Synthesis of Nonracemic Dimethyl α-(Hydroxyfarnesyl)phosphonates via Oxidation of Dimethyl Farnesylphosphonate with (Camphorsulfonyl)oxaziridines

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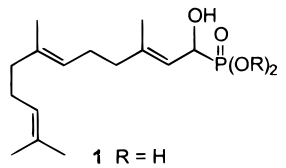
Several strategies for synthesis of nonracemic dimethyl α-(hydroxyfarnesyl)phosphonate and the parent phosphonic acid have been explored. Separation of diastereomeric derivatives prepared by esterification of racemic α-hydroxy phosphonate with (*S*)-(+)-*O*-methylmandelic acid was possible, and these diastereomers could be assigned absolute stereochemistry on the basis of literature precedent. However, hydrolysis to the α-hydroxy phosphonic acid was accompanied by extensive isomerization. Addition of a nonracemic phosphonamidite to farnesal also gave nonracemic material, but again hydrolysis was problematic. Oxidation of dimethyl farnesylphosphonate anion with nonracemic (camphorsulfonyl)oxaziridines was shown to be regio- and stereoselective for formation of the α-hydroxy phosphonate. Enantiomeric excess of ~70% ee was established by conversion of the oxidation products to their (*S*)-(+)-*O*-methylmandelate derivatives. Although hydrolysis of these methyl esters was accompanied by extensive racemization, both enantiomers of α-(hydroxyfarnesyl)-phosphonic acid were obtained in low ee by this strategy.

Various α-hydroxy phosphonates have activity as inhibitors of a diverse group of enzymes, including renin,[1] enolpyruvylshikimate-3-phosphate (EPSP) synthase,[2] farnesyl protein transferase (FPTase),[3] and HIV protease.[4] Some of the active α-hydroxy phosphonates have been studied only in racemic form, even though the absolute configuration at the α position of substituted phosphonic acids has been shown to influence their biological properties in some cases.[5] A number of strategies have been reported for preparation of nonracemic α-hydroxy phosphonates.[6] The more prominent of these synthetic methods include addition of nonracemic phosphorus reagents to aldehydes[7] or use of chiral catalysts[8] to control absolute stereochemistry when achiral phosphorus reagents are used. Enantioselective reductions of α-keto phosphonates[9] and enzymatic resolution of racemic mixtures of α-hydroxy phosphonates[10] also have been reported. Finally, [2, 3]-Wittig rearrangements of nonracemic α-allylic heterosubstituted methylphosphonates and phosphonamidates have been developed which provide access to some nonracemic α-hydroxy phosphonates.[11] Although each of these strategies has proven successful with specific substrates, a completely general procedure for synthesis of nonracemic α-hydroxy phosphonates has not yet been developed.

An α-hydroxy phosphonate of particular interest to our studies of RAS farnesylation[12] is α-(hydroxyfarnesyl)-phosphonic acid (**1**), a compound which in its racemic



1 R = H
2 R = CH_3

form has been shown to inhibit FPTase with an IC_{50} of 30 nmol.[3] Given the widespread knowledge of the importance of stereochemistry to biological activity,[13] it was somewhat surprising that racemic α-(hydroxyfarnesyl)-phosphonic acid was used in all reported studies on the effect of this compound on FPTase. Thus, preparation of the individual enantiomers of compound **1** became our objective. After examination of several well-precedented strategies failed to provide the target enantiomers, further elaboration[14] of a strategy involving stereocon-

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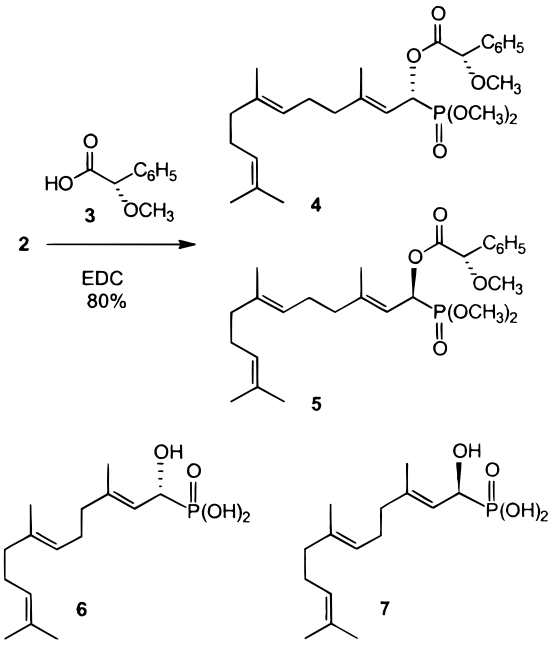
trolled oxidation of alkyl phosphonate anions was pursued. The results of these efforts form the basis of this article.

Results and Discussion

Racemic α-(hydroxyfarnesyl)phosphonic acid (**1**) can be prepared easily via addition of dimethyl phosphite anion to farnesal and subsequent hydrolysis of the methyl esters, as first reported by Pompliano and co-workers.[3] The individual enantiomers of the product would be available through separation of diastereomeric ester derivatives and subsequent hydrolysis. In 1994, the use of *O*-methylmandelate esters[15] for determination of enantiomeric purity and absolute configuration of several α-hydroxy phosphonates was reported by Spilling and coworkers.[16] They also noted that the resulting diastereomers could be separated by chromatography and that the absolute configuration of the α-carbon could be assigned through ^{1}H NMR methods once both diastereomers were in hand. To explore an extension of this method, racemic phosphonate **2** was treated with (*S*)-(+)-*O*-methylmandelic acid (**3**) and the carbodiimide EDC[17] to provide *O*-methylmandelate diastereomers **4** and **5**. These diastereomers were cleanly separated by column chromatography into the less polar isomer and the more polar isomer.



Comparison of the ^{1}H and ^{31}P NMR spectra of diastereomers **4** and **5** revealed a number of significant differences (Table 1). In the ^{1}H NMR spectrum of the less polar isomer (**4**), the hydrogens of the phosphonate methoxy groups showed an upfield shift of ~0.3 to 0.4 ppm relative to the parent α-hydroxy phosphonate, in accord with the literature precedent.[16a] The separation of the resonances for the two methoxy signals also increased from 0.02 ppm in the parent alcohol (**2**) to 0.16 ppm in the less polar isomer. In the spectrum of the more polar isomer (**5**), the phosphonate methoxy signals were shifted slightly upfield of the parent alcohol (~0.1 ppm) but were still well downfield of the less polar isomer (~0.2 to 0.3 ppm). The resonances for the C-2 hydrogen of the farnesyl chains were shifted in the opposite sense. In the more polar isomer, the resonance for this vinylic hydrogen was shifted upfield at δ 5.00−5.15, overlaid with resonances from the other vinylic hydrogens. In the less polar isomer, the C-2 vinylic hydrogen was shifted downfield to δ 5.25−5.33, quite distinctly downfield of the other vinylic resonances. Finally, the ^{31}P NMR data displayed trends similar to those observed with the methoxy resonances. The less polar isomer had an upfield ^{31}P NMR resonance at 21.5 ppm, whereas the more polar isomer was observed downfield at 21.9 ppm.

Table 1. ^{1}H NMR Shifts of Racemic Dimethyl α-(Hydroxyfarnesyl)Phosphonate (2) and the Corresponding *O*-Methylmandelates (4) and (5)

	α-hydroxy phosphonate	less polar *O*-methylmandelate (**4**)		more polar *O*-methylmandelate (**5**)	
^{1}H	(**2**) δ	δ	$\Delta\delta^a$	δ	$\Delta\delta^a$
CH_3O	3.82	3.54	0.28	3.74	0.08
CH_3O'	3.80	3.38	0.42	3.71	0.11
C(2)-H	5.34	5.30	0.04	5.00	0.34

[a] The $\Delta\delta$ refers to the difference in chemical shift between the parent alcohol and each mandelate derivative.

On the basis of shifts observed in the ^{1}H and ^{31}P NMR spectra of diastereomers **4** and **5**, the absolute stereochemistry of the α-carbon could be assigned. These chemical shift differences can be traced to deshielding effects of the phenyl group which differ in the two diastereomers. By analogy with previous assignments,[15,16a] which have been confirmed by a diffraction analysis of one phosphonate,[16a] the less polar diastereomer derived from dimethyl α-(hydroxyfarnesyl)phosphonate (**2**) and (*S*)-(+)-*O*-methylmandelic acid (**3**) was assigned as the (*R*,*S*)-diastereomer **4**, and the more polar compound was assigned as the (*S*,*S*)-diastereomer **5**.

Once the diastereomers were identified, hydrolysis of the mandelate and phosphonate esters would afford the desired enantiomers **6** and **7**. Cleavage of mandelate esters from α-hydroxy carboxylic acids has been accomplished through transesterification with methanol and potassium carbonate to obtain the free alcohol without racemization.[15a] However, when these conditions were applied with mandelates **4** and **5**, all isolated material had undergone isomerization. Transesterification also was attempted by treatment with a Lewis acid and isopropyl alcohol, as previously applied to some carboxylic acids,[18] but in our case, only decomposition was observed.

Because hydrolysis of the mandelate esters proved problematic, an alternative method for synthesis of nonracemic α-(hydroxyfarnesyl)phosphonic acid (**1**) was examined. The reported addition of a nonracemic phosphonamidite to cinnamaldehyde was one of the few strategies known to give 1,2-addition to a conjugated

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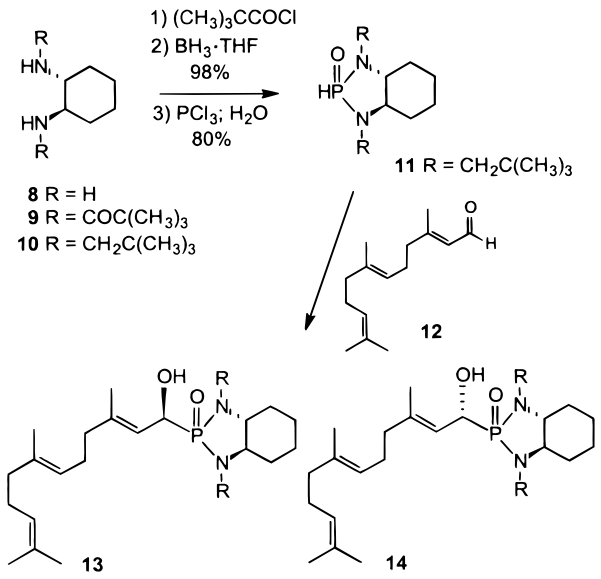
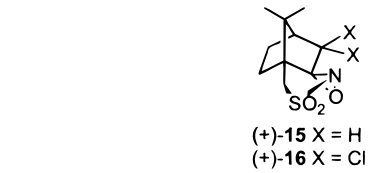
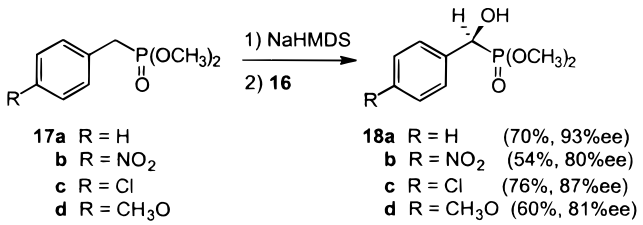
aldehyde, producing an allylic α-hydroxy phosphonamide in good yield with good diastereoselectivity.[7] The resulting phosphonamide was then converted to the corresponding phosphonic acid by acid-catalyzed hydrolysis. To examine this approach, the desired *N*,*N*′-neopentyl-substituted phosphonamidite[19] (**10**) was prepared by a variation of the literature synthesis.[7] Thus, (1*R*,2*R*)-*trans*-diaminocyclohexane[20] (**8**) underwent condensation with 2 equiv of pivaloyl chloride to give the expected diamide (**9**), followed by reduction with borane−THF complex[21] to provide the *N*,*N*′-bisneopentyl derivative **10** in virtually quantitative yield. Compared to the reported reductive amination of diamine **8** with trimethylacetaldehyde (83% yield),[19] amide formation and subsequent reduction required one additional step, but compound **10** was produced in greater purity and somewhat better yield through the two-step sequence.

After diamine **10** was converted to phosphonamidite **11** under standard conditions,[19] treatment with base and *trans*,*trans*-farnesal (**12**) provided phosphonamides **13** and **14** in 58% yield, as a 10.6:1 ratio of diastereomers on the basis of inspection of the ^{31}P NMR spectrum of the product. Although complete separation of the diastereomeric products was not readily achieved by chromatography, diastereomeric ratios as high as 52:1 were obtained. Assuming that the stereochemistry of this addition follows literature precedents,[7] the (*R*,*R*,*S*)-diastereomer would be the major product when the (*R*,*R*)-diamide is employed. Unfortunately, attempted hydrolysis of the phosphonamides by reaction with 4 M HCl in dioxane resulted only in decomposition. Thus, we were encouraged to develop a new approach to synthesis of the nonracemic α-(hydroxyfarnesyl)phosphonic acids.



A well-known strategy for introduction of the hydroxyl group at an activated methylene position is based on reaction of oxaziridines with the corresponding enolate.[22] Stereocontrolled oxidations have been obtained with nonracemic (camphorsulfonyl)oxaziridine (**15**)[23] and 8,8-disubstituted derivatives such as the dichloro compound **16**,[24] and these reagents are readily prepared in large quantities.[25] We have found that several benzyl phosphonates (e.g., **17a**−**d**) undergo enantioselective hydroxylation upon treatment of the corresponding anions with nonracemic oxaziridines, giving the corresponding α-hydroxyphosphonates **18a**−**d** in reasonable yields and ee's.[14] Although a parallel reaction can be readily envisioned for conversion of a farnesyl phosphonate to its α-hydroxy derivative, this application would have to address an issue of α versus γ reactivity that is not likely to complicate oxidations of benzyl phosphonates.





Dimethyl farnesylphosphonate (**19**), readily prepared by an Arbuzov reaction of farnesyl bromide and trimethyl phosphite,[26] was treated with base and an oxaziridine under various conditions to gauge the extent of regio- and enantioselectivity possible in oxidation of an allylic phosphonate (Table 2). In all cases, oxidation was favored at the α position, as definitively established by comparison of the reaction product with racemic **1** prepared by addition of dimethyl phosphite to farnesal.[12a] Nonracemic products also were produced in all cases, but both low yields and low rotations were observed with the oxaziridine (+)-**15**. Even though the yields were still modest, the dichloro oxaziridine (+)-**16** resulted in product with significantly higher optical rotation, parallel to reports on oxidation of enolates,[24,25,27] as well as our previous study with benzyl phosphonate hydroxylation.[14] As expected, an enantiomeric product of almost equal rotation was obtained when the (−)-enantiomer of reagent **16** was employed in the oxidation of the dimethyl farnesylphosphonate anion. However, because there is no previous description of the enantiomers **20** and **21**, the enantio-

(19) Koeller, K. J. Ph.D. Thesis, University of Missouri−St. Louis, 1994.

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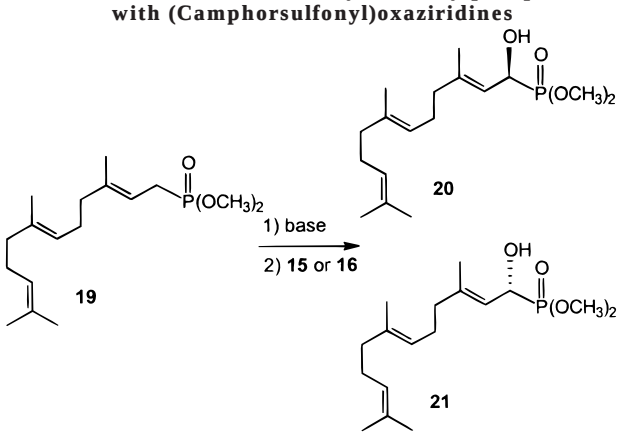
Table 2. Oxidation of Dimethyl Farnesylphosphonate with (Camphorsulfonyl)oxaziridines



entry	base	T (°C)	15/16	% yield	opt. rot.
1	*n*-BuLi	−75	(+)-**15**	50	−10.5
2	*n*-BuLi	−75	(+)-**15**	52	−8.1
3	LDA	−70	(+)-**15**	67	−9.9
4	NaHMDS	−90	(+)-**16**	51	−26.4
5	LDA	−75	(+)-**16**	50	−22.1
6	LDA	−75	(−)-**16**	46	+24.4
7	NaHMDS	−90	(−)-**16**	35	+19.9

meric excess could not be established directly from the optical rotations.

Diastereomeric excess was readily established by conversion of these reaction products to their (*S*)-*O*-methylmandelate derivatives **4** and **5** and integration of the ^{31}P NMR spectrum. On the basis of this analysis, the sample with the strongest negative rotation (entry 4, Table 2) was found to be a 6.2:1 ratio of the (*S*,*S*)- and (*R*,*S*)-diastereomers, indicating an ee of approximately 72%. By a parallel analysis, the sample of largest positive rotation (entry 6) was found to give a 1:5.3 ratio of the (*S*,*S*)- and (*R*,*S*)-diastereomers, consistent with an ee of ca. 68%.

To obtain the desired enantiomers of α-(hydroxyfarnesyl)phosphonic acid (**1**), samples of the phosphonate esters **20** and **21** were treated with TMSBr and collidine, followed by hydrolysis with aqueous acid to obtain the phosphonic acids **6** and **7**. Hydrolysis of ester **20** gave the (*S*)-acid **7** in low yield but in optically active form ($[\alpha]_D = -4.6°$ ($c = 0.55$, MeOH)), whereas the parallel reaction of ester **21** gave the nonracemic *R*-acid **6**, also in nonracemic form ($[\alpha]_D = +5.7°$ ($c = 0.55$, MeOH)). To establish the stereochemical fidelity of the hydrolysis, a sample of the acid **7** was converted back to the methyl ester **20** by reaction with diazomethane. Unfortunately, the methyl ester obtained this way had a rotation significantly lower than the material from which it was obtained (−3.3° versus −21.5°), suggesting that substantial racemization had occurred during hydrolysis. Further reaction of this ester with (*S*)-*O*-methylmandelic acid and integration of the diastereomer resonances in the ^{31}P NMR spectrum indicated that the low rotation corresponds to ∼8% ee.

These studies have shown that both enantiomers of dimethyl α-(hydroxyfarnesyl)phosphonate can be prepared by oxidation of the parent dimethyl farnesylphosphonate with a nonracemic oxaziridine. The oxidation proved to be α selective in this case, although whether that is a general phenomenon with allylic phosphonates will require further study. The absolute stereochemistry and enantiomeric excess of the oxidation products can be assigned via preparation of the (*S*)-*O*-methylmandelate derivatives and detailed analysis of their NMR spectra. Enantiomeric excesses of about 70% were observed in these oxidations, which may be sufficient to probe the importance of this stereocenter to the biological activity of the enantiomeric phosphonate esters. However, hydrolysis of these dimethyl esters was accompanied by partial racemization, giving phosphonic acids of low optical activity. If the ee obtained during oxidation of the dimethyl phosphonate is not to be sacrificed during conversion to the phosphonic acid, investigation of ester groups that can be cleaved without racemization will be required.

Experimental Section

Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. All nonaqueous reactions were conducted in oven-dried glassware, under an atmosphere of nitrogen or argon, and with magnetic stirring. Flash chromatography was carried out on Baker silica gel with 40 μm average particle diameter. Melting points are uncorrected. NMR spectra (^{1}H at 300 MHz and ^{13}C at 75 MHz) were recorded with $CDCl_3$ as solvent and $(CH_3)_4Si$ (^{1}H) or $CDCl_3$ (^{13}C, 77.0 ppm) as internal standards, unless otherwise noted. ^{31}P NMR chemical shifts are reported in ppm relative to 85% H_3PO_4 (external standard). Both low- and high-resolution mass spectra were obtained at an ionization potential of 70 eV; only selected ions are reported here. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA).

(1*R*,2*E*,6*E*)-1-(Dimethoxyphosphinyl)-3,7,11-trimethyl-2,6,10-dodecatrienyl (*S*)-Methoxyphenylacetate (4) and (1*S*,2*E*,6*E*)-1-(Dimethoxyphosphinyl)-3,7,11-trimethyl-2,6,10-dodecatrienyl (*S*)-Methoxyphenylacetate (5). To a mixture of α-hydroxyphosphonate **2** (865 mg, 2.62 mmol), EDC (2.51 g, 13.1 mmol), and DMAP (1.77 g, 14.5 mmol) in CH_2Cl_2 (25 mL) was added (*S*)-acid **3** (544 mg, 3.27 mmol) and the mixture was stirred at room temperature. After 28 h of stirring, hexanes (50 mL) were added, and the solution was extracted with 1 M HCl (3 × 50 mL), saturated $NaHCO_3$ (2 × 50 mL), and brine (50 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated to provide a yellow oil. Purification by flash column chromatography (70:30 ethyl acetate/hexanes) gave a total yield of 969 mg (77%) including fractions of pure (*R*,*S*)-ester **4** and (*S*,*S*)-ester **5**, each as a clear oil.

(*R*,*S*)-ester **4**, less polar isomer: 459 mg; $[\alpha]^{25}_D$ +59.9° (c = 1.0, $CHCl_3$); ^{1}H NMR δ 7.28−7.49 (m, 5H), 5.92 (dd, J = 11.5, 10 Hz, 1H), 5.25−5.34 (m, 1H), 5.03−5.14 (m, 2H), 4.80 (s, 1H), 3.54 (d, J = 10.6 Hz, 3H), 3.38 (d, J = 10.6 Hz, 3H), 3.38 (s, 3H), 1.93−2.17 (m, 8H), 1.79 (dd, J = 3.0, 1.4 Hz, 3H), 1.67 (s, 3H), 1.59 (s, 6H); ^{13}C NMR δ 168.8 (d, J_{CP} = 7.4 Hz), 145.8 (d, J_{CP} = 13.1 Hz), 135.4, 135.1, 130.7, 128.3, 128.1 (2C), 127.0 (2C), 123.8, 122.9, 114.7 (d, J_{CP} = 3.1 Hz), 81.8, 66.0 (d, J_{CP} = 173.9 Hz), 56.7, 52.8 (d, J_{CP} = 2.8 Hz), 52.7 (d, J_{CP} = 2.2 Hz), 39.2, 39.2 (d, J_{CP} = 1.5 Hz), 26.4, 25.6 (d, J_{CP} = 2.1 Hz), 25.2, 17.2, 16.7 (d, J_{CP} = 1.2 Hz), 15.5; ^{31}P NMR δ 21.5. Anal. Calcd for $C_{26}H_{39}O_6P$: C, 65.24; H, 8.22. Found: C, 65.33; H, 8.21.

(*S*,*S*)-ester **5**, more polar isomer: $[\alpha]^{25}_D$ +17.4° (c = 1.0, $CHCl_3$); ^{1}H NMR δ 7.28−7.48 (m, 5H), 5.93 (dd, J = 11.6, 9.8 Hz, 1H), 4.99−5.16 (m, 3H), 4.84 (s, 1H), 3.74 (d, J = 10.7 Hz, 3H), 3.71 (d, J = 10.7 Hz, 3H), 3.43 (s, 3H), 1.85−2.10 (m, 8H), 1.69 (s, 6H), 1.60 (s, 3H), 1.56 (s, 3H); ^{13}C NMR δ 169.4 (d, J_{CP} = 6.4 Hz), 146.5 (d, J_{CP} = 13.5 Hz), 135.7, 135.6, 131.3, 128.7, 128.5 (2C), 127.1 (2C), 124.2, 123.2, 114.7 (d, J_{CP} = 3.0), 82.4, 66.4, (d, J_{CP} = 174.2), 57.4, 53.5 (d, J_{CP} = 3.7 Hz), 53.4 (d, J_{CP} = 2.4 Hz), 39.6, 39.5, 26.6, 26.1, 25.7 (d, J_{CP} = 2.4 Hz), 17.6, 17.1, 15.9; ^{31}P NMR δ 21.9; IR (thin film, cm^{-1}) 1752, 1260, 1040. Anal. Calcd for $C_{26}H_{39}O_6P \cdot 0.5\ H_2O$: C, 64.05; H, 8.27. Found: C, 64.47; H, 8.16.

***N*,*N*′-[(1*R*,2*R*)-1,2-Cyclohexylene]bis(pivalamide) (9).** To a stirred solution of (1*R*,2*R*)-1,2-diaminocyclohexane[20] (**8**,

2.00 g, 17.5 mmol) and DMAP (4.49 g, 36.8 mmol) in benzene (45 mL) at 0 °C was added trimethylacetyl chloride (4.55 mL, 36.9 mmol) in benzene (22 mL) via cannula over 30 min. After the mixture warmed to room temperature and was stirred for 19 h, water (125 mL) was added and the solution was extracted with ether (3 × 100 mL). The organic fractions were combined, washed with saturated NH_4Cl (100 mL), dried over $MgSO_4$, and concentrated in vacuo to give diamide **9** as a white solid (4.86 g, 98%). A sample suitable for elemental analysis was purified by sublimation: mp 243−245 °C; $[\alpha]^{25}_D$ +48.1° (c = 1.0, $CHCl_3$); ^{1}H NMR (C_6D_6) δ 6.10−6.24 (br s, 2H), 3.56−3.71 (m, 2H), 2.00−2.11 (m, 2H), 1.68−1.82 (m, 2H), 1.17−1.42 (m, 4H), 1.15 (s, 18H); ^{13}C NMR (C_6D_6) δ 179.1, 53.6, 38.4, 32.3, 27.5, 24.7. Anal. Calcd for $C_{16}H_{30}N_2O_2$: C, 68.03; H, 10.71; N, 9.92. Found: C, 67.81; H, 10.58; N, 10.11.

(1*R*,2*R*)-*N*,*N*′-Bis(2,2-dimethylpropyl)-1,2-cyclohexanediamine (10).[19] To a solution of diamide **9** (1.29 g, 4.57 mmol) in THF (18 mL) at 0 °C was added BH_3−THF (18.4 mL, 1 M in THF, 18.4 mmol). The reaction was stirred at 0 °C for 20 min and then allowed to warm to room temperature. After 3 days of stirring, the reaction mixture was cooled to 0 °C, and water (10 mL) was added slowly until evolution of gas ceased. The mixture was acidified by addition of 6 M HCl to pH 2, and the resulting solution was stirred for 12 h. The solution was then made basic by addition of KOH pellets at 0 °C to pH 12. Ether (10 mL) was added, the resulting organic layer was separated, and the aqueous layer was continuously extracted with ether for 24 h. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford diamine **10**[19] as a clear oil (1.16 g, 100%): ^{1}H NMR δ 2.56 (d, J = 11.1 Hz, 2H), 2.10 (d, J = 11.1 Hz, 2H), 2.02−2.14 (m, 4H), 1.63−1.76 (m, 2H), 1.42−1.56 (br s, 2H), 1.16−1.27 (m, 2H), 0.87−1.04 (m, 2H), 0.91 (s, 18H); ^{13}C NMR δ 63.1, 59.8, 32.0, 31.5, 27.7, 25.1.

2-(1′-Hydroxy-3′,7′,11′-trimethyl-(2′*E*,6′*E*,10′*E*)-2′,6′,10′-dodecatrienyl)-2,3,3a,4,5,6,7,7a-octahydro-1,3-bis(2,2-dimethylpropyl)-1*H*-1,3,2-benzodiazaphosphole 2-Oxide (13/14). A solution of phosphonamidite **11**[19] (1.25 g, 4.15 mmol) in THF (15 mL) was cooled to −60 °C, and *n*-BuLi (4.40 mL, 0.94 M in hexanes, 4.14 mmol) was added. After 2 h of stirring at −60 °C, *trans*,*trans*-farnesal (**12**, 732 mg, 3.32 mmol) in THF (18 mL) was added dropwise via cannula over 1 h. After 2.5 h of stirring at −60 °C, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (5 mL) and allowed to warm to room temperature slowly. Chloroform (100 mL) was added, and the mixture was extracted with water (2 × 80 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo to afford the crude product. A ^{31}P NMR spectrum of this material indicated a ratio of diastereomers of 10.6:1 (δ 41.0:40.5). Purification by flash column chromatography (30:70 ethyl acetate/hexane) gave compounds **13**/**14** as a clear oil in a 52:1 mixture of diastereomers (996 mg, 58%). For the major diastereomer: ^{1}H NMR δ 5.30−5.39 (m, 1H), 5.05−5.20 (m, 2H), 4.82 (dd, J = 9.5, 6.7 Hz, 1H), 3.29 (dd, J = 14.5, 12.0 Hz, 1H), 3.21 (dd, J = 16.6, 14.7 Hz, 1H), 3.15−3.50 (br s, 1H), 2.70−2.91 (m, 2H), 2.50 (dd, J = 14.7, 3.8 Hz, 1H), 2.46 (d, J = 14.5 Hz, 1H), 1.88−2.19 (m, 10H), 1.73−1.84 (m, 2H), 1.75 (dd, J = 3.4, 1.1 Hz, 3H), 1.68 (s, 3H), 1.61 (s, 3H), 1.60 (s, 3H), 1.15−1.35 (m, 4H), 0.97 (s, 9H), 0.93 (s, 9H); ^{13}C NMR δ 141.4 (d, J_{CP} = 12.8 Hz), 135.6, 131.3, 124.2, 123.6, 119.8 (d, J_{CP} = 4.3 Hz), 68.1 (d, J_{CP} = 123.3 Hz), 65.5 (d, J_{CP} = 7.3 Hz), 65.2 (d, J_{CP} = 6.7 Hz), 56.1 (d, J_{CP} = 1.2 Hz), 54.3 (d, J_{CP} = 3.0 Hz), 40.1 (d, J_{CP} = 1.8 Hz), 39.7, 32.8, 31.9, 30.7, 30.6, 30.3, 30.2, 28.7 (3C), 28.4 (3C), 26.7, 25.6, 24.8, 24.3, 17.6, 15.9; ^{31}P NMR δ 40.9; HR FAB MS calcd for $C_{31}H_{57}NO_2PNa$ $(M + Na)^+$ 543.4055; found 543.4067.

Dimethyl (*S*)-Hydroxy-(phenyl)methylphosphonate (18a).[8b,10a] To a mixture of phosphonate **17a**[28] (150 mg, 0.75 mmol) in THF (12 mL) at −95 °C was added NaHMDS (980 μL, 1 M in hexanes, 0.98 mmol). After the golden yellow solution was stirred for 5 min, the reaction mixture was allowed to warm to −40 °C in a liquid nitrogen/acetonitrile bath. After 20 min at −40 °C, the reaction mixture was again cooled to −95 °C for 5 min and then added to a solution of oxaziridine (+)-**16** (367 mg, 1.23 mmol) in THF (12 mL) via cannula. The reaction mixture was allowed to stir at −75 °C for 3 h, quenched by addition of saturated NH_4Cl (20 mL), and allowed to warm to room temperature. Water (10 mL) was added, the resulting solution was extracted with ethyl acetate (3 × 25 mL), and the combined organic layers were dried over $MgSO_4$ and finally concentrated to give a white solid. Final purification by flash column chromatography (gradient of 15:85 acetone/chloroform to 30:70 acetone/chloroform) gave phosphonate **18a** as a white crystalline solid (113 mg, 70%, 93% ee): mp 100−102 °C, lit.[8b] 100−101 °C; $[\alpha]^{29}_D$ −43° (c = 1.0, acetone), lit.[8b] $[\alpha]^{20}_D$ −46° (c = 1.0, acetone); ^{1}H NMR and ^{13}C NMR were identical to literature data;[8a] ^{31}P NMR δ 24.3.

Dimethyl (*S*)-Hydroxy-(*p*-nitrophenyl)methylphosphonate (18b).[8a] According to the procedure described for preparation of phosphonate **18a**, phosphonate **17b**[29] (184 mg, 0.75 mmol) was treated with NaHMDS (1.13 mL, 1 M in hexanes, 1.13 mmol) and oxaziridine (+)-**16** (449 mg, 1.51 mmol). Standard workup and final purification by flash column chromatography (gradient of 20:80 acetone/chloroform to 30:70 acetone/chloroform) gave phosphonate **18b** as a white solid (106 mg, 54%, 80% ee): mp 119−120 °C, lit.[8a] 119 °C; $[\alpha]^{25}_D$ −54.2° (c = 1.0, $CHCl_3$), lit.[8a] $[\alpha]^{22}_D$ −69.2° (c = 1.0, $CHCl_3$); ^{1}H NMR and ^{13}C NMR were identical to literature data;[8a] ^{31}P NMR δ 22.5.

Dimethyl (*S*)-hydroxy-(*p*-chlorophenyl)methylphosphonate (18c).[8a] According to the procedure described for preparation of phosphonate **18a**, phosphonate **17c**[30] (184 mg, 0.75 mmol) was treated with NaHMDS (1.15 mL, 1 M in hexanes, 1.15 mmol) and oxaziridine (+)-**16** (450 mg, 1.51 mmol). Standard workup and final purification by flash column chromatography (gradient of 20:80 acetone/chloroform to 30:70 acetone/chloroform) gave phosphonate **18c** as a white solid (143 mg, 76%, 87% ee): mp 68−69 °C, lit.[8a] 69 °C; $[\alpha]^{26}_D$ −51.4° (c = 1.0, $CHCl_3$), lit.[8a] $[\alpha]^{25}_D$ −59.2° (c = 1.0, $CHCl_3$); ^{1}H NMR and ^{13}C NMR were identical to literature data;[8a] ^{31}P NMR δ 23.6.

Dimethyl (*S*)-Hydroxy-(*p*-methoxyphenyl)methylphosphonate (18d).[8a] According to the procedure described for preparation of phosphonate **18a**, phosphonate **17d**[31] (173 mg, 0.75 mmol) was treated with NaHMDS (1.15 mL, 1 M in hexanes, 1.15 mmol) and oxaziridine (+)-**16** (449 mg, 1.51 mmol). Standard workup and final purification by flash column chromatography (gradient of 20:80 acetone/chloroform to 30:70 acetone/chloroform) gave phosphonate **18d** as a white solid (112 mg, 60%, 81% ee): mp 69−70 °C, lit.[8a] 70 °C; $[\alpha]^{26}_D$ −40.0° (c = 1.0, $CHCl_3$), lit.[8a] $[\alpha]^{25}_D$ −59.2° (c = 1.0, $CHCl_3$); ^{1}H NMR and ^{13}C NMR were identical to literature data;[8a] ^{31}P NMR δ 24.4.

Dimethyl[3,7,11-Trimethyl-(*E*,*E*)-2,6,10-dodecatrienyl]-phosphonate (19).[26] A solution of farnesyl bromide (2.51 g, 8.80 mmol) and trimethyl phosphite (2.4 mL, 20.4 mmol) was heated to reflux. After 12 h of heating at reflux, the reaction mixture was allowed to cool to room temperature, and all volatiles were removed in vacuo. The remaining orange oil was purified by flash column chromatography (20:80 acetone/chloroform) to afford phosphonate **19** as a clear, colorless oil (2.74 g, 99%): ^{1}H NMR δ 5.13−5.24 (m, 1H), 5.04−5.14 (m, 2H), 3.73 (d, J = 10.7 Hz, 6H), 2.58 (dd, J_{HP} = 22.0, 7.8 Hz, 2H), 1.92−2.15 (m, 8H), 1.67 (s, 3H), 1.66 (s, 3H), 1.60 (s, 6H); ^{13}C NMR δ 140.0 (d, J_{CP} = 14.0 Hz), 134.9, 130.8, 124.0, 123.4, 111.8 (d, J_{CP} = 11.0 Hz), 52.1 (d, J_{CP} = 6.7 Hz), 39.4, 39.3 (d, J_{CP} = 3.1 Hz), 26.4, 26.1, 25.3, 25.1 (d, J_{CP} = 135.5 Hz), 17.3, 15.9, 15.6; ^{31}P NMR δ 31.2; IR (thin film, cm^{-1}) 1660, 1260, 1044.

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(−)-(*S*)-Dimethyl [1-Hydroxy-3,7,11-trimethyl-(2*E*,6*E*)-2,6,10-dodecatrienyl]phosphonate (20). To a mixture of phosphonate **19** (473 mg, 1.50 mmol) in THF (12 mL) at −90 °C was added NaHMDS (2.25 mL, 1 M in hexanes, 2.25 mmol). After the orange-brown solution was stirred at this temperature for 5 min, the reaction mixture was allowed to warm to −40 °C in a liquid nitrogen/acetonitrile bath. After 20 min at −40 °C, the reaction mixture was again cooled to −90 °C for 5 min and then added dropwise to a solution of oxaziridine (+)-**16** (896 mg, 3.01 mmol) in THF (12 mL) via cannula. The reaction mixture was allowed to stir at −90 °C for 1 h, quenched by addition of saturated NH_4Cl (20 mL), and allowed to warm to room temperature. Water (10 mL) was added, the resulting solution was extracted with ethyl acetate (3 × 30 mL), and the combined organic layers were dried over $MgSO_4$ and finally concentrated to give a yellow solid. Final purification by flash column chromatography (gradient of 20:80 acetone/chloroform to 30:70 acetone/chloroform) gave phosphonate **20** as a clear oil (251 mg, 51%): $[\alpha]^{25}_D$ −26.4° (*c* = 1.0, $CHCl_3$); all spectra were identical to those of racemic phosphonate; IR (thin film, cm^{-1}) 3359 (br), 1664, 1633, 1234, 1034.

Formation of the (*S*)-(+)-*O*-methylmandelic acid derivatives (**4**/**5**) confirmed the stereochemistry of the product as *S* in a 6.2:1 ratio of diastereomers, corresponding to a 72% ee.

(+)-(*R*)-Dimethyl [1-Hydroxy-3,7,11-trimethyl-(*E*,*E*)-2,6,10-dodecatrienyl]phosphonate (21). To a mixture of phosphonate **18** (472 mg, 1.50 mmol) in THF (8 mL) at −75 °C was added a solution of LDA [made by adding of *n*-BuLi (2.00 mL, 1.18 M in hexanes, 2.36 mmol) to a solution of diisopropylamine (320 μL, 2.28 mmol) in THF (8 mL) at 0 °C, stirring for 15 min, and cooling to −75 °C for 5 min] via cannula. After the yellow solution was stirred at this temperature for 15 min, the reaction mixture was added dropwise to a solution of oxaziridine (−)-**16** (899 mg, 3.02 mmol) in THF (8 mL) at −75 °C via cannula. The reaction mixture was allowed to stir at −75 °C for 1 h, quenched by addition of saturated NH_4Cl chloride (20 mL), and allowed to warm to room temperature. Water (10 mL) was added, the resulting solution was extracted with ethyl acetate (3 × 30 mL), and the combined organic layers were dried over $MgSO_4$ and finally concentrated to give a yellow solid. Final purification by flash column chromatography (gradient of 20:80 acetone/chloroform to 30:70 acetone/chloroform) gave phosphonate **20** as a clear oil (227 mg, 46%): $[\alpha]^{25}_D$ +24.4° (*c* = 1.0, $CHCl_3$); all spectra were identical to those of racemic phosphonate **2**.

Formation of the (*S*)-(+)-*O*-methylmandelic acid derivatives (**4**/**5**) confirmed the stereochemistry of the product as *R* in a 5.3:1 ratio of diastereomers, corresponding to 68% ee.

(+)-(*R*)-[1-Hydroxy-3,7,11-trimethyl-(*E*,*E*)-2,6,10-dodecatrienyl]phosphonic Acid (6). According to the published procedure,[3] phosphonate **20** (118 mg, 0.36 mmol) was treated with trimethylsilyl bromide (200 μL, 1.51 mmol) and 2,4,6-collidine (200 μL, 1.51 mmol) in dichloromethane (6 mL) to obtain the corresponding phosphonic acid **6** (27 mg, 25%): $[\alpha]^{25}_D$ +5.7° (*c* = 0.55, MeOH); all spectra were identical to those of racemic phosphonate **1**.

(−)-(*S*)-[1-Hydroxy-3,7,11-trimethyl-(*E*,*E*)-2,6,10-dodecatrienyl]phosphonic Acid (7). According to the published procedure,[3] phosphonate **19** (116 mg, 0.35 mmol) was treated with trimethylsilyl bromide (200 μL, 1.51 mmol) and 2,4,6-collidine (200 μL, 1.51 mmol) in dichloromethane (6 mL) to obtain the corresponding phosphonic acid **7** (37 mg, 35%): $[\alpha]^{25}_D$ −4.6° (*c* = 0.55, MeOH); all spectra were identical to those of racemic phosphonate **1**;[3] IR (Nujol, cm^{-1}) 3180 (br), 1152.

To establish the ee, excess diazomethane in ether was added dropwise to a solution of acid **7** (30 mg, 0.1 mmol, $[\alpha]^{25}_D$ −3.8°) in methanol (3 mL) until the color persisted for 5 min. The reaction was quenched by addition of acetic acid. Standard workup and purification by column chromatography gave ester **20** (30 mg, 92%, $[\alpha]^{25}_D$ −3.34°). Esterification of this α-hydroxy phosphonate with (*S*)-*O*-methylmandelic acid as described above and integration of the ^{31}P NMR spectrum of the product indicated material of ∼8% de.

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