeds smoothly (82% yield) as described above for the analogous lactones **11**.

The two hydroxyl groups of diol **32a** are readily differentiated on steric grounds: the *tert*-butyldimethylsilyl ether and dimethyl phosphate ester are introduced sequentially by using the silyl chloride, triethylamine, and DMAP and dimethyl phosphorochloridate and potassium hydride, respectively. Methanolysis of **32c** provides ester **33** in an unoptimized yield of 72% from diol



33 **34**

32a. Although the phosphate dimethyl ester is not advantageous for ultimate conversion to 3-phosphoshikimate, as indicated above, we explored the utility of the allylic phosphate rearrangement with compound **33**.

The palladium-catalyzed rearrangement of allylic phosphate **33** to the conjugated isomer **34** is considerably more difficult than analogous reactions with carboxylate esters.[39] We obtained the best results using 1 equiv of bis(acetonitrile)palladium(II) chloride $[(MeCN)_2PdCl_2]$ in THF solvent at room temperature for 7 days. After chromatographic purification a 65% yield of the rearranged product **34** can be isolated. Although formally an equilibrium process, no starting material is evident at the end of the reaction, and the remaining material appears to result from decomposition. We investigated a number of modifications in an attempt to reduce the amount of catalyst or length of time required. The reaction

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appears to proceed more slowly under nitrogen than in the presence of air; however, the addition of cupric chloride as a mild oxidant does not lead to any rate acceleration. The benzonitrile complex $(PhCN)_2PdCl_2$ is comparable to the aceonitrile complex in efficiency; however, (cyclooctadiene)$PdCl_2$ is without effect. In view of the report of Tamaru et al.[42] on the rearrangement of allylic thiophosphates with Pd(0) catalysts, we treated **33** with tetrakis(triphenylphosphine)palladium(0) in glyme at 70 °C, but obtained no reaction. Moreover, there appears to be an interplay between the rearrangement itself and the hydroxyl functional groups: attempted rearrangement of the diol derived from deprotection of **33** under the conditions most favorable for silyl ether **33** led to a plethora of products and that of the corresponding bis(ethoxyethyl)acetal to virtually no reaction, even after 1 week.

Although the allylic phosphate rearrangement was demonstrated successfully with the conversion of **33** to **34**, it did not appear to offer a real improvement over the more conventional route to 3-phosphoshikimate derivatives described above. We therefore elected not to pursue the process with a more suitable phosphate ester derivative.

Experimental Section

General. Reaction mixtures were routinely worked up by drying the organic solution over anhydrous $MgSO_4$ and evaporation of the solvent under reduced pressure using a rotary evaporator. All boiling points and melting points are uncorrected.

The ^1H NMR reference in D_2O was CH_3OH at 3.39 ppm; in CD_3OD, the reference was residual CHD_2OD at 3.30 ppm. ^{13}C NMR chemical shifts are reported in ppm on the δ scale relative to $CDCl_3$ solvent at 77.0 ppm, CH_3OH at 49.9 ppm in D_2O solvent, CD_3OD solvent at 49.0 ppm, and CD_3SOCD_3 solvent at 39.7 ppm. ^{31}P NMR chemical shifts are reported in ppm on the δ scale (downfield positive) relative to external trimethyl phosphate at 3.086 ppm in D_2O. All coupling constants (J values) are reported in hertz.

Methyl (3α,4α,5β)-3,4,5-Trihydroxy-1-cyclohexene-1-carboxylate (1b) (Methyl Shikimate). To a solution of 144 mg (0.923 mmol) of epoxy lactone **14b** (see below) in 0.50 mL of anhydrous methanol at 25 °C was added 10 mg of K_2CO_3. The reaction was quenched with excess NH_4Cl after 30 min. The mixture was concentrated under reduced pressure and purified by flash chromatography (20% ethanol/chloroform) to give 171 mg (98% yield) of methyl shikimate (**1b**) as a white solid: mp 176.5–177.5 °C (lit.[7] 172 °C); ^1H NMR (CD_3OD, 250 MHz) δ 2.20 (dddd, 1, J = 1.7, 1.7, 5.4, 18.2), 2.69 (dddd, 1, J = 2.0, 2.0, 4.9, 18.2), 3.68 (dd, 1, J = 4.2, 7.2), 3.74 (s, 3), 3.99 (ddd, 1, J = 5.2, 5.2, 7.1), 4.36 (m, 1).

(3α,4α,5β)-4,5-Dihydroxy-3-phosphonoxy-1-cyclohexene-1-carboxylic Acid, Disodium Salt (2) (Disodium 3-Phosphoshikimate). To a solution of 1.03 g (1.45 mmol) of phosphate **23b** (see below) in 15 mL of pyridine was added 0.75 mL (5.0 mmol) of DBU. After stirring for 3 days, the reaction mixture was partitioned between 100 mL of 2 N NaOH and 100 mL of $CHCl_3$. The aqueous layer was washed with $CHCl_3$ and acidified to a pH of 2.3 using a cation exchange resin (Dowex 50W-X8, H^+ form). After 1 h the resin was removed by filtration, and the pH was adjusted to 11 with NaOH. The solution was lyophilized and applied to an anion exchange column (DEAE Sephadex A-25, HCO_3^- form) and eluted with a linear gradient of triethylammonium bicarbonate (0.0–0.4 M, flow rate 0.67 mL/min, 10-min fractions). The faintly UV-active fractions (8–19, corresponding to 0.16–0.38 M triethylammonium bicarbonate) were combined and lyophilized to yield 590 mg (89% yield) of the tris(triethylammonium salt) of **2** as a slightly yellow solid: ^1H NMR (D_2O, 200 MHz) δ 1.2 (t, 27), 2.2 (dd, 1), 2.7 (dd, 1), 2.85 (dd, 1), 3.5 (q, 18), 3.85 (dd, 1, J = 2.5, 4), 4.05 (m, 1), 6.5 (t, 1, J = 1.7).

Cation exchange (Dowex 50W-X8, Na^+ form) and lyophilization gave 427 mg (92% yield) of the disodium salt of **2** as a light yellow solid: ^1H NMR (D_2O, 250 MHz) δ 2.19 (dd, 1, J = 6.1, 18.4), 2.69 (dd, 1, J = 4.9, 18.1), 3.84 (dd, 1, J = 4.0, 8.1), H-3 is under HDO signal; 6.55 (t, 4, J = 1.8); ^{13}C NMR (D_2O) δ 32.4, 67.7, 71.4, 71.5, 131.9, 135.7, 174.7; ^{31}P NMR (D_2O) δ 0.8 (s). Anal. Calcd for $C_7H_8O_8PNa_3 \cdot H_2O$: C, 24.22; H, 3.19; P, 8.92. Found: C, 24.19; H, 3.65; P, 8.73.

1-(Phenylthio)-6-oxabicyclo[3.2.1]oct-3-en-7-one (7). A mixture of 36.7 g (99.4 mmol) of iodo lactone **10** (see below) and 22.5 mL of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was refluxed for 12 h in the dark. The white crystalline hydroiodide salt of DBU was removed by filtration. The filtrate was combined with 1 L of diethyl ether, washed with 1 N HCl and saturated NaCl, dried, and concentrated under reduced pressure to afford 23 g of a slightly yellow solid. The crude product was washed with 100 mL of cold diethyl ether to give 20.7 g (90% yield) of olefin **7** as a white crystalline solid: mp 93.5–95 °C. The mother liquor was concentrated, and the resulting solid was recrystallized from ethyl acetate/hexane to give an additional 1.9 g (8% yield; 98% total yield) of olefin **7**: mp 92.5–93.5 °C; IR ($CHCl_3$) 950, 1120, 1260, 1780 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.10 (d, 1, J = 11), 2.48–2.59 (m, 3), 4.70 (dt, 1, J = 0.9, 5.4), 5.87–5.94 (m, 1), 6.19–6.37 (m, 1), 7.25–7.7 (m, 5). ^{13}C NMR ($CDCl_3$) δ 35.7, 39.9, 53.9, 71.3, 128.4, 128.7, 129.2, 130.5, 136.5, 176.1. Anal. Calcd for $C_{13}H_{12}O_2S$: C, 67.22; H, 5.21; S, 13.80. Found: C, 67.11; H, 5.24; S, 13.65.

Methyl 1-(Phenylthio)-3-cyclohexene-1-carboxylate (8). To a solution of 25.5 mL of diisopropylamine in 125 mL of THF at −78 °C was added 84.6 mL (195 mmol) of a 2.3 M solution of *n*-butyllithium in hexane. The reaction mixture was stirred for 20 min before the addition of 26 mL (185 mmol) of methyl 3-cyclohexene-1-carboxylate. A solution of 44.2 g (203 mmol) of diphenyl disulfide in 375 mL of THF was added after 20 min, and the reaction mixture was allowed to warm to −30 °C over the next 12 h before it was quenched by the addition of 100 mL of water. The THF was removed under reduced pressure, and diethyl ether was added. The aqueous layer was discarded, and the ether layer was washed with 2 N NaOH, 1 N HCl, and saturated NaCl, and dried. The solvent was removed under reduced pressure to leave a thick yellow oil which was purified by flash chromatography (5% ethyl acetate/hexane) to give 38.7 g (85% yield) of sulfide **8** as a plae yellow oil: IR (film) 695, 740, 1080, 1200, 1245, 1290, 1440, 1720, 2840, 2950, 3050 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.7–2.8 (m, 6), 3.54 (s, 3), 5.55 (m, 2), 7.3 (m, 5). Anal. Calcd for $C_{14}H_{16}O_2S$: C, 67.71; H, 6.49; S, 12.91. Found: C, 67.85; H, 6.47; S, 12.76. Alternatively, the crude product can be partially purified by bulb-to-bulb distillation and carried on with a slight contamination of diphenyl disulfide.

1-(Phenylthio)-3-cyclohexene-1-carboxylic Acid (9). A cloudy suspension of 5.7 g (2.3 mmol) of ester **8** and 1.88 g (4.7 mmol) of NaOH in 25 mL of 20% aqueous methanol was stirred at 21 °C for 18 h. The resulting clear solution was washed with diethyl ether and acidified with 1 N HCl. The aqueous layer was extracted with diethyl ether, and the combined organic layers were dried and concentrated under reduced pressure. The resulting yellow oil was purified by bulb-to-bulb distillation to afford 4.3 g (80%) of acid **9** as a semicrystalline solid: IR ($CHCl_3$) 1725, 3100 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.7–2.8 (m, 6), 5.6 (m, 2), 7.35 (m, 5), 10.9 (br s, 1). An analytical sample was recrystallized from petroleum ether: mp 72–74 °C. Anal. Calcd for $C_{13}H_{14}SO_4$: C, 66.64; H, 6.02; S, 13.68. Found: C, 66.92; H, 6.13; S, 13.68.

***exo*-1-(Phenylthio)-4-iodo-6-oxabicyclo[3.2.1]octan-7-one (10).** A solution of 1.09 g (8.6 mmol) of iodide and 4.23 g (25.7 mmol) of KI in 13.5 mL of water was added to a solution of 1.0 g (4.3 mmol) of acid **9** and 1.1 g (12.9 mmol) of $NaHCO_3$ in 26 mL of water. The reaction was stirred for 15 h in the dark. The yellow precipitate was separated by filtration, dissolved in diethyl ether, and washed with saturated $Na_2S_2O_3$, $NaHCO_3$, and NaCl. The diethyl ether layer was dried and concentrated under reduced pressure to give 1.44 g (93%) of iodolactone **10** as a white crystalline solid: mp 123–124 °C; IR ($CHCl_3$) 935, 1020, 1130, 1275, 1315, 1785 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.81–1.89 (m, 1), 1.98–2.21 (m, 2), 2.29–2.50 (m, 2), 2.80 (d, 1, J = 12.2), 4.44 (br t, 1, J = 4.4), 4.67 (dd, 1, J = 4.1, 6.0), 7.27–7.40 (m, 3), 7.58–7.62 (m, 2). An analytical sample was recrystallized from hexane: mp 123–124 °C. Anal. Calcd for $C_{13}H_{13}IO_2S$: C, 43.35; H, 3.64; S, 8.90; I, 35.23. Found: C, 43.38; H, 3.81; S, 8.97; I, 35.30.

(1α,2β,4β,6β)-6-(Phenylsulfonyl)-3,8-dioxatricyclo[4.2.1.0^{2,4}]nonan-7-one (11a) Using *m*-CPBA. A solution of 335 mg (1.44 mmol) of olefin **7**, 5 mg of 2,6-di-*tert*-butyl-4-methylphenol (BHT), and 1.25 g (7.2 mmol) of *m*-chloroperbenzoic acid in 15 mL of $CHCl_3$ was refluxed for 4 h. After addition of 249 mg (1.44 mmol) more of the peracid, the mixture was refluxed for 7 h. A final portion of 249 mg of peracid was added, and the mixture was refluxed for an additional 16 h. The reaction was quenched with 10% aqueous Na_2SO_3. The organic layer was washed with saturated $NaHCO_3$, and saturated NaCl, dried, and concentrated under reduced pressure to give a yellow oil. The crude prduct was purified by flash chromatography (50% ethyl acetate/hexane) to afford 300 mg (75% yield) of epoxide **11a** as a clear oil, which crystallized on standing. A sample was recrystallized from ethyl acetate/hexane: mp 145–147 °C; IR ($CHCl_3$) 805, 905, 1130, 1150, 1240, 1310, 1320, 1790 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.9–2.7 (m, 4), 3.18 (t, 1, J = 3), 3.34 (m, 1), 5.0 (m, 1), 7.38–8.1 (m, 5). Anal. Calcd for $C_{13}H_{12}O_5S$: C, 55.71; H, 4.32; S, 11.44. Found: C, 55.39; H, 4.43; S, 11.32.

(1α,2β,4β,6β)-6-(Phenylsulfonyl)-3,8-dioxatricyclo[4.2.1.0^{2,4}]nonan-7-one (11a) and the (1α,2α,4α,6β) Isomer (12) Using Trifluoroperacetic Acid. To a solution of 46 mL (0.33 mol) of trifluoroacetic anhydride in 150 mL of CH_2Cl_2 at 0 °C was added 7.6 mL (0.27 mol) of 90% hydrogen peroxide. The resulting solution was stirred at 25 °C for 30 min and then added to a solution of 11.4 g (0.05 mol) of olefin **7** in 200 mL of CH_2Cl_2 at 0 °C. The mixture was stirred at 25 C for 2 h. After being washed with saturated Na_2SO_3 and saturated $NaHCO_3$, the CH_2Cl_2

solution was dried and concentrated under reduced pressure. The crude product was purified by recrystallization from ethyl acetate/hexane to afford 11.4 g (83% yield) of a white crystalline solid: mp 144–145 °C; ^{1}H NMR spectral analysis indicated that this material was 98% exo isomer **11** and 2% endo isomer **12**. The mother liquor was concentrated under reduced pressure to give 746 mg of a white solid which was purified by flash chromatography (ethyl acetate) to afford an additional 563 mg (4% yield, 85% total yield) of the major isomer **11a** and 133 mg (1% yield, 3% total yield) of the minor isomer **12**: mp 192–193 °C; IR ($CHCl_3$) 1150, 1310, 1320, 1795 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.30 (d, 1, J = 11.7), 2.48 (br d, 1, J = 14.8), 2.59 (dd, 1, J = 14.8), 3.01 (ddd, 1, J = 1.2, 5.3, 11.7), 3.32 (dt, 1, J = 0.9, 3.3), 3.49 (t, 1, J = 4), 5.05 (t, 1, J = 4.9), 7.55–7.80 (m, 8), 8.0–8.1 (m, 2). Anal. Calcd for $C_{13}H_{12}O_5S$: C, 55.71; H, 4.32; S, 11.44. Found: C, 55.68; H, 4.43; S, 11.39.

(1α,2β,4β,6α)-3,8-Dioxatricyclo[4.2.1.0^{2,4}]nonan-7-one (11b) and the (1α,2α,4α,6α) Isomer. A solution containing 4.70 g (37.9 mmol) of olefin **20** (see below), 14.7 g (64.4 mmol) of 3,5-dinitroperbenzoic acid, and 100 mg (0.45 mmol) of 2,6-di-*tert*-butyl-4-methylphenol (BHT) in 300 mL of CH_2Cl_2 was refluxed for 11 h. The precipitate was removed by filtration and washed with CH_2Cl_2. The filtrate was washed with saturated Na_2SO_4 and saturated $NaHCO_3$, dried, and concentrated under reduced pressure to give a yellow solid. The crude product was purified by flash chromatography (40% ethyl acetate/hexane) to give as the first fraction 4.31 g (81% yield) of the exo isomer **11b**, as a white crystalline solid. An analytical sample was prepared by recrystallization from ethyl acetate/hexane: mp 112–112.5 °C; IR ($CHCl_3$) 910, 990, 1120, 1780 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.18 (m, 4), 3.25 (m, 1), 3.26 (m, 1), 5.08 (m, 1); ^{13}C NMR ($CDCl_3$) δ 24.6, 28.2, 36.3, 49.8, 50.6, 76.0, 178.1. Anal. Calcd for $C_7H_8O_3$: C, 60.00; H, 5.75. Found: C, 60.09; H, 5.79.

A second fraction contained 323 mg (6%) of the minor, endo epoxide as a white solid. An analytical sample was prepared by recrystallization from ethyl acetate/hexane: mp 94–95 °C; IR ($CHCl_3$) 940, 1110, 1780 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.97 (d, 1, J = 11), 2.15 (ddd, 1, J = 3.4, 5.4, 15.7), 2.41 (m, 3), 3.16 (dd, 1, J = 3.5, 3.5), 3.46 (dd, 1, J = 3.9, 3.9), 5.00 (dd, 1, J = 4.5, 4.5); ^{13}C NMR ($CDCl_3$) δ 28.0, 32.4, 34.4, 47.2, 51.0, 71.7, 178.5. Anal. Calcd for $C_7H_8O_3$: C, 60.00; H, 5.75. Found: C, 60.06; H, 5.80.

***exo*-1-(Phenylsulfonyl)-4-hydroxy-6-oxabicyclo[3.2.1]oct-2-en-7-one (13a) via Selenyl Alcohol (16).** To a solution of 4.25 g (13.6 mmol) of diphenyl diselenide in 150 mL of CH_2Cl_2 was added a 25% solution of diisobutylaluminum hydride in toluene until the solution was only slightly yellow (10.5 mL). This solution was added to a solution of 6.05 g (21.6 mmol) of epoxide **11** in 100 mL of CH_2Cl_2 at −78 °C. The reaction mixture was warmed to 21 °C and stirred for 6 h. Moist Na_2SO_4 was added to quench the reaction. The mixture was filtered, dried, and concentrated under reduced pressure to give 8.74 g of a yellow oil. The crude product was purified by flash chromatography (50% ethyl acetate/hexane) to afford 6.46 g (68% yield) of selenide **16** as a white solid: mp 139–140 °C; IR ($CHCl_3$) 625, 685, 1010, 1150, 1310, 1320, 1440, 1790, 3500 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.14 (br d, 1, J = 14.3), 2.63 (dd, 1, J = 14.3, 7.0), 2.69 (d, 1, J = 11.8), 2.84 (ddd, 1, J = 11.8, 5.7, 2.0), 3.35 (d, 1, J = 3.9), 3.59 (dd, 1, J = 1.7, 7), 4.29 (br s, 1, OH), 4.80 (dd, 1, J = 5.7, 3.9), 7.08–7.3 (m, 5), 7.5–7.6 (m, 2), 7.65–7.78 (m, 1), 7.9–8.0 (m, 2).

Ozone was bubbled through a solution of 3.2 g (7.32 mmol) of selenide **16** in 75 mL of CH_2Cl_2 at −78 °C until the solution turned purple. Nitrogen was passed through the solution for 1 h before the addition of 1.8 mL (17.4 mmol) of diethylamine. The resulting solution was warmed to 21 °C and stirred for 25 h. A white precipitate was removed by filtration, and the filtrate was concentrated under reduced pressure to a dark green oil. The crude oil was purified by flash chromatography (5% ethanol/chloroform) to give 1.74 g (85% yield) of allylic aclohol **13a** as a pale yellow solid: IR ($CHCl_3$) 1155, 1310, 1325, 1445, 1795, 3500 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.11 (d, 1, J = 6.25, OH), 2.42 (d, 1, J = 11.3), 2.86 (ddd, 1, J = 1.8, 5.9, 11.3), 4.28 (ddd, 1, J = 2.9, 3.4, 6.2), 4.72 (ddd, 1, J = 1.8, 2.9, 5.9), 6.01 (ddd, 1, J = 1.8, 3.4, 1.8), 6.43 (dd, 1, J = 1.8, 9.6), 7.6–7.8 (m, 3), 8.05–8.15 (m, 2). An analytical sample was prepared by recrystallization from $CHCl_3$: mp 169.5–170 °C. Anal. Calcd for $C_{13}H_{12}O_5S$: C, 55.71; H, 4.32; S, 11.44. Found: C, 55.71; H, 4.54; S, 11.53.

***exo*-1-(Phenylsulfonyl)-4-hydroxy-6-oxabicyclo[3.2.1]oct-2-en-7-one (13a) via the Me$_3$SiBr/DBU Method.** To a solution of 591 mg (2.1 mmol) of epoxide **11** and 94 mg (0.36 mmol) of triphenylphosphine in 10 mL of acetonitrile at 0 °C was added 0.55 mL (4.2 mmol) of trimethylsilyl bromide. The solution was warmed to 21 °C and stirred for 90 min before the addition of 0.73 mL (4.9 mmol) of DBU. The reaction mixture was refluxed for 7.5 h then stirred at 21 °C for 10 h. Diethyl ether was added, the white precipitate was removed by filtration, and the filtrate was acidified with concentrated HCl (ca. 0.5 mL) and stirred for 1 h. The solution was concentrated under reduced pressure to a brown oil which was purified by flash chromatography (25% hexane/ethyl acetate) to give 535 mg (90% yield) of allylic alcohol **13a** as a white solid: mp 169.5–170 °C; ^{1}H NMR spectral data identical with that reported above.

***exo*-4-Hydroxy-6-oxabicyclo[3.2.1]oct-2-en-7-one (13b).** To a solution of 1.005 g (7.17 mmol) of epoxide **11b** and 363 mg (1.39 mmol) of triphenylphosphine in 50 mL of acetonitrile at 0 °C was added 2.3 mL (17.6 mmol) of trimethylsilyl bromide. The reaction mixture was warmed to 25 °C and stirred for 1 h before adding 3.1 mL (20.73 mmol) of DBU. After refluxing for 21 h, the reaction mixture was cooled to 0 °C and 50 mL of diethyl ether was added. The tan precipitate was removed by filtration, and the filtrate was combined with 25 mL of 1 N HCl and stirred for 25 min. The aqueous layer was discarded, and the solvent was removed under reduced pressure to give a brown oil. Purification of this material by flash chromatography (25% hexane/ethyl acetate) gave 860 mg (85% yield) of **13b** as a white solid: mp 86–87 °C; IR ($CHCl_3$) 975, 1015, 1050, 1150, 1770, 3000, 3425 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.16 (d, 1, J = 11.5), 2.33 (m, 1), 2.80 (br s, 1), 3.00 (dd, 1, J = 4.5, 7.1), 4.28 (m, 1), 4.72 (m, 1), 5.84 (ddd, 1, J = 1.8, 3.3, 9.3), 6.27 (ddd, 1, J = 1, 7.3, 9.2); ^{13}C NMR ($CDCl_3$, CD_3OD) δ 29.3, 37.8, 64.3, 78.9, 128.8, 128.9, 177.4. Anal. Calcd for $C_7H_8O_3$: C, 60.00; H, 5.75. Found: C, 60.13; H, 5.81.

(1α,2α,4α,5β,6β)-1-(Phenylsulfonyl)-5-hydroxy-3,7-dioxatricyclo-[4.2.1.0^{2,4}]nonan-8-one (14a). To a solution of 4.5 mL (31.9 mmol) of trifluoroacetic anhydride in 15 mL of CH_2Cl_2 was added 0.8 mL (28.5 mmol) of 90% hydrogen peroxide. The reaction was exothermic so the reaction mixture was cooled to 0 °C and stirred for 15 min. A solution of 2.49 g (8.88 mmol) of allylic alcohol **13a** in 40 mL of CH_2Cl_2 was added. The reaction mixture was refluxed for 8 h. After being washed with saturated Na_2SO_3 and $NaHCO_3$, the CH_2Cl_2 solution was dried and concentrated under reduced pressure to give 2.4 g (91% yield) of epoxy alcohol **14a** as a white solid: IR ($CHCl_3$) 720, 1160, 1200, 1330, 1450, 1800 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.1 (br s, 1), 2.48 (d, 1, J = 12.2), 2.61 (br ddd, 1, J = 1.2, 6.0, 12.2), 3.43 (ddd, 1, J = 2.0, 4.1, 4.1), 4.04 (m, 2), 4.50 (ddd, 1, J = 2.8, 4.1, 6.0), 7.6–7.85 (m, 3), 8.0–8.15 (m, 2). An analytical sample was obtained by recrystallization from $CHCl_3$: mp 174–175 °C. Anal. Calcd for $C_{13}H_{12}O_6S$: C, 52.70; H, 4.08; S, 10.82. Found: C, 52.47; H, 3.98; S, 10.66.

(1α,2β,4β,5α,6α)-5-Hydroxy-3,7-dioxatricyclo[4.2.1.0^{2,4}]nonan-8-one (14b). A solution of 202 mg (1.44 mmol) of allylic alcohol **13b**, 664 mg (2.91 mmol) of 3,5-dinitroperbenzoic acid, and 10 mg (0.04 mmol) of 2,6-di-*tert*-butyl-4-methylphenol in 10 mL of CH_2Cl_2 was refluxed for 9 h and then stirred at 25 °C for 10 h. The precipitate was removed by filtration, and the filtrate was concentrated under reduced pressure. The crude solid was purified by flash chromatography (40% hexane/ethyl acetate) followed by a second flash chromatography (10% EtOH/$CHCl_3$) to give 200 mg (89% yield) of the epoxy alcohol **14b** as a white solid: mp 122.5–123 °C (lit.[8] 123–125 °C); IR ($CHCl_3$) 950, 1065, 1125, 1175, 1790, 3020 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.07 (ddd, 1, J = 1.0, 6.2, 12.4), 2.42 (d, 1, J = 12.5), 2.83 (br s, 1), 3.06 (dd, 1, J = 4.6, 4.6), 3.36 (m, 1), 3.66 (dd, 1, J = 4.1, 4.1), 4.06 (m, 1), 4.49 (ddd, 1, J = 2.2, 2.4, 6.0); ^{13}C NMR (Me_2SO-d_6) 25.0, 37.7, 49.8, 50.4, 64.4, 78.6, 175.9. Anal. Calcd for $C_7H_8O_4$: C, 53.85; H, 5.16. Found: C, 53.77; H, 5.14.

Methyl (1α,2β,4α,5β,6α)-2-(Phenylsulfonyl)-4,5-dihydroxy-7-oxabicyclo[4.1.0]heptane-2-carboxylate (15a). To a solution of 250 mg (0.84 mmol) of lactone **14a** in 60 mL of anhydrous methanol was added 24 mg (0.17 mmol) of anhydrous K_2CO_3. Saturated NH_4Cl was added after 5 h, and the methanol was removed under reduced pressure. The aqueous solution was extracted with copious amounts of 10% ethanol/$CHCl_3$, and the combined organic layers were concentrated under reduced pressure. The crude product was purified by flash chromatography (8% ethanol/$CHCl_3$) to afford 39 mg (15% yield) of starting lactone **14a** and 236 mg (85% yield) of diol **15a** as a white solid: mp 128–129 °C; IR ($CHCl_3$) 1080, 1150, 1310, 1325, 1430, 1450, 1735, 3300 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.6 (br s, 2), 2.34 (dd, 1, J = 2.4, 14.7), 2.48 (dd, 1, J = 5.7, 14.7), 3.51 (dt, 1, J = 0.8, 3.9, 3.9), 3.76 (s, 3), 3.9 (m, 3), 7.54 (m, 2), 7.73 (m, 1), 7.93 (m, 2). An analytical sample was obtained by recrystallization from ethyl acetate/hexane: mp 128–129 °C. Anal. Calcd for $C_{14}H_{16}O_7S$: C, 51.21; H, 4.91; S, 9.77. Found: C, 50.98; H, 4.92; S, 9.54.

Methyl (1α,2α,4α,5β,6α)-4,5-Dihydroxy-7-oxabicyclo[4.1.0]heptane-2-carboxylate (15b). To a solution of 860 mg (5.51 mmol) of lactone **14b** in 40 mL of methanol at 0 °C was added 85 mg (0.61 mmol) of anhydrous K_2CO_3. After stirring for 5 min, the reaction mixture was quenched by the addition of 500 mg (9.35 mmol) of NH_4Cl and 300 mL of $CHCl_3$. The solids were removed by filtration, and the filtrate was concentrated under reduced pressure. Purification by flash chromatog-

raphy (10% EtOH/$CHCl_3$) gave 945 mg (91% yield) of diol **15b** as a white solid: mp 96.5–97 °C; IR (KBr) 1065, 1210, 1305, 1430, 1725, 3210, 3340 cm^{-1}; ^1H NMR ($CDCl_3/CD_3OD$, 200 MHz) δ 1.62 (ddd, 1, J = 11.6, 11.6, 11.8), 2.03 (dddd, 1, J = 1.4, 3.3, 6.3, 11.7), 3.03 (dd, 1, J = 6.3, 11.8), 3.37 (m, 1, obscured by the CD_3OD signal), 3.6 (m, 2), 3.75 (m, 1), 3.76 (s, 3); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.63–1.80 (m, 1), 1.99–2.12 (dddd, 1, J = 1.1, 3.2, 6.4, 13.4), 2.65 (br s, 1, OH), 2.74 (br d, 1, J = 6.7; OH), 3.06 (dd, 1, J = 6.4, 10.7), 3.43 (dd, 1, J = 2.4, 3.7), 3.64–3.87 [m, 6; includes a br d at 3.65 (J = 3.6) and a methyl carboxylate at 3.76]. ^{13}C NMR δ 34.2, 42.1, 53.3, 56.7, 58.9, 69.9, 74.8, 174.9. Anal. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 51.11; H, 6.50.

(1α,2β,3β)-5-(Phenylsulfonyl)-4-cyclohexene-1,2,3-triol (18). A solution of 42 mg (0.14 mmol) of epoxy sulfone **14a** and 77 μL of 2 N NaOH in 0.5 mL of methanol was kept at 21 °C for 30 min. Saturated NH_4Cl was added, and the mixture was extracted with 10% ethanol/$CHCl_3$. The organic layer was dried and evaporated to give 31 mg (82% yield) of the sulfone **18**: ^1H NMR ($CDCl_3$, 250 MHz) δ 2.09 (dddd, 1, J = 1.4, 1.4, 4.4, 17.6), 2.52 (dddd, 1, J = 2.1, 2.1, 4.4, 17.6), 3.70 (dd, 1, J = 4.0, 6.2), 3.98 (ddd, 1, J = 4.4, 4.4, 6.3), 4.4 (br s, 1), 6.83 (d, 1, J = 1.4), 7.6–7.9 (m, 5).

***exo*-4-Iodo-6-oxabicyclo[3.2.1]octan-7-one (19).** To a solution of 8.08 g (64 mmol) of 3-cyclohexene-1-carboxylic acid and 16 g (0.19 mol) of $NaHCO_3$ in 375 mL of water was added a solution of 16.16 g (64 mmol) of iodine and 63 g (0.38 mol) of KI in 200 mL of water, and the reaction mixture was stirred in the dark at 21 °C for 21 h. The yellow precipitate was collected and dissolved in $CHCl_3$, and the solution was washed with aqueous $Na_2S_2SO_3$, aqueous $NaHCO_3$, and brine, dried, and evaporated to give 15.1 g (94% yield) of iodo lactone **19** as slightly yellow crystals: mp 134.5–135 °C (lit.[31a] 134 °C).

6-Oxabicyclo[3.2.1]-oct-3-en-7-one (20). A solution of 1.92 g (7.6 mmol) of iodolactone **19** and 1.4 mL of DBU in 50 mL of THF was heated at reflux for 16 h. After the mixture cooled to 0 °C, the DBU·HI was removed by filtration, the solution was evaporated, and the residue was dissolved in $CHCl_3$. This solution was washed with 1 N HCl and brine, dried, and evaporated, and the residue was distilled (bulb-to-bulb, 110 °C (15 torr)) to give 840 mg (89% yield) of olefinic lactone **20**:[31] ^1H NMR ($CDCl_3$, 250 MHz) δ 2.10 (d, 1, J = 11.1), 2.4–2.6 (m, 2), 2.9 (br s, 1), 4.77 (dd, 1, J = 5.4, 5.4), 5.85 (m, 1), 6.24 (m, 1).

Methyl (1α,2α,4α,5β,6α)-4,5-Bis(1-ethoxyethoxy)-7-oxabicyclo-[4.1.0]heptane-2-carboxylate (21). To a solution of 309 mg (1.64 mmol) of diol **15b** in 200 mL of THF was added 1.2 mL (12.5 mmol) of ethyl vinyl ether followed by 20 mg of pyridinium 4-toluenesulfonate (PPTS). After 25 h, excess K_2CO_3 was added, and the mixture was filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography (25% ethyl acetate/hexane) to give 510 mg (94% yield) of **21** as a clear oil: IR ($CHCl_3$) 950, 1050, 1130, 1730, 2775 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.15–1.40 (m, 12), 1.57–1.83 (m, 1), 1.97–2.20 (m, 1), 2.94–3.04 (m, 1), 3.37–4.08 (m, 11; includes methyl ester at 3.74), 4.75 (m, 1), 4.98 (m, 1). Anal. Calcd for $C_{16}H_{28}O_7$: C, 57.82; H, 8.49. Found; C, 57.94; H, 8.36.

Methyl (3α,4α,5β)-3-Hydroxy-4,5-bis(1-ethoxyethoxy)-1-cyclo-hexene-1-carboxylate (22). To a solution of 141 mg (0.42 mmol) of epoxide **21** in 7 mL of anhydrous methanol was added 5 mg of anhdrous K_2CO_3. After 35 min, excess NH_4Cl was added, and the solvent was removed under reduced pressure. The crude product was suspended in 50% ethyl acetate/hexane and purified by flash chromatography (50% ethyl acetate/hexane) to give 139 mg (98% yield) of alcohol **22** as a clear oil: IR ($CHCl_3$) 950, 1040, 1090, 1250, 1380, 1700, 2975, 3400 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.17–1.37 (m, 12), 2.37–2.68 (m, 2), 3.43–3.71 (m, 5), 3.75 (s, 3), 3.80–3.94 (m, 1), 4.06–4.24 (m, 1), 4.47 (br s, 1), 4.76–4.85 (m, 2), 6.82 (br d, 1). Anal. Calcd for $C_{16}H_{28}O_7$: C, 57.82; H, 8.49. Found: C, 57.68; H, 8.37.

An alternative procedure omitted the purification of crude **21**. In this case, 240.3 mg (1.128 mmol) of diol **15b** was converted to 417.1 mg of **22** (98% overall yield for the two steps).

Methyl (3α,4α,5β)-3-[(Dimethoxyphosphinyl)oxy]-4,5-bis(1-ethoxy-ethoxy)-1-cyclohexene-1-carboxylate (23a). To a solution of 99 mg (0.30 mmol) of alcohol **22** in 1 mL of pyridine at 0 °C was added 64 μL (0.60 mmol) of dimethyl phosphorochloridate. After stirring at 0 °C for 4.5 h, the reaction mixture was partitioned between saturated $NaHCO_3$ and $CHCl_3$. The organic layer was washed with brine, dried, and concentrated under reduced pressure to give a yellow oil. Purification by flash chromatography (25% hexane/ethyl acetate) gave 53 mg (61% yield) of **23a** as a clear oil: IR ($CHCl_3$) 850, 950, 1050, 1130, 1260, 1385, 1437, 1655, 1715, 2960, 3000 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.25 (m, 12), 2.4 (m, 1), 2.7 (m, 1), 3.4–4.25 (m, 15; includes methyl carboxylate at 3.76 and four methyl phosphate doublets at 3.79, 3.80, 3.81, 3.82, all with J = 11.2), 4.85 (m, 2), 5.2 (m, 1), 6.8 (br d, 1). Anal. Calcd for $C_{18}H_{33}O_{10}P$: C, 49.09; H, 7.55; P, 7.03. Found: C, 49.48; H, 7.59; P, 6.89.

Methyl (3α,4α,5β)-3-[[Bis(2-(4-nitrophenyl)ethoxy)phosphinyl]oxy]-4,5-bis(1-ethoxyethoxy)-1-cyclohexene-1-carboxylate (23b). To 0.81 mL (9.95 mmol) of sulfuryl chloride in 23 mL of carbon tetrachloride was added a solution of 3.4 g (9 mmol) of bis(4-nitrophenethyl) phosphite in 20 mL of CH_2Cl_2 over a 30-min period. After stirring for an addition 15 min, the reaction mixture was concentrated under reduced pressure to a yellow oil. A solution of 576 mg (4.72 mmol) of 4-dimethylaminopyridine in 20 mL of pyridine at 0 °C was added followed by a solution of 1.59 g (4.79 mmol) of alcohol **22** in 20 mL of CH_2Cl_2 at 0 °C. After 36 h, the reaction mixture was concentrated and partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic layer was dried and concentrated, and the residue was purified by flash chromtography (33% hexane/ethyl acetate) to give 2.84 g of a thick yellow oil, containing CH_2Cl_2 (4%) and phosphate **23b** (81% yield): IR ($CHCl_3$) 858, 950, 1015, 1055, 1080, 1260, 1350, 1380, 1440, 1520, 1605, 1660, 1715, 2995 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.1–1.9 (m, 12), 2.3–2.9 (m, 2), 3.07 (t, 4, J = 6.4), 3.4–3.7 (m, 4), 3.77 (s, 3), 3.85–4.35 (m, 6), 4.7–4.9 (m, 2), 5.05–5.2 (m, 1), 6.65 (br s, 0.5), 6.72 (br s, 0.5), 7.38 (br d, 4, J = 8.7), 8.16 (dd, 4, J = 1.4, 8.7). An analytical sample was prepared by concentrating the yellow oil repeatedly from diethyl ether. Anal. Calcd for $C_{32}H_{43}O_{14}N_2P$: C, 54.08; H, 6.10; N, 3.94; P, 4.36. Found: C, 54.31; H, 6.20; N, 3.86; P, 4.10.

***exo*-1-Hydroxy-4-iodo-6-oxabicyclo[3.2.1]octan-7-one (29).** A solution of 34.0 g (0.13 mol) of iodine and 66.7 g (0.40 mol) of KI in 150 mL of water was added to a solution of 9.5 g (0.067 mol) of 1-hydroxy-3-cyclohexene-1-carboxylic acid[43] and 16.8 g (0.20 mol) of $NaHCO_3$ in 250 mL of water. A thick brown precipitate was formed over 23 h in the dark. CH_2Cl_2 and $CHCl_3$ were added, and the organic layer was washed with saturated $Na_2S_2O_3$ and saturated $NaHCO_3$, dried, and concentrated under reduced pressure to give 15.7 g of a yellow solid. The crude product was purified by recrystallization from ethyl acetate-/hexane to afford 14.8 g (83% yield) of iodo lactone **29** as a white solid: mp 116–117 °C. The aqueous layer was continuously extracted with CH_2Cl_2. The resulting CH_2Cl_2 solution was combined with the above mother liquors, and the mixture was concentrated to a yellow solid, which was recrystallized to give an additional 660 mg (4% yield; 87% total yield) of iodo lactone, **29**: mp 113–115 °C. IR ($CHCl_3$) 850, 925, 960, 1100, 1270, 1320, 1450, 1785, 3400 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.7–1.9 (m, 1), 2.0–2.7 (m, 5), 3.0 (d, 1, J = 12.1), 3.4 (br s, 1), 4.45 (m, 1), 4.9 (m, 1). Anal. Calcd for $C_7H_9IO_3$: C, 31.37; H, 3.38; I, 47.34. Found: C, 31.38; H, 3.43; I, 47.46.

1-Hydroxy-6-oxabicyclo[3.2.1]oct-3-en-7-one (30). A mixture containing 867 mg (3.2 mmol) of iodo lactone **29** and 0.53 mL (3.5 mmol) of DBU in 20 mL of THF was refluxed in the dark for 12 h. The white crystalline hydriodide salt of DBU was removed by filtration and washed with diethyl ether. The combined filtrates were concentrated under reduced pressure to an oil, which was purified by flash chromatography (5% ethanol/$CHCl_3$) to give 381 mg (82% yield) of olefin **30** as a white crystalline solid: mp 74–76 °C (lit.[43] 73–75 °C); IR ($CHCl_3$) 910, 950, 965, 1130, 1270, 1310, 1780, 3450 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.28 (d, 1, J = 10.8), 2.6 (m, 3, J = 5.5), 3.84 (br s, 1), 4.86 (ddd, 1, J = 1.3, 5.5, 5.5), 6.00 (dddd, 1, J = 1.3, 3.4, 3.4, 9.2), 6.23 (m, 1).

(1α,2β,4β,6β)-6-Hydroxy-3,8-dioxatricyclo[4.2.1.$0^{2,4}$]nonan-7-one (31). To a 5-mm NMR tube were added 33 mg (0.235 mmol) of olefin **30**, 55 mg (0.32 mmol) of *m*-chloroperbenzoic acid, and 0.60 mL of $CDCl_3$. The resulting solution was refluxed for 12 h before 20 mg (0.12 mmol) of additional peracid was added. After 12 h the mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography (50% ethyl acetate/hexane) followed by recrystallization from ethyl acetate/hexane to give 23 mg (63% yield) of epoxide **31** as a white solid: mp 151.5–153 °C; IR ($CHCl_3$) 810, 960, 1010, 1078, 1095, 1250, 1320, 1420, 1790, 3340 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.13 (ddd, 1, J = 2.5, 4.5, 15.0), 2.20 (ddd, 1, J = 2.3, 6.1, 11.5), 2.31 (d, 1, J = 15.0), 2.48 (d, 1, J = 11.5), 2.79 (br s, 1), 3.26 (dd, 1, J = 4.0, 4.2), 3.47 (dd, 1, J = 3.4, 3.7), 5.10 (dd, 1, J = 3.6, 5.8). Anal. Calcd for $C_7H_8O_4$: C, 53.85; H, 5.16. Found: C, 53.79; H, 5.16.

***exo*-1,4-Dihydroxy-6-oxabicyclo[3.2.1]oct-2-en-7-one (32a).** To a solution of 1.93 g (13.8 mmol) of epoxide **31** and 724 mg (3 mmol) of triphenylphosphine in 150 mL of acetonitrile at 0 °C was added 5.4 mL (41.3 mmol) of trimethylsilyl bromide. The solution was warmed to 21 °C and stirred for 1 h before the addition of 8.3 mL of DBU. The dark brown solution was refluxed for 22 h, then cooled to 0 °C, and 600 mL of diethyl ether was added. The resulting tan precipitate was removed by filtration, and the filtrate was acidified with 3 mL of 6 N HCl. Hydrolysis was not complete after 30 min, therefore 2 mL of 1 N HCl was added. The two layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 500 mL). The combined organic layers were dried and concentrated under reduced pressure to afford a brown

oil which was purified by flash chromatography (10% ethanol/$CHCl_3$) to give 1.6 g (82% yield) of allylic alcohol **32a** as a white solid: mp 120–121.5 °C; IR (KBr) 830, 935, 955, 1030, 1040, 1050, 1135, 1185, 1260, 1270, 1340, 1765, 3310 cm^{-1}; ^1H NMR (CD_3OD, 250 MHz) δ 2.32 (m, 2), 4.14 (dd, 1, J = 2.8, 3.0), 4.70 (m, 1), 5.76 (ddd, 1, J = 2.1, 3.3, 9.7), 6.06 (ddd, 1, J = 1.0, 1.5, 9.6); ^{13}C NMR (CD_3OD) δ 37.1, 65.9, 74.2, 77.9, 128.9, 136.9, 178.9. Anal. Calcd for $C_7H_8O_4$: C, 53.85; H, 5.16. Found: C, 53.58; H, 5.15.

***exo*-1-Hydroxy-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6-oxabicyclo[3.2.1]oct-2-en-7-one (32b).** To a solution of 747 mg (4.79 mmol) of allylic alcohol **32a** in 20 mL of CH_2Cl_2 at 0 °C was added a solution of 865 mg (5.74 mmol) of *tert*-butyldimethylsilyl chloride in 7 mL of CH_2Cl_2 followed by 0.8 mL (5.74 mmol) of triethylamine and 123 mg (1.0 mmol) of 4-dimethylaminopyridine. The mixture was refluxed for 2 d before an additional 401 mg (2.66 mmol) of *tert*-butyldimethylsilyl chloride and 0.5 mL (3.59 mmol) of triethylamine were added. The mixture was refluxed for 1 day before the addition of 50 mg (0.73 mmol) of imidazole. The mixture was refluxed for 1 day and then concentrated under reduced pressure. The crude product was purified by flash chromatography (a gradient of 10% ethyl acetate/hexane at 100% ethyl acetate) to give 54 mg (7% yield) of recovered allylic alcohol **32a** and 1.14 g (88% yield) of silyl alcohol **32b** as a white solid: mp 75–76.5 °C; IR ($CHCl_3$) 830, 855, 890, 970, 1090, 1115, 1260, 1785, 2870, 2940, 2970, 3420 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.12 (s, 6), 0.90 (s, 9), 2.36 (ddd, 1, J = 1.9, 5.9, 10.9), 2.47 (d, 1, J = 10.9), 3.15 (s, 1; OH), 4.22 (dd, 1, J = 3.2, 3.2), 4.55 (ddd, 1, J = 2.6, 2.9, 5.2), 5.64 (ddd, 1, J = 2.2, 3.2, 9.7), 6.04 (ddd, 1, J = 0.5, 1.9, 9.6); ^{13}C NMR ($CDCl_3$) δ −5.0, −4.8, 17.9, 25.6, 36.1, 65.4, 73.3, 77.1, 128.0, 135.2, 178.1. Anal. Calcd for $C_{13}H_{22}O_4Si$: C, 57.74; H, 8.20. Found: C, 57.60; H, 8.25.

***exo*-1-[(Dimethoxyphosphinyl)oxy]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6-oxabicyclo[3.2.1]oct-2-en-7-one (32c).** A suspension of 756 mg (3.77 mmol) of 20% KH in mineral oil was washed with 1 mL of pentane. The residue was suspended in 10 mL of THF and cooled to 0 °C. A solution of 5.24 mg (1.94 mmol) of silyl alcohol **32b** in 10 mL of THF was added. The mixture was stirred at 0 °C for 30 min then warmed to 21 °C, and 0.5 mL (4.69 mmol) of dimethyl phosphorochloridate was added. The mixture was stirred for 14.5 h and was concentrated under reduced pressure. The crude product was purified by flash chromatography (a gradient of 20% ethyl acetate/hexane to 100% ethyl acetate) to give 636 mg (87% yield) of phosphate **32c** as a clear oil: IR ($CHCl_3$) 835, 855, 890, 990, 1055, 1095, 1140, 1270, 1810, 3870, 2940, 2965 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.12 (s, 6), 0.90 (s, 9), 2.64 (d, 1, J = 10.8), 2.87 (ddd, 1, J = 2.1, 6.1, 10.8), 3.83 (d, 3, J = 11.4), 3.86 (d, 3, J = 11.4), 4.22 (dd, 1, J = 3, 3), 4.60 (ddd, 1, J = 2.3, 3, 6), 5.70 (ddd, 1, J = 2.4, 3, 9.8), 6.20 (dd, 1, J = 2.0, 9.9); ^{13}C NMR ($CDCl_3$) δ −5.3, −5.0, 17.6, 25.3, 34.4, 54.4 (J_{CP} = 7.4), 54.5 (J_{CP} = 7.0), 64.1, 65.0, 76.2, 128.5 (J_{CP} = 10.6), 131.8 (J_{CP} = 6.9), 171.9. Anal. Calcd for $C_{15}H_{27}O_7PSi$: C, 47.61; H, 7.19; P, 8.18. Found: C, 47.55; H, 7.23; P, 7.99.

Methyl (1α,4α,5β)-1-[(Dimethyloxyphosphinyl)oxy]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-hydroxy-2-cyclohexene-1-carboxylate (33). To a solution of 420 mg (1.11 mmol) of lactone **32c** in 30 mL of anhydrous methanol at 0 °C was added 10 mg (0.07 mmol) of anhydrous K_2CO_3. Saturated NH_4Cl was added after 15 min, and the methanol was removed under reduced pressure. The residue was suspended in 50% ethyl acetate/hexane and purified by flash chromatography (50% ethyl acetate/hexane) to give 426 mg (94% yield of alcohol **33** as a white solid: mp 97–98 °C; IR ($CHCl_3$) 850, 1000, 1060, 1100, 1260, 1750, 2870, 2940, 2970, 3440 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.12 (s, 6), 0.19 (s, 9), 2.03 (ddd, 1, $J_{H,P}$ = 4.5, J = 11.7, 13.9), 2.38 (br s, 1), 2.42 (ddd, 1, J = 1.7, 3.6, 13.9), 3.71 (d, 3, J = 11.4), 3.81 (s, 3), 3.81 (d, 3, J = 11.4), 3.90 (ddd, 1, J = 3.5, 7.7, 11.5), 4.10 (ddd, 1, J = 1.9, 1.9, 7.7), 5.89 (dd, 1, J = 1.9, 10.0), 6.05 (ddd, 1, J = 1.8, 1.8, 10.0); ^{13}C NMR ($CDCl_3$) δ −5.1, −4.8, 17.7, 25.5, 38.9 (J_{CP} = 8), 52.7, 53.9 (J_{CP} = 7), 54.1 (J_{CP} = 7), 68.8, 73.3, 80.3 (J_{CP} = 7), 124.0 (J_{CP} = 2), 136.9, 170.7. Anal. Calcd for $C_{16}H_{31}O_8PSi$: C, 46.82; H, 7.61; P, 7.55. Found: C, 46.98; H, 7.59; P, 7.48.

Methyl (3α,4α,5β)-3-[(Dimethoxyphosphinyl)oxy]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-hydroxy-1-cyclohexene-1-carboxylate (34). To an orange-red solution of 115.3 mg (0/.49 mmol) of dichlorobis(acetonitrile)palladium(II) in 5 mL of THF under normal atmosphere was added 199 mg (0.48 mmol) of phosphate **33**. The reaction mixture was stirred for 6 days, then an additional 20 mg (0.09 mmol) of the palladium complex was added. After an additional 24 h, the solvent was removed under reduced pressure, and 3 mL of $CDCl_3$ was added. The resulting suspension was filtered through Celite. The solution was concentrated under reduced pressure, and the residue was purified by flash chromatography (33% hexane/ethyl acetate) to give 129 mg (65% yield) of phosphate **34** as a clear oil: IR ($CHCl_3$) 840, 855, 940, 1025, 1050, 1140, 1260, 1440, 1470, 1660, 1720, 2870, 2940, 2965, 3015, 3420 cm^{-1}; ^1H NMR ($CDCl_3$, 200 and 250 MHz) δ 0.12 (s, 3), 0.13 (s, 3), 0.90 (s, 9), 2.1 (br s, 1), 2.28 (dddd, 1, J = 1.4, 1.4, 5.3, 18.6), 2.84 (dddd, 1, J = 1.8, 1.8, 4.8, 18.5), 3.73–3.81 [m, 9; includes methyl carboxylate at 3.76 and two methyl phosphate doublets at 3.75 (J = 11.2) and 3.78 (J = 11.2)], 3.87 (dd, 1, J = 3.5, 7.2), 4.07 (m, 1, J = 5.5, 12.5), 5.06 (m, 1, J = 4.0, 8.0), 6.83 (m 1, J = 1.7, 3.5); ^{13}C NMR ($CDCl_3$) δ −5.2, −4.9, 17.9, 25.5, 29.7, 51.8, 54.2 (J_{CP} = 6.0), 54.4 (J_{CP} = 6.2), 67.6, 70.9 (J_{CP} = 4.9), 73.4 (J_{CP} = 5.3), 130.5, 133.8 (J_{CP} = 2.4), 166.6. Anal. Calcd for $C_{16}H_{31}O_8PSi$: C, 46.82; H, 7.61; P, 7.55. Found: C, 46.57; H, 7.69; P, 7.40.

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