# Efficient Synthesis of 1α-Fluoro A-Ring Phosphine Oxide, a Useful Building Block for Vitamin D Analogues, from (*S*)-Carvone via a Highly Selective Palladium-Catalyzed Isomerization of Dieneoxide to Dieneol

Marek M. Kabat, Lisa M. Garofalo, Andrzej R. Daniewski, Stanley D. Hutchings, Wen Liu, Masami Okabe, Roumen Radinov,* and Yuefen Zhou

*Chemical Synthesis - Process Research, Non-Clinical Development, Pre-Clinical Research and Development, Hoffmann-La Roche Inc., Nutley, New Jersey 07110*

*roumen.radinov@roche.com*

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The 1α-fluoro A-ring phosphine oxide **1**, a useful building block for fluorinated vitamin D analogues, was synthesized from (*S*)-carvone in 13 synthetic steps, and only five isolations, in 22% overall yield. In the key synthetic step, a highly selective palladium-catalyzed isomerization of dieneoxide **18** to dieneol **20** was achieved using an appropriately selected fluorinated alcohol as a catalytic proton source.

## Introduction

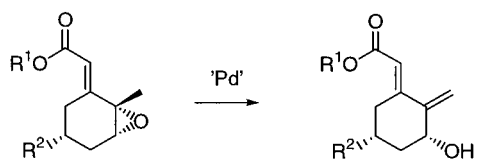
A number of vitamin D analogues containing the 1α-fluorosubstituted A-ring fragment[1] have been shown to possess interesting biological activities.[2] Earlier studies have shown that 1α-fluoro-25-hydroxyvitamin $D_3$ has strong phagocytic activity toward human promyelocytic leukemia cells.[3] More recently, modified D-ring and side chain analogues, such as Ro 26−9228 (**3**), were reported to increase bone mineral density, while showing reduced calciuria and calcemia in rats compared to 1,25-dihydroxyvitamin $D_3$,[4] and have been under evaluation for the treatment of osteoporosis. Closely related compounds were found to stimulate HL-60 cell differentiation, and could be of use for the treatment of leukemia.[5]

The A-ring phosphine oxide **1**[6] (Scheme 1) is a useful building block for the synthesis of 1α-fluoro vitamin D analogues, such as **3**, via Wittig−Horner coupling with the appropriate CD-ring portion **2**, followed by desilylation.

Three syntheses of **1** have been reported thus far. The first synthesis, and the most efficient of the three, proceeds in seventeen steps from (*S*)-carvone and in an overall yield of 3.9%.[6] More recently, **1** has been prepared in eleven steps from vitamin $D_3$ in a lower yield of 2.4%.[7] Finally, an alternative approach from (*S*)-carvone has been developed, using a more effective fluorination procedure but, overall, resulted in a much longer and lower-yielding process.[8]

In the first synthesis (Scheme 2),[6] the conversion of the 1α-epoxide **5** to allylic alcohol **9** required 10 steps. Four steps were needed for the formal isomerization of the dieneoxide moiety in **5** with inversion of configuration at C-1 to obtain the 1*β*-epimeric allylic alcohol with exocyclic double bond in **9**. The remaining six steps from **7** to **8** were necessary for the oxidative degradation of the isopropenyl substituent to the corresponding silylated alcohol, which also involved the sequential protection of the other two hydroxyl groups in the process.

We envisioned that the appropriate dieneoxide moiety, such as in the 1*β*-epimer **11**, could be isomerized *directly* to the requisite allylic alcohol **12** with an exocyclic double bond using palladium catalysis. In addition, this approach obviates the extensive protecting group manipulation, as no intermediary protection of the alcohol group would be needed.




**11** **12**

Noyori et al. have reported that simple alkyl-substituted 1,3-diene monoepoxides (dieneoxides) can isomerize

* Corresponding author. Tel: (973) 235-3292. Fax: (973) 235-7239.

(1) The α and *β* designations and atom numbering used in the text follow the conventional steroid nomenclature, see: Rose, I. A.; Hanson, K. R.; Wilkinson, K. D.; Wimmer, M. J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 2439.

(2) (a) Vickery, B. H.; Avnur, Z.; Uskoković, M.; Peleg, S. *Proc. Workshop Vitam. D 2000, 11th (Vitam. D: Endocrine System)*, 887−92. (b) Kobayashi, Y.; Taguchi, T. *Proc. Workshop Vitam. D 1988, 7th (Vitam. D: Mol., Cell. Clin. Endocrinol.)*, 3−11.

(3) (a) Oshima E.; Sai, H.; Takatsuto, S.; Ikekawa, N.; Kobayashi, Y.; Tanaka, Y.; DeLuca H. F. *Chem. Pharm. Bull.* **1984**, *32*, 3525. (b) Oshima E.; Takatsuto, S.; Ikekawa, N.; DeLuca H. F. *Chem. Pharm. Bull.* **1984**, *32*, 3518.

(4) (a) Nestor, J. J., Jr.; Manchand, P. S.; Uskoković, M. R.; Vickery, B. H. US Patent US 5872113 1999; CAN 130 168545 1999. (b) Manchand, P. S.; Nestor, J. J., Jr.; Uskoković, M. R.; Vickery, B. H. Eur. Pat. Appl. EP 808832 1996; CAN 128 34927 1997.

(5) Iacobelli, J. A.; Uskoković, M. R. US Patent US 6030963 2000; CAN 132 175819 2000.

(6) Shiuey, S.-J.; Kulesha, I.; Baggiolini, E. G.; Uskoković, M. R. *J. Org. Chem.* **1990**, *55*, 243.

(7) Kiegiel, J.; Wovkulich, P. M.; Uskoković, M. R. *Tetrahedron Lett.* **1991**, *32*, 6057.

(8) Barbier, P.; Mohr, P.; Muller, M.; Masciadri, R. *J. Org. Chem.* **1998**, *63*, 6984.

10.1021/jo015788y CCC: $20.00 
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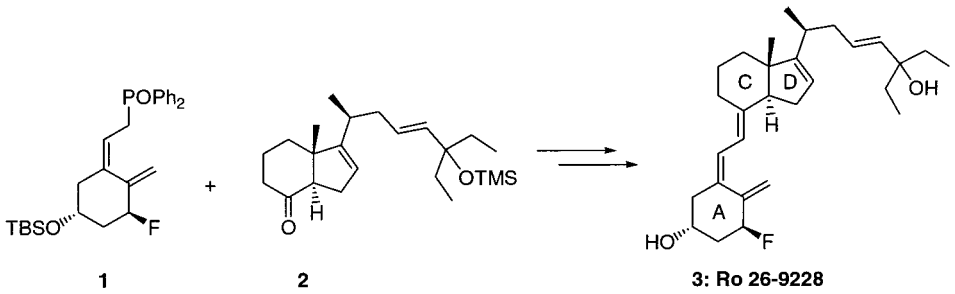
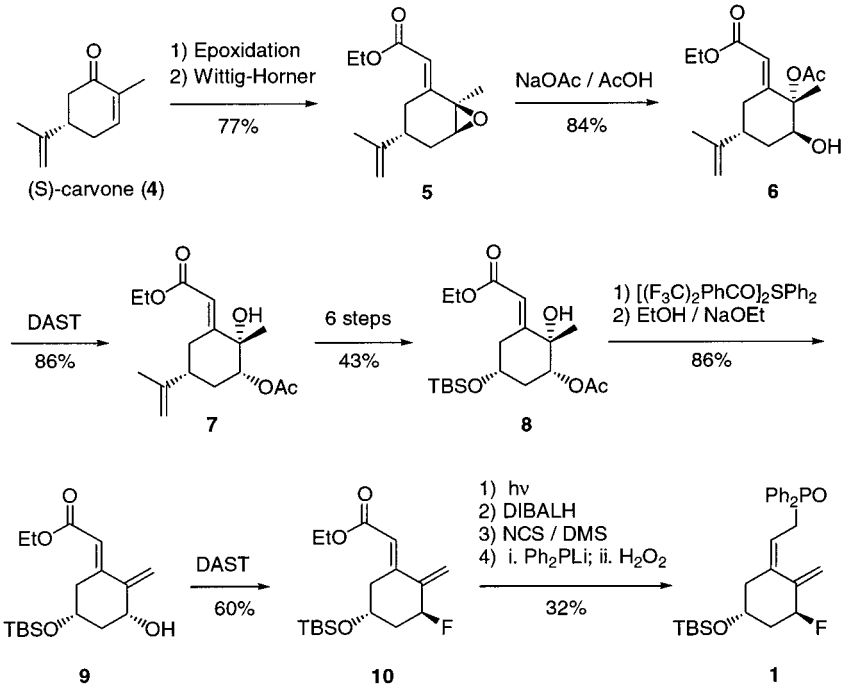
**Scheme 1**




**Scheme 2**




to dieneols, or to enones, under the influence of a catalytic amount of tetrakis(triphenylphosphine)palladium [Pd(PPh$_3$)$_4$].[9] The course of such rearrangements was typically dependent on the structure of the substrates, and to some extent on the ligands used.[10] However, no clear rationale for selectivity control is available in order to direct the reaction of a given substrate to the desired dieneol product.

We wish to report here the complete selectivity control of the isomerization of **11** to **12**, and its application for a highly efficient synthesis of **1**, aimed at minimizing intermediate isolation and purification steps.

## Results and Discussion

The requisite substrate for the rearrangement, dieneoxide **18**, was readily obtained in 7 synthetic steps from (*S*)-carvone as shown in Scheme 3. The correct 1$\beta$-configuration of the epoxide was initially established in **14**, by transfer of chirality from the existing stereocenter in (*S*)-carvone, using a two-step aldol addition/directed epoxidation sequence via the tertiary allylic alcohol **13**.

Stereoselective aldol addition of ethyl acetate to (*S*)-carvone (**4**) promoted by cerium(III) chloride has been described,[11] in which 2 equivalents of both its lithium enolate and the expensive cerium salt were used. We found that the amounts of these reagents could be reduced to 1.3 equivalents each and complete conversion of **4** to inter alia **13** still occurred when using *tert*-butyl acetate as the reagent. However, further reduction in the equivalents of the cerium(III) chloride, while using 1.3 equiv of the enolate, resulted in incomplete reaction; ca. 50% conversion with 0.5 equiv of $CeCl_3$, while no reaction occurred without this additive. Nevertheless, to our pleasant surprise, complete conversion to **13** was achieved when 0.5 equiv of the relatively inexpensive cerium(III) fluoride was used instead. It was subsequently found that even 0.25 equiv of $CeF_3$ was enough to drive the reaction to completion. Using *tert*-butyl acetate instead of ethyl acetate in this first step allowed for easy purification of subsequent intermediates **15** and **16** by crystallization.

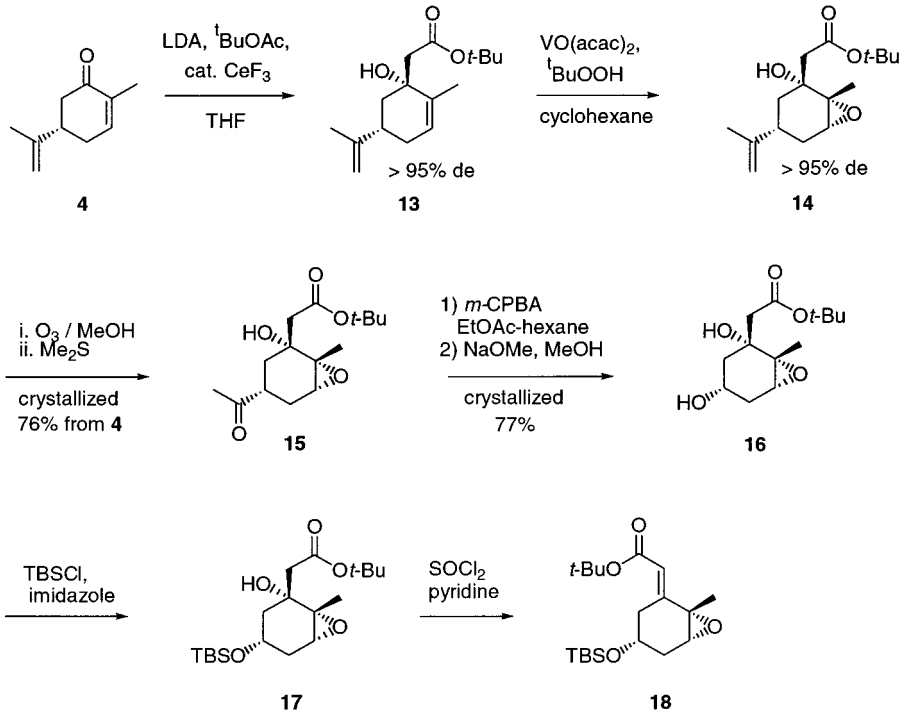
The regio- and stereoselective directed epoxidation of crude tertiary allylic alcohol **13** with *tert*-butyl hydroperoxide, catalyzed by vanadyl acetylacetonate VO(acac)$_2$, then afforded epoxide **14**. The epoxidation of **13** in dichloromethane was sluggish, even in the presence of molecular sieves and with a large excess of reagents, and

(9) Suzuki, M.; Oda, Y.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 1623.

(10) (a) Tsuda, T.; Tokai, M.; Ishida, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 5216. (b) Visentin, G.; Piccolo, O.; Consiglio, G. *J. Mol. Catal.* **1990**, *61*, L1.

(11) Liu, H.-J.; Zhu, B.-Y. *Can. J. Chem.* **1991**, *69*, 2008.

**Scheme 3**

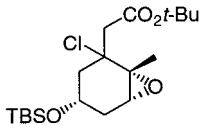



gave only a modest yield of **14**. A clean conversion and good yield of **14** was realized by carrying out the reaction in refluxing cyclohexane with a Dean−Stark condenser. This procedure resulted in complete reaction after 5 h using 1.2 mol % of $VO(acac)_2$ and 1.2 equiv of the *tert*-butyl hydroperoxide as a 5−6 M nonane solution. Epoxide **14** was relatively unstable and was used directly in the next step, after extractive workup, as a mixture with nonane.

Oxidative cleavage of the isopropenyl group was then achieved in a two-step ozonolysis/Baeyer−Villiger sequence, without protection of the tertiary hydroxyl group. Thus, crude epoxide **14** in MeOH was ozonized at −70 °C, in the presence of sodium bicarbonate. The hydroperoxide intermediate was reduced in situ with dimethyl sulfide to obtain ketone **15**, in 76% yield from **4**, after crystallization from EtOAc−hexane.[12]

The Baeyer−Villiger oxidation of **15** was attempted under standard conditions using *m*-CPBA in dichloromethane,[13] but the reaction was very slow producing a large amount of byproducts. Other reagents examined were either ineffective or resulted in complete decomposition of the substrate. It was subsequently found that the *m*-CPBA oxidation could be accelerated in less polar solvents. Thus, using 2 equivalents of *m*-CPBA in common solvents, the following conversions of **15** were obtained after 16 h at room temperature: toluene (80% + byproducts) > 1:1 hexanes−EtOAc (67%) > EtOAc (55%) > *tert*-butyl methyl ether (51%) > acetonitrile (20% + byproducts) > DMF (10%). Finally, fast and clean oxidation was achieved using a 3:1 mixture of hexanes−EtOAc. The resulting acetate intermediate was then hydrolyzed with a catalytic amount (15 mol %) of sodium methoxide in MeOH at 0 °C, and alcohol **16** was isolated by crystallization from EtOAc−hexane in 77% yield from **15**.

After selective protection of the secondary hydroxyl over the tertiary hydroxyl group in **16**, the $\beta$-elimination of the tertiary alcohol in ester **17** was readily achieved. Thus, after silylation of **16** using *tert*-butyldimethylsilyl chloride (TBSCl) and imidazole in THF, the salts were removed by filtration, and the THF solution of **17** was subjected to dehydration with thionyl chloride in pyridine to give (*E*)-dieneoxide **18** exclusively. Adding the THF solution of **17** to a preformed, cold thionyl chloride/pyridine mixture minimized the formation of chloride **19**, which was otherwise a major byproduct. Although **19** could be converted to **18** separately upon subsequent treatment with DBU, the desired dehydrochlorination did not occur under the reaction conditions described above.

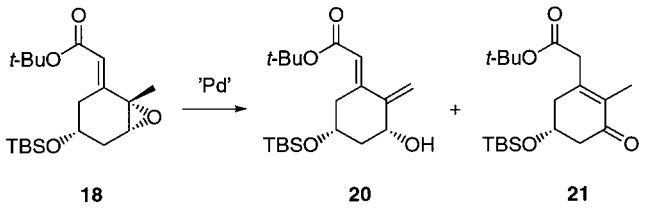



**19**

Now the success of the synthesis hinged upon the selective isomerization of dieneoxide **18** to dieneol **20**. Before attempting the palladium-catalyzed isomerization, several other methods known to effect the rearrangement of epoxides to allylic alcohols were tried, but failed to give even a trace amount of the desired product. However, when dieneoxide **18** was treated with $Pd(PPh_3)_4$ in THF at 65 °C, a mixture of the desired allylic alcohol **20** and the isomeric $\alpha,\beta$-unsaturated ketone **21** was obtained in the unfavorable ratio of 1:3.

(12) Alternatively, the hydroperoxide intermediate could be isolated from the ozonolysis, acetylated, and the isolated peracetate subjected to Criegee rearrangement; see: Schreiber, S. L.; Liew, W.-F. *Tetrahedron Lett.* **1983**, *24*, 2363. However, this procedure gave alcohol **16** in low yield after chromatographic separation, and ketone **15** as the major byproduct.

(13) For a review on the Baeyer−Villiger oxidation, see: Krow, G. R. *Org. React.* **1993**, *43*, 251.




Eventually, the ratio was improved to 3:1 when tris-(2-furyl)phosphine ligand was used instead of $Ph_3P$, but 20 mol % of the palladium catalyst was still necessary for complete conversion. Further ligand screening revealed, that an identical selectivity could be achieved with only 1.5 mol % of a palladium/1,2-bis(diphenylphosphino)ethane catalyst. Still, the selectivity could not be improved any further using other ligands.

Serendipitously, it was then found, that addition of a fluorinated alcohol, 1,1,1,3,3,3-hexafluoro-2-phenyl-2-propanol (**22c**), increased formation of allylic alcohol **20** versus the undesired enone **21** and simultaneously improved the turnover frequency of the original palladium-triphenylphosphine catalyst. Remarkably, even a catalytic amount of 10 mol % of **22c** was sufficient to increase the selectivity for allylic alcohol **20** formation to 10:1. Increasing the amount of this additive further to 50 mol % and 100 mol % gave an improved 16:1 and 19:1 ratio of **20**:**21**, respectively.

This interesting effect was explored using other alcohol additives, and the selectivity was found to correlate with the p$K_a$ of these additives. Indeed, the more acidic fluorinated alcohols[14] with p$K_a$ < 9 were particularly effective. As shown in Table 1 and Figure 1, a sharp increase in selectivity for the desired allylic alcohol **20** was observed when the p$K_a$ of the additive decreased from 9.1 to 8.5. The 'titration curve' shown in Graph 1 strongly suggests that the reaction pathways leading to either **20** or **21** diverge in a protonation step of a common intermediate of comparable basicity. Interestingly, only the fluorinated alcohols performed well in this reaction. Other more common proton sources, such as aliphatic alcohols, phenols and carboxylic acids, resulted in no or incomplete reaction and no effect on selectivity.

Although perfluoro-*tert*-butyl alcohol (**22e**) gave a better selectivity (95:5) than the less acidic **22c** and **22d** (91:9 and 92:8, respectively), the reactions run with the latter compounds were cleaner, than that with **22e**. Thus, **22c** and **22d** were studied in more detail in different solvents to determine their catalytic efficiency and the results are shown in Figure 2. Diol **22d** gave better turnover frequency than **22c**, particularly so in less polar solvents. Moreover, diol **22d** is a monomer commonly used for the preparation of fluoropolymers,[15] and it is available in bulk at a relatively low cost.[16] The reaction using this additive was, therefore, optimized further.

Ultimately, virtually complete selectivity (>99:1) for the desired **20** was obtained by carrying out the reaction with 1 mol % of the palladium catalyst, prepared in situ from 0.5 mol % $Pd_2dba_3(CHCl_3)$ and 5 mol % of triphenylphosphine, and 2 mol % of **22d** in a less polar solvent, toluene, and at the lower temperature of 35 °C. This reaction temperature also resulted in an increased purity of the product. It was found that two major polar byproducts were formed on prolonged heating of the product **20** in concentrated solutions, or even upon allowing the solidified **20** to stand at ambient temperature overnight. These byproducts were found to be

**Table 1. p$K_a$ of Additives vs Selectivity**

| alcohol additive | mol % | p$K_a$ (relative to water) | selectivity % **20** vs **21** |
|---|---|---|---|
| none | | | 25 |
| *tert*-BuOH | 100 | 19 | 25 |
| $MeC(CF_3)_2OH$ (**22a**) | 10 | 9.51 | 26 |
| $(CF_3)_2CHOH$ (**22b**) | 10 | 9.13 | 32 |
| $PhC(CF_3)_2OH$ (**22c**) | 10 | 8.52 | 91 |
| $1,3\text{-}C_6H_4[C(CF_3)_2OH]_2$ (**22d**) | 10 | 8.48 | 92 |
| $(CF_3)_3COH$ (**22e**) | 10 | 5.18 | 95 |

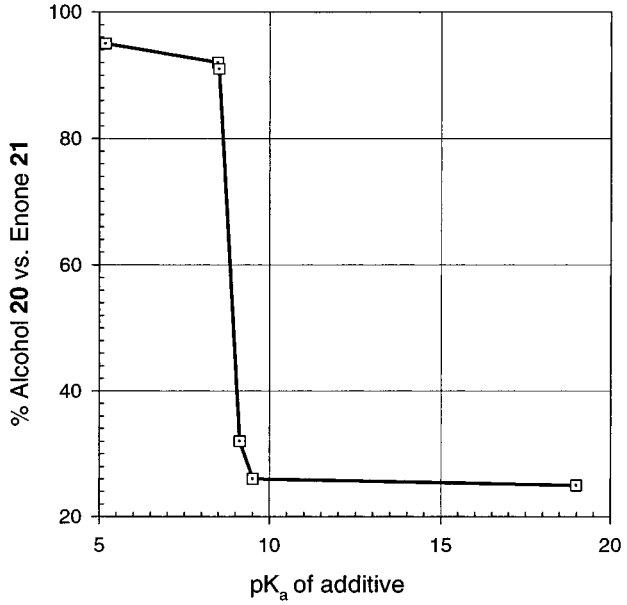



**Figure 1.** p$K_a$ of additives vs selectivity.

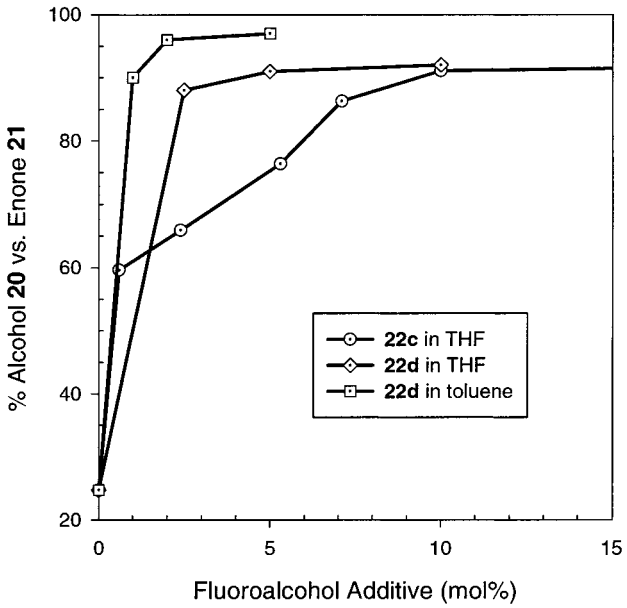


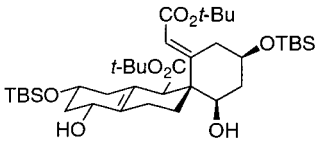

**Figure 2.** Catalytic effect of fluorinated alcohols on selectivity at 65 °C.

(14) (a) Filler, R.; Schure, R. M. *J. Org. Chem.* **1967**, *32*, 1217. (b) Chang, I. S.; Price, J. T.; Tomlinson, A. J.; Willis, C. J. *Can. J. Chem.* **1972**, *50*, 512.

(15) Cassidy, P. E.; Aminabha, T. M.; Reddy, S.; Fitch, J. W., III. *Eur. Polym. J.* **1995**, *31*, 353.

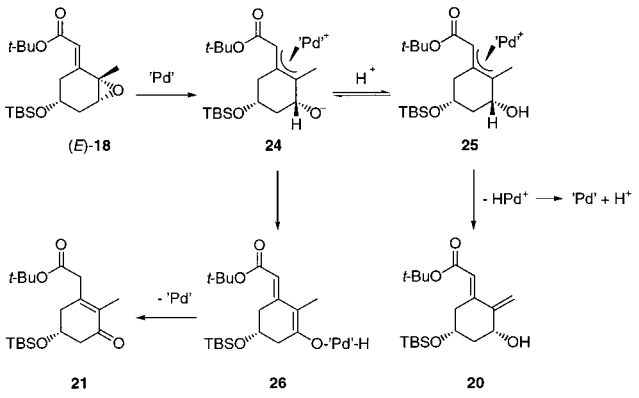
(16) **22d** is available from PCR, Inc. at $295/500 g, compared to $98/25 g for **22c**.

isomers resulting from the Diels−Alder dimerization of **20**, and the structure of one of them was subsequently determined unequivocally as **23** by X-ray crystallography.




**23**

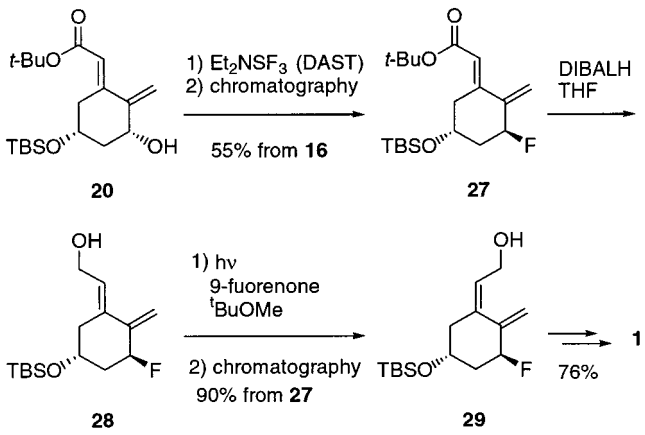
The remarkable catalytic effect of a proton source on the chemoselectivity of $\beta$-hydride elimination may be explained as follows. The palladium(0) catalyst formed in situ reacts initially with the dieneoxide to form a zwitterionic $\pi$-allyl palladium alkoxide complex **24**. Without a suitable proton source to protonate the alkoxide, the hydrogen next to the alkoxide migrates preferentially to the cationic palladium to give the enolate **26**, which then collapses to give the undesired enone **21** as the major product. This selectivity of the H-shift comes from the increased electron density of the C−H bond, due to electron-donation from the alkoxide. When a proton source of appropriate p$K_a$ is present, the zwitterionic intermediate **24** can be protonated, possibly via precoordination, to give Pd-complex **25** as an ion-pair with the corresponding conjugate base of the proton source used.[17] Now the inductive effect of the resulting hydroxyl group in **25**, as compared to the electron-donating ability of the alkoxide in **24**, prevents the formation of enolate **26**. Thus, $\beta$-hydride elimination from the methyl group occurs, preferentially, instead to give the desired allylic alcohol **20** as the major product, regenerating the proton source and palladium catalyst. Protonation of **24** is facilitated in nonpolar solvents such as toluene, as opposed to THF, which explains the solvent effect observed.



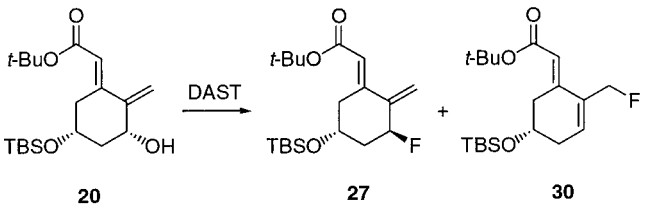

The allylic alcohol **20**, containing an exocyclic double bond, thus obtained, was then converted to the 1α-fluoro A-ring phosphine oxide **1** in 5 steps as shown in Scheme 4.

The reaction of the corresponding ethyl ester analogue of **20** (i.e. alcohol **9**, see Scheme 2 above) with DAST had been previously described to give the desired fluorinated product **10** in 60% yield, when carried out in 0.025 M dichloromethane solution with 8 equivalents of DAST at

**Scheme 4**




−95 °C.[6] In our hands under similar conditions (0.07 M dichloromethane solution at −90 °C), fluorination of *tert*-butyl ester **20** with 4 equivalents of DAST gave a mixture of the desired $S_n2$ product **27** and the corresponding $S_n2'$ product **30** in a ratio of 2.5:1. The former was then isolated in a modest 52% yield by chromatography.




To improve the isolated yield of **27**, many solvents were investigated. Trichloroethylene was found to be the best solvent, both in terms of a slightly better isomer ratio (2.9:1 at −78 °C in a 0.07 M solution of **20**), and the highest isolated yield of **27** (70% from pure **20**). Modified DAST reagents (dimethylaminosulfur trifluoride, bis(2-methoxyethyl)aminosulfur trifluoride,[18] and morpholinosulfur trifluoride) were examined under the same conditions, but gave inferior results (**27**:**30** ratios of 2.5:1, 2.2:1, and 2.0:1, respectively).

Concentration and excess reagent were also found to affect selectivity. With 4 equivalents of DAST, inferior ratio were obtained both at a higher (0.60 M; ratio 1.7:1) and lower (0.016 M, ratio 2.4:1) concentration. Furthermore, at a substrate concentration of 0.22 M, **27**:**30** ratios of 2.2:1, 2.5:1, and 2.6:1 were obtained with 1.5, 2.0 and 2.5 equivalents of DAST, respectively.

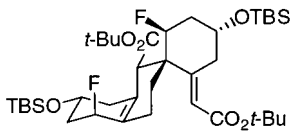
As high dilution and a large excess of the expensive reagent are not desirable for scale-up, larger scale reactions were carried out at concentration of 0.22 M of **20** in trichloroethylene using 2 equivalents of DAST, although these conditions were slightly inferior in terms of selectivity. From these reactions fluoride **27** was consistently obtained in 55% yield over the four steps from alcohol **16** without purification of intermediates (i.e. **17**, **18**, and **20**).

Fluoride **27** also undergoes Diels−Alder dimerization similar to alcohol **20**, especially in the solid state, but in contrast to **20** the reaction is highly regio- and stereoselective to give dimer **31** exclusively. The structure of **31**

(17) Alternatively, direct protonation of epoxide **18** is also possible, see, e.g.: Das, U.; Crousse, B.; Kesavan, V.; Bonnet-Delpon, D.; Bégué, J.-P. *J. Org. Chem.* **2000**, *65*, 6749. However, only the combination of an appropriate fluoro alcohol with palladium gave the desired reaction.

(18) Deoxo-Fluor was made available courtesy of Air Products & Chemicals, Inc.

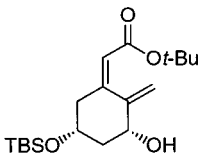
was also confirmed by X-ray crystallography.[19] Thus, concentration of solutions containing **27** were carried out as rapidly as possible at, or below, room temperature, and this product was then stored in a freezer to prevent its cyclodimerization.



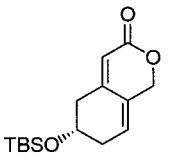

**31**

Alternative methods of fluorination were also studied: displacement of the corresponding mesylate with fluoride,[20] reactions with perfluoro-1-butanesulfonyl fluoride/DBU,[21] *N*,*N*-diisopropyl-1-fluoro-2-methylpropenamine,[22] etc. None of those methods, however, proved fruitful.

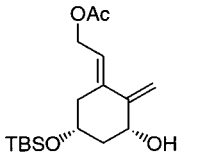
Fluorination of related compounds (*Z*)-ester **32**, (*E*)-allyl acetate **34**, and (*Z*)-allyl acetate **35** with DAST were also examined. The former gave lactone **33** exclusively. The allyl acetates, **34** and **35**, reacted to give 2.5:1 and 4:1 ratios of the desired $S_n2$ product and the undesired $S_n2'$ product, respectively. Although a better ratio was obtained from the latter, its preparation requires two additional steps and, therefore, it was deemed impractical.



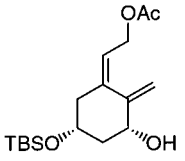

**32**




**33**

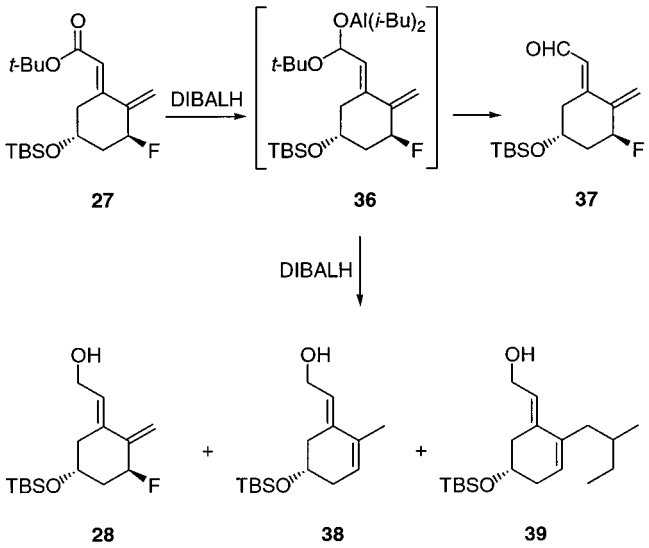



**34**




**35**

The reduction of the *tert*-butyl ester in **27** turned out to be surprisingly difficult, presumably due to the steric bulk of the *tert*-butyl group. With DIBALH in hexane, toluene, or dichloromethane at −70 °C, a relatively stable complex, presumably **36**, was formed, which gave aldehyde **37** upon hydrolysis. With 2.5 equiv of DIBALH at 0 °C, a mixture of the desired **28**, defluorinated **38**, and isobutylated **39**[23] was obtained. In hexane, only **38** and **39** were formed in a 1:1 ratio under these conditions. Alternative reducing agents proved ineffective.




**27** **36** **37**

**28** **38** **39**

It was subsequently found, however, that ester **27** was smoothly reduced to **28** when the reaction was run in THF,[24] at −40 °C for 5 h, leading to the formation of only a trace amount of **38**.

A solution of the crude (*E*)-allylic alcohol **28** in *tert*-butyl methyl ether was then irradiated with a 450W medium-pressure mercury lamp through uranium filter, in the presence of 10 mol % of 9-fluorenone[25] as the photosensitizer. The uranium filter was essential for clean conversion, as previously reported.[6] After chromatography to remove the sensitizer, the known[6] *(Z)*-allylic alcohol **29** was obtained in 90% yield over the two steps from **27**.

Finally, alcohol **29** was converted to the desired phosphine oxide **1** in 76% yield, through an improved two-step procedure, by a substitution reaction using triphosgene/pyridine, directly followed by displacement of the resulting allylic chloride with diphenylphosphine oxide sodium salt.[26]

In summary, we have developed a new efficient process for the preparation of 1α-fluoro A-ring phosphine oxide **1**, which is useful for the synthesis of **3** and other vitamin D analogues bearing the same A-ring fragment. The new process, which compares very favorably to the previous syntheses, gave the key precursor fluoride **27** in 9 steps and 32% overall yield, with only three isolations (two crystallizations and one chromatography), and without intermediate purification. Using this process, phosphine oxide **1** was ultimately prepared, via **27**, in 13 steps and 22% overall yield from (*S*)-carvone, with only two additional chromatographic purifications, bringing the total number of isolations to five. Further synthetic applications of the selective isomerization of dieneoxides using the catalytic system described herein are being investigated in our laboratories and will be reported in due course.

(19) For a recent study of stereoselectivity in Diels−Alder cycloadditions of allylic fluorides, see: Grée, D.; Laurent, V.; Grée, R.; Toupet, L.; Washington, I.; Pelicier, J.-P.; Villacampa, M.; Pérez, J.-M.; Houk, K. N. *J. Org. Chem.* **2001**, *66*, 2374. The thermal instability of the corresponding methyl ester analogue of **27** has been previously noted (see ref 8), but has been attributed to polymerization.

(20) Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166.

(21) Bennua-Skalmowski, B.; Vorbrüggen, H. *Tetrahedron Lett.* **1995**, *36*, 2611.

(22) Munyemana, F.; Frisque-Hesbain, A.-M.; Devos, A.; Ghosez, L. *Tetrahedron Lett.* **1989**, *30*, 3077.

(23) For related chemistry, see: Ooi, T.; Uraguchi, D.; Kagoshima, N.; Maruoka, K. *Tetrahedron Lett.* **1997**, *38*, 5679.

(24) Commercial 1 M DIBALH solution in THF (Aldrich) was found less effective in this reaction than a freshly prepared solution of DIBALH in THF.

(25) Fluorene, used previously as a sensitizer,[6] was less effective, requiring a large excess and prolonged irradiation.

(26) For an improved preparation of A-ring phosphine oxides from allylic alcohols, see: Daniewski, A. R.; Garofalo, L. M.; Kabat, M. M. *Synth. Commun.*, accepted for publication.

## Experimental Section

**General Materials and Procedures.** All reactions were performed in dried glassware under a positive pressure of nitrogen. Reaction extracts and chromatography fractions were concentrated using a rotary evaporator at approximately 10 Torr using a diaphragm pump, then at high vacuum to approximately 0.01 Torr using an oil pump. TLC analysis was performed using silica gel 60 $F_{254}$ precoated glass plates (EM Science), and detected by $UV_{254}$ or phosphomolybdic acid (PMA) stain. $^1H$ NMR spectra were recorded at 300 MHz. $CDCl_3$ was treated with basic alumina prior to use. Melting points were obtained on a capillary melting point apparatus and are uncorrected. A Polymetrics Laboratory Ozonator Model T-816 was used to generate ozonized air (shell pressure 6 PSIG; flow rate 4 LPM; 110V). Commercial grade reagents and solvents were used without purification, except as indicated. *m*-CPBA (57−86% Aldrich) was dried under high vacuum at room temperature for 24 h (ca. 24% weight loss upon drying) and the ratio of *m*-CPBA to *m*-chlorobenzoic acid (*m*-CBA) was determined by NMR analysis in $CDCl_3$. Diphenylphosphine oxide was prepared according to the literature procedure[27] with minor modifications as follows: Chlorodiphenylphosphine (92 g, Fluka 97%) was added to 1 N HCl (500 mL) and the mixture was stirred at room temperature overnight. Then, the mixture was extracted with methylene chloride and the organic layer was washed with saturated aqueous $NaHCO_3$ solution and saturated aqueous NaCl solution, dried over $Na_2SO_4$, and concentrated to give 74.6 g (88.5%) of diphenylphosphine oxide as a white solid of mp 55−56 °C.

***tert*-Butyl 2-[(5*S*,1*R*)-1-Hydroxy-2-methyl-5-(1-methylvinyl)cyclohex-2-enyl]acetate (13).** A THF (400 mL) solution of diisopropylamine (136 mL, 1.04 mol) was cooled to −40 °C. Butyllithium, 2.5 M in hexanes (416 mL, 1.04 mol) was added over 7 min, while maintaining the reaction temperature at −40 ± 10 °C. After stirring at that temperature for 5 min and then cooling to −70 °C, *tert*-butyl acetate (140 mL, 1.04 mol) was added over 8 min, while maintaining the temperature of the reaction mixture below −60 °C. After stirring at −70 °C for 20 min, cerium(III) fluoride (78.8 g, 0.40 mol) was added in one portion. Three minutes later, (*S*)-carvone (**4**) (125 mL, 0.80 mol) was added over 7 min, while maintaining the temperature of the reaction mixture below −60 °C. After stirring for 5 min at −70 °C, TLC analysis indicated complete reaction. The reaction was quenched by the addition of a 1:1 mixture of AcOH and EtOH (240 mL). An exotherm ensued that raised the temperature of the mixture to −30 °C. After the exotherm had subsided, the cooling bath was removed, and the resulting thick suspension was diluted with EtOH (300 mL) and EtOAc (400 mL), and allowed to warm to ambient temperature. The solid was removed by filtration through a pad of Celite and washed with EtOAc (3 × 300 mL). The combined filtrate and washes were washed sequentially with water (400 mL), 0.5 N HCl (400 mL), saturated aqueous $NaHCO_3$ solution (400 mL), and saturated aqueous NaCl solution (400 mL), dried over $Na_2SO_4$, and concentrated to dryness. Further drying at 70 °C/5 Torr gave 207 g (97.0%) of **13** as a pale yellow oil. TLC 4:1 hexanes−EtOAc; short-wave UV detection for **4** and PMA stain for **13**, both $R_f = 0.7$. Since both **4** and **13** have the same $R_f$ value, but the starting material **4** strongly absorbs short-wave UV light, the reaction was judged complete when TLC analysis showed only a faint spot for **4** under $UV_{254}$, and a strong one for **13** by staining with PMA. This material was used directly in the next step without further purification.

***tert*-Butyl 2-[(4*S*,1*R*,2*R*,6*R*)-2-Hydroxy-1-methyl-4-(1-methylvinyl)-7-oxabicyclo[4.1.0]hept-2-yl]acetate (14).** ***Caution!*** Since *tert*-butyl hydroperoxide is a strong oxidizing agent, the following precautions were taken: (1) an addition funnel was placed at a height to prevent the hot cyclohexane vapor from heating the hydroperoxide solution, (2) a stream of nitrogen was passed from the addition funnel, through the reaction flask, then the condenser in order to prevent the hot vapors from reaching the addition funnel, and (3) an explosion shield was placed in front of the reaction vessel. A solution of crude **13** as obtained above (207 g, 776 mmol) and vanadyl acetylacetonate (3.09 g, 11.7 mmol) in cyclohexane (770 mL) was heated to gentle reflux and *tert*-butyl hydroperoxide, 5.0−6.0 M in nonane (170 mL, 850−1020 mmol) was added (*Caution!*) over 90 min. The green solution turned deep red upon initiation of the addition and a mild exotherm ensued. After completion of the addition, the resulting orange-green solution was heated to reflux for 3 h with constant removal of water by a Dean−Stark condenser. The volume of the water in the trap increased by ca. 4 mL. TLC analysis indicated the presence of only a small amount of starting material. After cooling to below room temperature with an ice−water bath, 1 M sodium bisulfite solution (77 mL) and saturated aqueous $NaHCO_3$ solution (150 mL) were added. After 5 min, an iodine-starch paper test indicated no peroxide to be present. The organic layer was separated, then washed with saturated aqueous $NaHCO_3$ solution (3 × 150 mL) and saturated aqueous NaCl solution (150 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure at <30 °C bath temp. Further drying at room temperature under high vacuum for 2 h gave 247 g (overweight) of crude **14**, containing nonane, as a pale yellow solid. TLC 3:1 hexanes−EtOAc; PMA stain; $R_f$ **13** = 0.80 and $R_f$ **14** = 0.55.

***tert*-Butyl 2((4*S*,1*R*,2*R*,6*R*)-4-Acetyl-2-hydroxy-1-methyl-7-oxabicyclo[4.1.0]hept-2-yl)acetate (15).** Crude **14** as obtained above (247 g, ca. 776 mmol) and $NaHCO_3$ (24 g, 286 mmol) in MeOH (1.8 L) was cooled with a dry ice/acetone bath, the nitrogen inlet-tube was replaced with a gas dispersion tube with a porous fritted glass tip (25−50 μ), and the gas outlet-tube was connected to a trap, through a wide 4 mm I. D. tube immersed in a 1 M solution of potassium iodide (2 L). Then, ozonized air (4 LPM) was continuously passed through the reaction mixture at −70 °C. The reaction turned pale blue after 5 h. After ozonized air was passed for an additional 15 min through the mixture at a reduced flow rate of 1 LPM, excess ozone was removed by purging with air (4 LPM) for 25 min. The resulting white suspension was treated with dimethyl sulfide (75 mL, 1.02 mol) and allowed to warm to room temperature overnight. An iodine-starch paper test indicated no peroxide to be present. The insoluble inorganic salts were removed by filtration and washed with EtOAc (100 mL). The combined filtrate and washes were concentrated under reduced pressure (bath temperature ≤ 30 °C) to remove essentially all of the MeOH. The resulting yellow, milky residue was partitioned between EtOAc (1 L) and water (300 mL). The aqueous layer was separated and extracted with EtOAc (50 mL). The combined organic extracts were washed with saturated aqueous NaCl solution (300 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure (bath temperature ≤ 35 °C). The resulting pale yellow oil was dissolved in EtOAc (150 mL) and hexane (600 mL) was added. The resulting suspension was then stored in the refrigerator overnight. The solids were collected by filtration, washed with cold hexanes−EtOAc (4:1) mixture (400 mL), and dried by suction, then under high vacuum at room temperature to give 155.9 g (68.5% over 3 steps) of **15** as a white solid (mp 92−94 °C). The combined mother liquor and washes were washed with saturated aqueous $NaHCO_3$ solution (3 × 100 mL) and saturated aqueous NaCl solution (100 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure (bath temperature ≤ 35 °C). The residue was diluted with EtOAc (40 mL) and hexane (280 mL) was added. The resulting slightly cloudy solution was stored in the refrigerator over the weekend. The resulting solid was collected by filtration, washed with a cold hexanes−EtOAc (7:1) mixture (4 × 40 mL), and dried by suction, then under high vacuum at room temperature to give to give 18.3 g (8.0% over 3 steps) of a second crop of **15** as a white solid (mp 91−93 °C). The two crops were combined to give a total yield of 174 g (76.5% over 3 steps) of **15**. TLC 1:1 hexanes−EtOAc; PMA stain; $R_f$ **14** = 0.70 and $R_f$ **15** = 0.50.

(27) Quin, L. D.; Montgomery, R. I. *J. Org. Chem.* **1963**, *28*, 3315.

***tert*-Butyl 2((4*S*,1*R*,2*R*,6*R*)-4-Acetyloxy-2-hydroxy-1-methyl-7-oxabicyclo[4.1.0]hept-2-yl)acetate. 15** (82.2 g, 289 mmol), *m*-CPBA, 91% (115 g, 606 mmol) and a 3:1 hexanes−EtOAc mixture (840 mL) were combined in a reaction flask. Upon mixing, an endotherm ensued and the temperature of the mixture decreased from 20 °C to 13 °C. The white suspension was stirred at room temperature (ca. 20 °C) for 3 days (***Note:*** *Reaction temperatures higher than 25 °C result in increased formation of byproducts*). NMR analysis indicated ∼98% conversion and a *m*-CPBA/*m*-CBA ratio of ∼2:3. The reaction was cooled to 5 °C in an ice−water bath and a 2.5 M $K_2CO_3$ solution (145 mL, 435 mmol) was added dropwise to the mixture at ≤ 12 °C over 8 min. Then, a 2 M sodium sulfite solution (180 mL, 360 mmol) was added over 25 min, while maintaining the temperature of the mixture below 12 °C. The cold bath was removed and the mixture was stirred at ambient temperature for 90 min. NMR analysis of the organic layer indicated the presence of a 1:4 mixture of *m*-CPBA to product. Then, dimethyl sulfide (6 mL, 82 mmol) was added and the resulting thin suspension was stirred for 15 min. An iodine-starch paper test then indicated complete reduction. The solid was removed by filtration and washed with EtOAc (100 mL). The filtrate and washes were combined and the phases were separated. The organic phase was washed with a 10% $KHCO_3$ solution (30 mL) and dried over magnesium sulfate. The aqueous phases were combined and back-extracted with EtOAc (200 mL), and the organic extract was washed with 10% $KHCO_3$ solution (20 mL) and dried over magnesium sulfate. The back-extraction process was repeated two more times. All of organic extracts were combined and concentrated at ≤ 30 °C under reduced pressure. The residue was dried under high vacuum at room temperature overnight to give 81.3 g (93.6%) of the crude acetate as a colorless oil. TLC 1:1 hexanes−EtOAc; PMA stain; $R_f$ **15** = 0.50 and acetate intermediate $R_f$ = 0.55.

***tert*-Butyl 2-((4*S*,1*R*,2*R*,6*R*)-2,4-Dihydroxy-1-methyl-7-oxabicyclo[4.1.0]hept-2-yl)acetate (16).** The crude product obtained above (81.3 g, 270 mmol) was dissolved in MeOH (270 mL). The solution was cooled for 30 min with an ice water bath, then a 25% NaOMe solution in MeOH (9.3 mL, 40.5 mmol) was added dropwise over 10 min. After stirring at 0 °C for 4 h, TLC analysis indicated complete reaction. The reaction mixture was quenched with AcOH (3.0 mL, 52.6 mmol), then concentrated at ≤ 30 °C under reduced pressure. The resulting milky residue was dried under high vacuum at room temperature for 30 min, then partitioned between EtOAc (500 mL) and a 5% $KHCO_3$ solution (50 mL). The layers were separated, and the organic phase was washed with a 5% $KHCO_3$ solution (50 mL) and saturated aqueous NaCl solution (50 mL). The combined aqueous phases were extracted with EtOAc (2 × 100 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated at ≤ 35 °C under reduced pressure. The resulting pale yellow oil (ca. 76 g) was dissolved in EtOAc (70 mL) and crystallization was induced by the addition of a seed crystal. Then, hexane (350 mL) was gradually added, and the resulting suspension was allowed to stand at room temperature overnight. The solids were collected by filtration, washed with a 5:1 hexane−EtOAc mixture (2 × 70 mL) and dried by suction, then under high vacuum at room temperature to give 54.8 g (78.4%) of **16** as a white solid (mp 91−92 °C). The combined mother liquor and washes were diluted with hexane (300 mL) and stored in the freezer overnight. The supernatant was removed by decantation, and the residue was dissolved in EtOAc (100 mL). The organic solution was washed with a 5% $KHCO_3$ solution (20 mL) and saturated aqueous NaCl solution (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure (bath temperature ≤ 35 °C). The residue (4.3 g) was dissolved in EtOAc (5 mL), and crystallization was induced by the addition of a seed crystal. Hexane (25 mL) was then gradually added, and the resulting suspension was allowed to stand at room temperature overnight. The solids were collected by filtration, washed with a 5:1 hexanes−EtOAc mixture (12 mL) and dried by suction, then under high vacuum at room temperature to give 2.5 g (3.6%) of a second crop of **16** as an off-white solid (mp 91−92 °C). The two crops were combined to give a total yield of 57.3 g (76.7% over 2 steps) of **16**. TLC 1:1 hexanes−EtOAc; PMA stain; $R_f$ **16** = 0.25.

***tert*-Butyl 2-[(4*S*,1*R*,2*R*,6*R*)-2-Hydroxy-1-methyl-7-oxa-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-bicyclo[4.1.0]-hept-2-yl]acetate (17). 16** (28.6 g, 111 mmol), imidazole (20.5 g, 301 mmol), *tert*-butylchlorodimethylsilane (19.6 g, 130 mmol), and THF (170 mL) were combined in a reaction flask. An initial mild exotherm (10 to 12 °C) subsided quickly. The mixture was then stirred overnight. TLC analysis indicated complete reaction. The solids were removed by filtration using a sintered glass funnel and washed thoroughly with THF (200 mL). The combined, colorless filtrate and wash were concentrated under reduced pressure at 25 °C, then under high vacuum for 30 min to yield 48.7 g (overweight) of crude **17** as a white solid. TLC 1:1 hexanes−EtOAc; PMA stain; $R_f$ **16** = 0.16 and $R_f$ **17** = 0.79. $^1$H NMR analysis indicated the presence of ca. one equivalent of protonated imidazole. This material was used directly in the next step without further purification.

***tert*-Butyl (2*E*)-2-[(1*S*,4*R*,6*R*)-1-Methyl-7-oxa-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-bicyclo[4.1.0]hept-2-ylidene]acetate (18).** Pyridine (136 mL, 1.68 mmol, water content ≤ 0.02%) was cooled in an ice water bath and thionyl chloride (13.6 mL, 186 mmol) was added. The initial exotherm to 27 °C was allowed to subside and the solution was stirred at ambient temperature for 40 min. The resulting yellow solution was then cooled to −34 °C and a solution of crude **17** as obtained above (48.7 g, 111 mmol in theory) in THF (86 mL) was added dropwise over 1 h at a rate to maintain the reaction temperature below −25 °C. The reaction mixture was allowed to warm to 0 °C over 100 min, then poured into a mixture of saturated aqueous $NaHCO_3$ solution (700 mL) and hexanes (350 mL). The resulting mixture was stirred for 30 min until no noticeable gas evolution was observed. The hexane layer was separated, washed with 1 M citric acid (350 mL), dried over $Na_2SO_4$, and concentrated to dryness under reduced pressure to yield 40.7 g (overweight) of **18** as a colorless oil. $^1$H NMR analysis indicated that this material contained some silyl byproducts, and was approximately 90% pure. TLC 9:1 hexanes−EtOAc; short-wave UV detection and PMA stain; $R_f$ **17** = 0.04 and $R_f$ **18** = 0.21. This material was used directly in the next step without further purification.

***tert*-Butyl (2*E*)-2-[(3*R*,5*R*)-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-hydroxy-2-methylene-cyclohexylidene]-acetate (20).** Tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (570 mg, 0.551 mmol) and triphenylphosphine (1.45 g, 5.55 mmol) were combined in a reaction flask. The flask was evacuated and refilled with nitrogen three times, then toluene (35 mL) was added via a syringe. The resulting deep purple mixture was stirred at ambient temperature for 1 h to give a yellow slurry (***Note:*** *It is critical to allow enough time, usually 30 min to 1 h, for the formation of the active catalyst before proceeding with the reaction. A color change from deep purple to yellow, as well as disappearance of purple particles indicate complete catalyst formation. Preparation in a more dilute solution is not recommended as it makes it more difficult for the active catalyst to form*). Then, 1,3-bis-(1,1,1,3,3,3-hexafluoro-2-hydroxypropyl)benzene (0.54 mL, 2.18 mmol) was added. The slurry became red-orange. After three minutes of stirring at ambient temperature (19 °C), a solution of crude **18** as obtained above (40.7 g, 110 mmol in theory) in toluene (160 mL) prepared under nitrogen, was added to the catalyst solution via cannula using a slight positive nitrogen pressure. After 10 minutes of stirring at ambient temperature, under a slight positive pressure of nitrogen, the reaction mixture was heated to 32 °C overnight, then to 35 °C for 2 h (***Note:*** *While 3% of the starting material **18** was still detected by HPLC, see below, reaction at 35 °C overnight gave complete conversion*). The reaction mixture was rapidly concentrated on a rotary evaporator at 25 °C (bath temperature), under reduced pressure, and the residue was dried under high vacuum for 30 min to give 44.8 g (overweight) of crude **20** as a reddish oil (***Note:*** *The product should not be allowed to stand at ambient temperature any longer than necessary as dimerization via Diels−Alder reaction occurs upon standing in a concentrated solution or, even more rapidly, in solid state. In the procedure*

*described, the concentration and drying process took ca. 90 min. The product may be stored in the freezer, where it partially solidifies, without deterioration*). TLC 3:1 hexanes−EtOAc; short-wave UV detection and PMA stain; $R_f$ **18** = 0.74, $R_f$ **20** = 0.45 and $R_f$ **21** = 0.50. HPLC analysis was performed on a Nucleosil 5$\mu$m, 4.6 × 2500 mm column with 2% 2-propanol in hexane at 0.5 mL/min. The percentages given are the area percentages of the corresponding peaks detected at 220 nm: $R_t$ **18** = 7.6 min, $R_t$ **21** = 8.8 min, $R_t$ = 8.9 min (dibenzylideneacetone), $R_t$ **20** = 12.1 min, and $R_t$ **23** = 18 min. HPLC analysis indicated this material, **20**, to be ca. 87% pure with ca. 3% of the starting material **18**, less than 1% of the ketone byproduct **21** and ca. 3% of the dimer **23** present. This material was used immediately in the next step without further purification.

***tert*-Butyl (2*E*)-2-[(3*S*,5*R*)-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-fluoro-2-methylene-cyclohexylidene]-acetate (27).** Diethylaminosulfur trifluoride (33 mL, 0.25 mol) was dissolved in trichloroethylene (290 mL). After cooling to −70 °C, a solution of crude **20** as obtained above (44.7 g, 111 mmol in theory) in trichloroethylene (210 mL) was added over 80 min, while maintaining the temperature of the reaction mixture below −70 °C. After stirring at −70 °C for 15 min, the mixture was allowed to warm to −50 °C and MeOH (30 mL) was added in one portion to quench the reaction. The resulting mixture was diluted with hexane (850 mL), washed with water (2 × 300 mL) and saturated aqueous $NaHCO_3$ solution (300 mL), dried over $Na_2SO_4$, and rapidly concentrated on a rotary evaporator at ≤ 30 °C (bath temperature) (***Note:*** *The product should not be allowed to stand at ambient temperature any longer than necessary as dimerization via Diels−Alder reaction occurs upon standing in a concentrated solution or, even more rapidly, in the solid state*). The residue was dried under high vacuum for 30 min, then purified by chromatography on silica gel 60 (1.5 kg), eluting with 4:1−2:1 hexane:dichloromethane. The appropriate fractions were combined and concentrated on a rotary evaporator at ≤ 30 °C (bath temperature). The residue was immediately placed in a freezer while it crystallized. Since the crystallization is exothermic, it should be carried out at a low temperature in order to prevent the Diels−Alder dimerization. The resulting solid was dried under high vacuum at room temperature for 1 h to give 21.6 g (54.7% yield over 4 steps from **16**) of **27** as a white solid. TLC 8:1 hexanes−EtOAc; short-wave UV detection and PMA stain; $R_f$ **20** = 0.3, $R_f$ **27** = 0.8 and $R_f$ **30** = 0.75.

**(2*E*)-2-[(3*S*,5*R*)-5-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-3-Fluoro-2-methylenecyclohexylidene]-ethanol (28).** **27** (10.3 g, 28.9 mmol) was dissolved in THF (70 mL), freshly distilled from sodium/benzophenone ketyl. After cooling to −70 °C, a solution (freshly prepared at −10 °C) of DIBALH, neat (13.4 mL, 75.2 mmol) in THF (75 mL) was added over 20 min via a cannula, while maintaining the temperature of the reaction mixture between −68 and −70 °C. This mixture was then stirred under nitrogen at −60 to −50 °C for 1.5 h and at −50 to −40 °C for 1h, then at −42 °C for 5 h. After this time, TLC analysis indicated the presence of very small amounts of **27** and the defluorinated byproduct **38**. The reaction mixture was quenched by the slow addition of water (15 mL) at −40 °C, then allowed to warm to 25 °C (occasional cooling is required to prevent the temperature of the mixture from exceeding 25 °C). After stirring at room temperature for 10 min, a gel formed. Thus, the mixture was diluted with EtOAc (100 mL), then stirred at room temperature for 1.5 h. Solids were removed by filtration using a pad of Celite and washed thoroughly with EtOAc (350 mL). The combined filtrate and washes were concentrated under reduced pressure at ≤ 30 °C (bath temperature) and the residue was dried under high vacuum for 1 h to give 8.33 g (100.3%) of crude **28** as a colorless oil. This product is relatively unstable at room temperature and should be stored in the freezer. TLC 4:1 hexanes−EtOAc; short-wave UV detection and PMA stain; $R_f$ **27** = 0.9, $R_f$ **28** = 0.3, $R_f$ **37** = 0.6 and $R_f$ **38** = 0.33.

**(2*Z*)-2-[(3*S*,5*R*)-5-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-3-Fluoro-2-methylenecyclohexylidene]-ethanol (29).**[6] A 500 mL photoreaction vessel equipped with a cooling jacket, Pyrex immersion well, nitrogen inlet tube (immersed deep into the reaction mixture) and outlet-bubbler, was charged with crude **28** as obtained above (8.33 g, 28.9 mmol), *tert*-butyl methyl ether (450 mL), and 9-fluorenone (524 mg, 2.91 mmol). While water and a 20 °C coolant were rapidly passed through the well and the cooling jacket, respectively, the above solution was irradiated through a uranium filter with a 450 W medium pressure mercury lamp. During the photolysis, nitrogen was continuously bubbled through the reaction solution via the inlet tube. After 6 h of irradiation, NMR analysis indicated complete reaction. The reaction mixture was concentrated to dryness to give 9.13 g of crude product as a yellow oil, which was subjected to chromatography on silica gel 60 (300 g). First, the column was eluted with 95:5 hexanes−EtOAc (2.5 L) to remove the sensitizer. Then, the column was further eluted with 9:1 hexanes−EtOAc (1 L), 8:2 hexanes−EtOAc (1 L), and 7:3 hexanes−EtOAc (1 L). The appropriate fractions (the 8:2 hexanes−EtOAc eluate) were combined and concentrated under reduced pressure. Further drying under high vacuum for 1 h gave 7.43 g (89.8%) of **29** as a colorless oil. This product is relatively unstable at room temperature and should be stored in the freezer. TLC 4:1 hexanes−EtOAc; short-wave UV detection and PMA stain; **28** and **29** both $R_f$ = 0.3, and fluorenone $R_f$ = 0.5.

**[[(1*R*,3*Z*,5*S*)-3-(2-chloroethylidene)-5-Fluoro-4-methylenecyclohexyl]oxy](1,1-dimethylethyl)-dimethylsilane.**[6] ***Caution!*** *This reaction should be performed in a well ventilated hood.* **29** (8.07 g, 28.2 mmol), hexanes (150 mL), and triphosgene (4.18 g, 14.1 mmol) were combined in a reaction flask. The resulting solution was then cooled to 0 °C with an ice-acetone bath and a solution of pyridine (4.50 mL, 55.6 mmol) in hexanes (20 mL) was added over 30 min. After stirring at 0 °C for 30 min, the cooling bath was removed and the resulting pale-yellow reaction mixture was stirred at room temperature for 30 min. Then, the reaction mixture was diluted with hexanes (250 mL) and washed with saturated copper (II) sulfate solution (3 × 200 mL). The combined aqueous washes were back-extracted with hexanes (2 × 100 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated to dryness on a rotary evaporator to give 9.0 g (overweight) of crude product as a pale yellow oil. This material was used immediately in the next step without further purification. This product is relatively unstable at room temperature and should be stored in the freezer. TLC 4:1 hexanes−EtOAc; short-wave UV detection and PMA stain; $R_f$ **29** = 0.3, and chloride product $R_f$ = 0.9.

**[(2*Z*)-2-[(3*S*,5*R*)-5-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-3-Fluoro-2-methylenecyclohexylidene]-ethyl]diphenylphosphine oxide (1).**[6] DMF (50 mL) and sodium hydride, 60% dispersion in mineral oil (1.33 g, 33.1 mmol) were combined in a reaction flask. While cooling with a water bath (10 °C), diphenylphosphine oxide (6.70 g, 33.1 mmol) was added in small portions over 15 min. The water bath was then removed and the resulting yellow solution was stirred at room temperature for 30 min. After cooling to −60 °C with a dry ice acetone bath, a solution of the crude product from the previous step (9.0 g, 28.2 mmol in theory) in DMF (20 mL) was added dropwise, via a syringe, over 15 min, while maintaining the temperature of the reaction mixture below −50 °C. The reaction mixture was stirred at −60 °C for 2 h, then allowed to warm to room temperature over 1 h. The reaction mixture was diluted with diethyl ether (600 mL) and washed with water (600 mL). The combined aqueous washes were extracted with diethyl ether (200 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated under reduced pressure to give a white solid. This crude product was recrystallized from diisopropyl ether (25 mL). The resulting solid was collected by filtration, washed with cold diisopropyl ether (5 mL) and dried under high vacuum to give 7.93 g (59.8%) of **1** as a white solid. The mother liquor was concentrated and the residue was subjected to chromatography on silica gel, eluting with hexanes−EtOAc (7:3 to 1:1). The appropriate fractions were combined and concentrated to dryness to give an additional 2.22 g (16.7%) of **1**. Thus, the total yield of **1** was 10.1 g (76.5% overall yield from **29**). TLC

1:1 hexanes−EtOAc; short-wave UV detection and PMA stain; $R_f$ **29** = 1.0 and $R_f$ **1** = 0.28.

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**Supporting Information Available:** $^1$H NMR spectra of 13 compounds, obtained as indicated in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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