A General Strategy to Enantiomerically Pure Aliphatic and Olefinic Ketone Cyanohydrins by Stereoselective Alkylation of Umpoled Aldehyde Derivatives

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We present the first general synthesis of optically pure (*R*)- and (*S*)-ketone cyanohydrins with olefinic and aliphatic substituents. Consecutive condensations of $POCl_3$ with pseudoephedrine (**1**) and racemic crotonaldehyde cyanohydrin (**3**, R = 1-propenyl) lead to the respective cyanohydrin phosphate **4c**. Deprotonation, followed by highly stereoselective alkylation and a single chromatographic purification step, afford diastereomerically pure ketone cyanohydrin phosphates **5a**−**e**. From these, enantiomerically pure tertiary cyanohydrins **6a**−**e** can be obtained by mild Lewis acid-assisted hydrolysis. Pseudoephedrine is simultaneously recovered without loss of optical purity. The unsaturated alkylation products **5a**−**d** are readily hydrogenated with diimide to aliphatic cyanohydrin phosphates **5f**−**i**, which can be cleaved to furnish the free optically pure cyanohydrins **6f**−**i**. Thus a broad variety of both saturated and unsaturated ketone cyanohydrins with R > Et becomes accessible in optically pure form for the first time. The free cyanohydrins are easily converted to optically pure α-branched α-hydroxy acids.

Introduction

Cyanohydrins are key building blocks for the one-step synthesis of many biologically active compounds that are otherwise only obtained with difficulty, such as α-hydroxy aldehydes,[1] α-amino alcohols,[2,3] α-azidonitriles,[4,5] *β*-hydroxy-α-amino acids,[6] and—perhaps most important—α-hydroxy acids.[2,7,8] Aliphatic cyanohydrins are especially valuable because from the respective α-hydroxy acids a great number of natural products can be made,[9] e.g., pyrrolizidine alkaloids[10] and insect pheromones[11] as insecticides, α-tocopherol (vitamine E),[12] bioactive metabolites of vitamine D_3,[13] synthetic prostaglandin analogues,[14] and many more. In view of these applications it is the more surprising that to date only very few ketone cyanohydrins can be prepared enantiomerically pure. The only practical method comes from Effenberger,[8,15] and Kula[16] and consists of hydrogen cyanide addition to ketones with *R*-oxynitrilases. Unfortunately, the substrate range of these enzymes is very limited, so that only nonaromatic methyl ketone cyanohydrins can be obtained in good optical and chemical yields. Furthermore, this is only true for the (*R*)-form.

We have recently presented an asymmetric synthesis of ketone cyanohydrins by chemical means that circumvents the substrate limitations of the enzymes (Scheme 1).[17,18] For this we use aldehyde cyanohydrins as "umpoled carbonyl compounds": Cyanohydrin **3** is first linked with its OH group to the phosphorus(V) chiral auxiliary **2**, which is readily prepared from pseudoephedrine. The resulting cyanohydrin phosphate **4** can be alkylated stereoselectively with high de's, and subsequent Lewis acid-assisted hydrolysis affords the free ketone cyanohydrins absolutely racemization-free. We would like to emphasize that we use an inexpensive auxiliary based on the renewable ressource pseudoephedrine;[19] this allows the deliberate preparation of (*R*)- or (*S*)-ketone cyanohydrins contrary to enzymatic synthesis. A special advantage is the broad substrate range because of the variety of electrophiles that can be used for the alkylation. However, so far only optically active phenyl ketone cyanohydrins (R = C_6H_5) have been synthesized by our new route. Now we have extended this method to open the path to alkyl and 2-alkenyl cyanohydrins with a generally applicable synthesis (Scheme 1). Our concept is based on replacement of the phenyl ring with a 1-propenyl moiety. The respective cyanohydrin phosphate **4c** gives an allylic carbanion, which is first regioselectively alkylated (**5a**−**e**, Scheme 3) and then chemoselectively hydrogenated to yield optically active saturated ketone cyanohydrin phosphates **5f**−**i** (Scheme 4).

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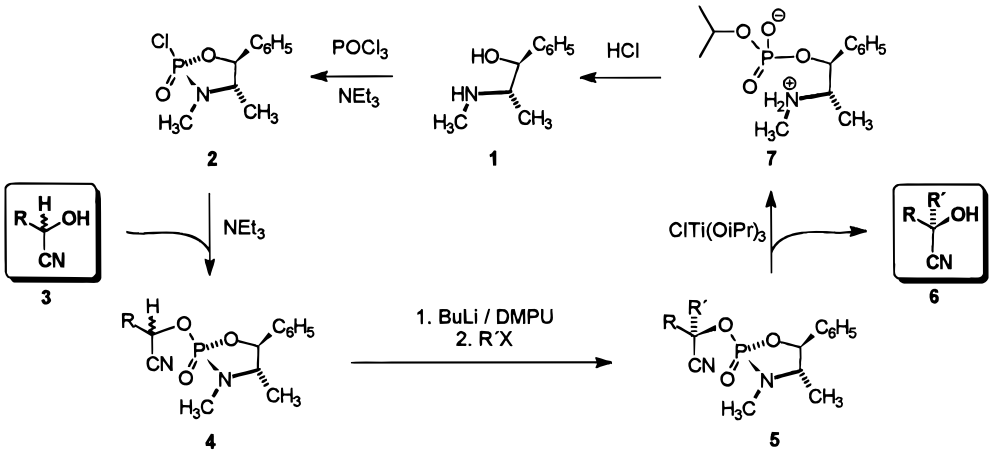
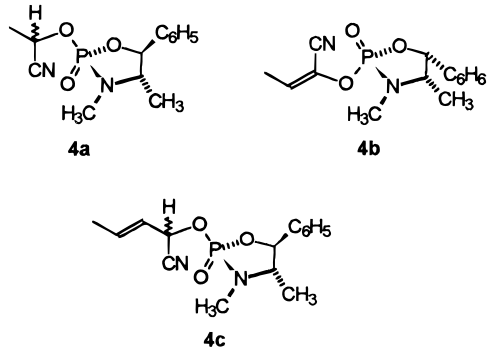
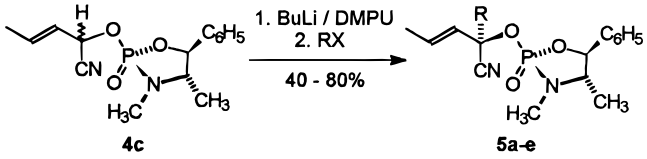
Scheme 1. The Cyanohydrin Phosphate Method—Overview



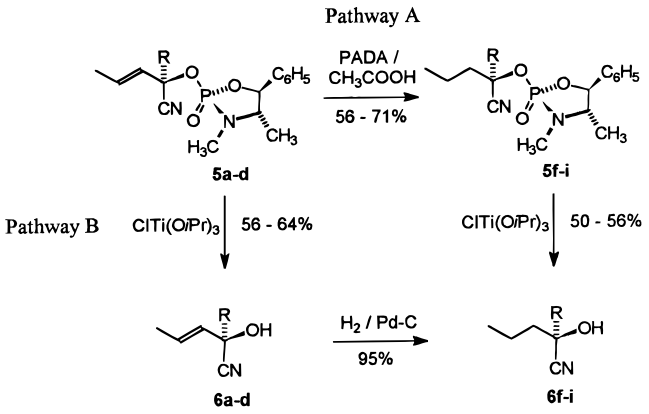
Scheme 2. Starting Materials for the Alkylation Reactions



Scheme 3. Diastereoselective Alkylation of Crotonaldehyde Cyanohydrin Phosphate 4c



Scheme 4. From Unsaturated Alkylation Products 5a—d to Aliphatic Ketone Cyanohydrins 6f—i



Results and Discussion

Crotonaldehyde cyanohydrin and related starting materials **3** were synthesized very efficiently by a cyanide-catalyzed transcyanation reaction between acetone cyanohydrine and the respective aldehyde. The cyanohydrin phosphates **4** are prepared in a two-step sequence: pseudoephedrine **1** and phosphoryl chloride stereoselectively yield the cyclic intermediate **2** (de ≥ 97%), which is subsequently esterified with racemic aldehyde cyanohydrin without racemization at the phosphorus atom.[19,20] In addition to **4c,** we prepared cyanohydrin phosphates **4a** and **4b**, which are accessible from acetaldehyde and acrolein (Scheme 2).

Table 1. Unsaturated Ketone Cyanohydrin Phosphates

compd	R	yield (%)	diastereomeric excess (%)[a]	de after purification (%)[a]
5a	CH_3	57	70	70
5b	C_2H_5	40	74	≥98
5c	CH_2Ph	72	77	≥98
5d	$CH_2CH{=}CHPh$	62	83	≥98
5e	$CH_2CH{=}CH_2$	80	82	≥98

[a] de's calculated from integration of the *N*-methyl signal (^{1}H NMR).

The simplest saturated cyanohydrin phosphate **4a** can be deprotonated (proven by epimerization of diastereomerically pure starting material), but even at 0 °C it cannot be alkylated by allyl iodide! We turned to the shortest possible unsaturated cyanohydrin phosphate, **4b**, which came from the condensation reaction of acrolein cyanohydrin and **2** as the thermodynamically more stable rearranged product. Deprotonation generates an ambident allylic anion, which was alkylated by methyl iodide to afford a 3:1 mixture of the α- and γ-methyl products. Formation of γ-products can be suppressed completely by introducing an electron-donating alkyl group in the γ-position, which destabilizes the γ-carbanion and sterically hinders the γ-alkylation (Scheme 3). Thus, alkylation of the crotonaldehyde cyanohydrin phosphate carbanion leads to exclusive formation of the desired α-alkyl products in good yields and with high diastereomeric excesses (Table 1).

Hydrogenation to the respective saturated compounds can be carried out at this stage or later with the free unsaturated cyanohydrins **6a—d**. The first alternative (pathway A) begins with hydrogenation of the unsaturated cyanohydrin phosphates **5a—d**. Initial attempts to use noble metal catalysts such as Pd, Pt, or Rh on carbon and elementary hydrogen for this reaction invariably led to reductive cleavage of the allylic phosphate accompanied by ring opening of the oxazaphospholidinone. In

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Table 2. Hydrogenation of Cyanohydrin Phosphates 5a−d

compd	R	yield (%)	de after purification (%)[a]
5f	CH_3	65	≥98
5g	C_2H_5	71	≥98
5h	CH_2Ph	55	≥98
5i	$CH_2CH_2CH_2Ph$	56	≥98

[a] de's calculated from integration of the *N*-methyl signal (^{1}H NMR).

Table 3. Free Olefinic (6a−e) and All-Aliphatic (6f−i) Ketone Cyanohydrins

compd	R′	yield (%)[a]	ee (%)
6a	CH_3	56	70
6b	C_2H_5	60	≥98
6c	CH_2Ph	64	≥98
6d	$CH_2CH{=}CHPh$	59	≥98
6e	$CH_2CH{=}CH_2$	62	≥98
6f	CH_3	56	≥98
6g	C_2H_5	50	≥98
6h	CH_2Ph	50	≥98
6i	$CH_2CH_2CH_2Ph$	53	≥98

[a] Crude product; chromatography on silica gel leads to a considerable amount of cleavage to the respective ketones.

contrast, the highly selective reagent diimide attacked only the nonpolarized C=C double bond. Diimide is easily generated from PADA[21] (potassium azodicarboxylate) by protonation with acetic acid and subsequent decarboxylation.[22] We found that slow addition of the acid is critical for complete and clean conversion of the olefin, because a high stationary concentration of diimide kinetically favors its disproportionation to nitrogen and hydrazine instead of releasing hydrogen for the olefin reduction. With the optimized procedure the unsaturated ketone cyanohydrin phosphates **5a−d** were easily converted to the all-aliphatic derivatives **5f−i** in high yields (Scheme 4, Table 2). As expected, NMR spectroscopic analysis reveals that no epimerization has occurred. All saturated ketone cyanohydrin phosphates could be obtained diastereomerically pure after one single chromatographic purification step.

The free olefinic and aliphatic ketone cyanohydrins **6a−i** were liberated in good yields (Table 3) by a mild hydrolysis procedure with chlorotitanium triisopropoxide developed by us earlier.[17] The reagent exerts selective P−O cleavage, which is completely racemization-free. With (4*R*,5*R*)-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol (TADDOL) as shift reagent[23] we demonstrated the retention of optical purity in the free ketone cyanohydrins **6f** and **6h** in an NMR spectroscopic experiment. All ketone cyanohydrins except for **6a** have been obtained in optically pure form.

In two examples for pathway B the free unsaturated ketone cyanohydrins **6a/b** have been subjected to Pd-catalyzed hydrogenation with hydrogen (Scheme 4). Yields are normally in the 95% range; in addition, the technique is much simpler and allows a one-pot synthesis of the respective α-branched α-hydroxy carboxylic acids, starting from unsaturated cyanohydrin phosphates **5**. The advantage of the diimide route, on the other hand, is the highly efficient chromatographic purification of the reduced cyanohydrin phosphates that leads in all cases to diastereomerically pure products.

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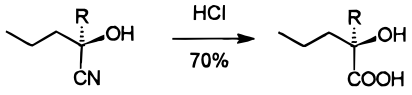
Scheme 5. Preparation of Optically Pure α-Branched α-Hydroxy Acids



6f,g **8a,b** R = CH_3 (**8a**), C_2H_5 (**8b**)

$[\alpha]_D^{299} \approx -9.5°\,(0.75g/100mL, CHCl_3)$ for **8a**

$Lit.: [\alpha]_D^{299} = -9.530°\,(2.12g/100mL, CHCl_3)$ [24]

To demonstrate the ease of conversion to α-hydroxy acids we stirred the free cyanohydrins **6f** and **6g** with concd HCl. This reaction also proceeds racemization-free and furnishes the desired stable hydroxy acids **8a** and **8b** in high yields (Scheme 5).[8] The specific rotation of **8a** corresponds to the literature value found for the optically pure (*R*)-compound. This result constitutes strong experimental evidence for the fact that the electrophile indeed alkylated the cyanohydrin carbanion from its *Si*-face and—as expected—all the above-mentioned consecutive reactions proceeded with complete retention of configuration. The optical purity of hydroxy acids can be measured more exactly than that of cyanohydrins, because the optical rotation values of the latter are very small.[8]

Summary and Outlook

We have thus successfully extended the scope of the cyanohydrin phosphate alkylation method to olefinic and aliphatic ketone cyanohydrins, which can both be obtained optically pure for the first time in a very general strategy. Although we studied only the *(R)*-series, it is self-evident that by choosing from (+)- or (−)-pseudoephedrine for the auxiliary both enantiomers of the ketone cyanohydrins can be synthesized. We anticipate that instead of crotonaldehyde any higher substituted analogues may be used as well, so that a broad variety of olefinic and aliphatic cyanohydrins are now accessible as optically pure.

Very recently we discovered that the unsaturated cyanohydrin phosphates **4c** and **5a−d** undergo a highly stereospecific Pd(II)-catalyzed phospha-Claisen rearrangement, which we will discuss in our next paper.

Experimental Section

General. All NMR spectra were recorded in $CDCl_3$, which was purchased from Aldrich Chemical Co. Preparative chromatography columns were packed with silica gel 60 (70−230 mesh) from Macherey & Nagel Co. All solvents were dried and freshly distilled before use. THF (p.a.) was purchased from Aldrich and dried over sodium metal; for the metalation reactions as well as for the titanium-assisted cleavages, it was always freshly distilled under nitrogen prior to use. These reactions were all carried out under rigorous exclusion of air and humidity by means of standard Schlenck techniques. All new compounds have been characterized by combustion analysis, except for the highly sensitive cyanohydrins, which could be characterized by NMR and mass spectra.

(2*R*,4*S*,5*S*)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (2). Phosphoryl chloride (13.8 mL, 151 mmol) was added through a dropping funnel to a solution of (+)-pseudoephedrine (25 g, 151 mmol) and triethylamine (48.5 mL, 348 mmol) in freshly dried benzene (350 mL). The mixture was stirred for 30 h at 50 °C. Then it was filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography. Elution with ethyl acetate/hexane (3:1) gave **2** (24.6 g, 66%) as an oil, de ≥ 97%:

^{1}H NMR δ 1.24 (d, J = 6.1 Hz, 3 H), 2.68 (d, J = 14.9 Hz, 3 H), 3.28 (dq, J = 9.3 Hz, J = 6.1 Hz, 1 H), 4.99 (dd, J = 9.3 Hz, J = 2.9 Hz, 1 H), 7.38 (m, 5 H); ^{31}P{^{1}H} NMR δ 25.56 (s).

2-Hydroxy-3-pentenonitrile (3). **A** 100 mL portion of crotonaldehyde (1.21 mol), 230 mL of acetone cyanohydrin (2.52 mol), and catalytic amounts of sodium cyanide (ca. 50 mg) were stirred at 45 °C for 48 h. Afterward the pH was set to 3−4, and excess acetone cyanohydrin and **3** (90.5 g, 77%) were obtained by distillation: bp 60 °C (1 mbar); ^{1}H NMR δ 1.80 (dd, J = 6.6 Hz, J = 1.7 Hz, 3 H), 3.75 (s (broad), 1 H), 4.93 (s (broad), 1 H), 5.62 (ddq, J = 15.3 Hz, J = 6.2 Hz, J = 1.7 Hz, 1 H), 6.08 (dq, J = 15.3 Hz, J = 6.6 Hz, 1 H).

(1′*R*/*S*,2*S*,4*S*,5*S*)-2-(1′-Cyano-but-2′-enoxy)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (4c). Compound **2** (7.0 g, 28.4 mmol) was mixed with triethylamine (5.9 mL, 42.6 mmol) in 120 mL of dichloromethane. Then **3** (5.5 g, 56.7 mmol) was added. The mixture was stirred overnight at room temperature. It was extracted with 1 N NaOH, and the organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by silica gel chromatography. Elution with ethyl acetate/hexane (2:1) gave separated diastereomers of **4c** (4.61 g, 53%): R_f = 0.37/0.24 (diastereomer I/diastereomer II); mp 62−65 °C/64−67 °C (diastereomer I/diastereomer II); NMR data recorded with diastereomer I: ^{1}H NMR δ 1.20 (d, J = 6.2 Hz, 3 H), 1.80 (dd, J = 7.3 Hz, J = 0.7 Hz, 3 H), 2.66 (d, J = 11.5 Hz, 3 H), 3.33 (dq, J = 6.1 Hz, J = 8.8 Hz, 1 H), 4.88 (dd, J = 2.6 Hz, J = 8.9 Hz, 1 H), 5.63−5.77 (m, 2 H), 6.19 (dq, J = 6.6 Hz, J = 14.2 Hz, 1 H), 7.29−7.40 (m, 5 H); ^{31}P{^{1}H} NMR δ 20.51 (s); ^{13}C{^{1}H} NMR δ 15.7 (d, J = 9.9 Hz), 17.7 (s), 28.3 (d, J = 3.6 Hz), 61.9 (d, J = 12.4 Hz), 65.2 (d, J = 6.0 Hz), 85.6 (s), 116.2 (d, J = 6.6 Hz), 123.2 (d, J = 4.7 Hz), 126.8 (s), 128.8 (s), 129.3 (s), 135.6 (s), 136.5 (d, J = 6.7 Hz); IR 1675, 1260, 1010, 965 cm^{-1}. Anal. Calcd for $C_{15}H_{19}N_2O_3P$: C, 58.82; H, 6.25; N, 9.15. Found: C, 58.90; H, 6.27; N, 9.00.

General Procedure for the Alkylation of 4c. Compound **4c** (750 mg, 2.45 mmol) was dissolved in a dry Schlenck tube under argon in 25 mL of dry THF. After cooling to −108 °C, 1.65 mL of 1.6 N *n*-butyllithium solution in hexane (2.70 mmol) was added dropwise until the color changed from the light yellow (monoanion) to the orange (dianion). After stirring for 20 min *N*,*N*′-dimethylpropyleneurea (DMPU) (0.44 mL, 3.67 mmol) was added and the reaction mixture was stirred for 20 min at −108 °C. Subsequently a neat solution of the desired electrophile (3 equiv, 7.35 mmol) was dropwise injected with a syringe and the solution was stirred for 4 h at −108 °C. Then the reaction was quenched with saturated aqueous ammonium chloride, and in order to dissolve some precipitated ammonium chloride, water was added. The organic layer was separated and extracted with THF, and the combined organic phases were dried over $MgSO_4$. After filtration and evaporation to dryness, a solid was obtained whose NMR spectrum shows complete conversion and indicates the diastereomeric excess. The crude product was purified by silica gel chromatography. Elution with ethyl acetate/hexane (2:1) gave diastereomerically pure ketone cyanohydrin phosphates, except for **5a**.

(1′*R*,2*S*,4*S*,5*S*)-2-(1′-Cyano-1′-methyl-but-2′-enoxy)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (5a): electrophile methyl iodide; yield 57%, de = 70%; mp 80−82 °C; ^{1}H NMR δ 1.19 (d, J = 6.1 Hz, 3 H), 1.79 (dd, J = 6.6 Hz, J = 1.6 Hz, 3 H), 1.99 (s, 3 H), 2.63 (d, J = 11.4 Hz, 3 H), 3.29 (dq, J = 6.1 Hz, J = 8.8 Hz, 1 H), 4.87 (dd, J = 2.9 Hz, J = 8.8 Hz, 1 H), 5.81 (dd, J = 15.4 Hz, J = 1.6 Hz, 1 H), 6.23 (dq, J = 6.6 Hz, J = 15.4 Hz, 1 H), 7.31−7.43 (m, 5 H); ^{31}P{^{1}H} NMR δ 16.95 (s); ^{13}C{^{1}H} NMR δ 15.5 (d, J = 10.2 Hz), 17.5 (s), 27.8 (d, J = 2.5 Hz), 28.4 (d, J = 3.1 Hz), 61.7 (d, J = 11.9 Hz), 74.4 (d, J = 7.8 Hz), 85.6 (s), 118.7 (d, J = 7.3 Hz), 127.0 (s), 128.7 (s), 129.2 (s), 131.6 (s), 136.8 (d, J = 6.5 Hz); IR 1670, 1260, 1010, 950 cm^{-1}. Anal. Calcd for $C_{16}H_{21}N_2O_3P$: C, 60.00; H, 6.61; N, 8.75. Found: C, 60.05; H, 6.60; N, 8.58.

(1′*R*,2*S*,4*S*,5*S*)-2-(1′-Cyano-1′-ethyl-but-2′-enoxy)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (5b): electrophile ethyl iodide; yield 40%, de = 74%; mp 89−90 °C; ^{1}H NMR δ 1.05 (t, J = 7.5 Hz, 3 H), 1.12 (d, J = 6.2 Hz, 3 H), 1.73 (dd, J = 6.6 Hz, J = 1.6 Hz, 3 H), 2.06 (dq, J = 13.9 Hz, J = 7.6 Hz, 1 H), 2.30 (dq, J = 13.9 Hz, J = 7.4 Hz, 1 H), 2.58 (d, J = 11.4 Hz, 3 H), 3.27 (dq, J = 6.2 Hz, J = 8.8 Hz, 1 H), 4.84 (dd, J = 8.8 Hz, J = 2.5 Hz, 1 H), 5.75 (dq, J = 15.4 Hz, J = 1.6 Hz, 1 H), 6.29 (dq, J = 6.6 Hz, J = 15.4 Hz, 1 H), 7.35−7.42 (m, 5 H); ^{31}P{^{1}H} NMR δ 16.69 (s); ^{13}C{^{1}H} NMR δ 8.6 (s), 15.5 (d, J = 10.1 Hz), 17.6 (s), 28.5 (s), 33.6 (s), 61.6 (d, J = 12.1 Hz), 79.6 (d, J = 8.5 Hz), 85.6 (s), 117.7 (s), 127.0 (s), 127.3 (d, J = 3.6 Hz), 128.7 (s), 129.1 (s), 133.2 (s), 136.8 (s); IR 1670, 1270, 1185, 985 cm^{-1}. Anal. Calcd for $C_{17}H_{23}N_2O_3P$: C, 61.07; H, 6.93; N, 8.38. Found: C, 60.91; H, 6.95; N, 8.16.

(1′*R*,2*S*,4*S*,5*S*)-2-(1′-Cyano-1′-benzyl-but-2′-enoxy)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (5c): electrophile benzyl bromide; yield 72%, de = 77%; mp 81−83 °C; ^{1}H NMR δ 1.08 (d, J = 6.1 Hz, 3 H), 1.68 (dd, J = 6.6 Hz, J = 1.6 Hz, 3 H), 2.46 (d, J = 11.4 Hz, 3 H), 3.20 (dq, J = 6.1 Hz, J = 8.9 Hz, 1 H), 3.29 (d, J = 13.7 Hz, 1 H), 3.51 (d, J = 13.7 Hz, 1 H), 4.82 (dd, J = 8.9 Hz, J = 2.5 Hz, 1 H), 5.84 (dq, J = 15.3 Hz, J = 1.4 Hz, 1 H), 6.19 (dq, J = 6.6 Hz, J = 15.4 Hz, 1 H), 7.26−7.40 (m, 10 H); ^{31}P{^{1}H} NMR δ 16.63 (s); ^{13}C{^{1}H} NMR δ 15.4 (d, J = 10.2 Hz), 17.55 (s), 28.4 (d, J = 3.1 Hz), 46.5 (d, J = 3.7 Hz), 61.6 (d, J = 12.0 Hz), 78.4 (d, J = 8.4 Hz), 85.7 (s), 117.5 (d, J = 7.8 Hz), 127.0 (s), 127.1 (d, J = 3.4 Hz), 127.7 (s), 128.3 (s), 128.7 (s), 129.1 (s), 131.0 (s), 133.2 (s), 133.3 (s), 136.6 (d, J = 6.7 Hz). Anal. Calcd for $C_{22}H_{25}N_2O_3P$: C, 66.66; H, 6.36; N, 7.07. Found: C, 66.55; H, 6.30; N, 6.97.

(1′*R*,2*S*,4*S*,5*S*)-2-(1′-Cyano-4′-phenyl-1′-prop-1″-enylbut-3′-enoxy)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (5d): electrophile cinnamyl bromide; yield 62%, de = 83%; mp 74−76 °C; ^{1}H NMR δ 1.11 (d, J = 6.0 Hz, 3 H), 1.73 (dd, J = 6.6 Hz, J = 1.7 Hz, 3 H), 2.54 (d, J = 11.4 Hz, 3 H), 2.98 (ddd, J = 14.1 Hz, J = 7.9 Hz, J = 1,1 Hz, 1 H), 3.18 (ddd, J = 14.1 Hz, J = 6.8 Hz, J = 1,3 Hz, 1 H), 3.24 (dq, J = 6.0 Hz, J = 8.8 Hz, 1 H), 4.84 (dd, J = 8.8 Hz, J = 3.2 Hz, 1 H), 5.85 (dq, J = 15.4 Hz, J = 1.7 Hz, 1 H), 6.21 (ddd, J = 15.9 Hz, J = 7.9 Hz, J = 6.8 Hz, 1 H), 6.31 (dq, J = 15.4 Hz, J = 6.6 Hz, 1 H), 6.64 (d, J = 16.1 Hz, 1 H), 7.22−7.37 (m, 10 H); ^{31}P{^{1}H} NMR δ 16.85 (s); ^{13}C{^{1}H} NMR δ 15.5 (d, J = 10.3 Hz), 17.6 (s), 28.6 (d, J = 3.2 Hz), 43.8 (d, J = 2.8 Hz), 61.7 (d, 12.0 Hz), 77.9 (d, J = 7.9 Hz), 85.6 (s), 117.7 (d, J = 8.6 Hz), 120.9 (s), 126.4 (s), 126.9 (s), 127.1 (d, J = 3.8 Hz), 127.8 (s), 128.6 (s), 128.7 (s), 129.1 (s), 133.5 (s), 136.2 (s), 136.6 (s), 136.8 (d, J = 6.5 Hz). Anal. Calcd for $C_{24}H_{27}N_2O_3P$: C, 68.23; H, 6.44; N, 6.63. Found: C, 68.30; H, 6.62; N, 6.39.

(1′*R*,2*S*,4*S*,5*S*)-2-(1′-Cyano-1′-prop-2″-enylbut-2′-enoxy)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (5e): electrophile allyl iodide; yield 80%, de = 82%; oil; ^{1}H NMR δ 1.18 (d, J = 6.1 Hz, 3 H), 1.79 (dd, J = 6.6 Hz, J = 1.7 Hz, 3 H), 2.62 (d, J = 11.4 Hz, 3 H), 2.85 (dd, J = 14.0 Hz, J = 7.5 Hz, 1 H), 3.08 (dd, J = 14.0 Hz, J = 6.8 Hz, 1 H), 3.29 (dq, J = 6.1 Hz, J = 8.9 Hz, 1 H), 4.87 (dd, J = 8.9 Hz, J = 2.9 Hz, 1 H), 5.32 (d, J = 15.4 Hz, 1 H), 5.32 (d, J = 8.4 Hz, 1 H), 5.78−5.92 (m, 2 H), 6.31 (dq, J = 6.6 Hz, J = 15.4 Hz, 1 H), 7.34−7.44 (m, 5 H); ^{31}P{^{1}H} NMR δ 16.73 (s); ^{13}C{^{1}H} NMR δ 15.5 (d, J = 10.3 Hz), 17.6 (s), 28.5 (d, J = 3.0 Hz), 44.5 (d, J = 2.9 Hz), 61.7 (d, J = 12.0 Hz), 77.8 (d, J = 7.8 Hz), 85.6 (s), 117.5 (d, J = 8.6 Hz), 121.5 (s), 127.0 (s), 128.7 (s), 129.2 (s), 129.8 (s), 133.5 (s), 136.8 (d, J = 6.7 Hz); IR 1660, 1640, 1270, 1010, 950 cm^{-1}. Anal. Calcd for $C_{18}H_{23}N_2O_3P$: C, 62.42; H, 6.69; N, 8.09. Found: C, 62.48; H, 6.72; N, 7.94.

General Procedure for the Hydrogenation of 5a−d. The cyanohydrin phosphates were dissolved in dry dioxane (25 mg/mL) and stirred with 20 equiv of PADA[25] at 50 °C under an argon atmosphere. Every 8 h 5 equiv of acetic acid were added, until no yellow solid could be seen in the mixture (max. 40 equiv). Now water and ethyl acetate were added, and the aqueous phase was extracted with ethyl acetate. The collected organic layers were washed with water, separated, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel chromatography. Elution with ethyl acetate/hexane (1:1) gave diastereomerically pure products **5f**−**i**.

(1′*R*,2*S*,4*S*,5*S*)-2-(1′-Cyano-1′-methylbutoxy)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (5f): yield

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65%; oil; ^{1}H NMR δ 0.95 (t, J= 7.6 Hz, 3 H), 1.13 (d, J = 6.2 Hz, 3 H), 1.59 (m, 2 H), 1.86 (s, 3 H), 1.90−2.05 (m, 2 H), 2.61 (d, J = 11.4 Hz, 3 H), 3.26 (dq, J = 6.2 Hz, J = 8.9 Hz, 1 H), 4.86 (dd, J = 8.9 Hz, J = 2.8 Hz, 1 H), 7.33−7.43 (m, 5 H); ^{31}P{^{1}H} NMR δ 17.41 (s); ^{13}C{^{1}H} NMR δ 13.7 (s), 15.5 (d, J = 10.3 Hz), 17.8 (s), 26.5 (s), 28.4 (s), 43.5 (d, J = 6.3 Hz), 61.8 (d, J = 12.1 Hz), 75.3 (d, J = 8.4 Hz), 85.5 (s), 119.6 (s), 126.9 (s), 128.8 (s), 129.2 (s), 136.8 (d, J = 6.2 Hz); IR 1270, 1185, 970 cm^{-1}. Anal. Calcd for $C_{16}H_{23}N_2O_3P$: C, 59.62; H, 7.19; N, 8.69. Found: C, 59.54; H, 6.99; N, 8.48

(1′*R*,2*S*,4*S*,5*S*)-2-(1′-Cyano-1′-ethylbutoxy)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (5g): yield 71%; mp 106−107 °C; ^{1}H NMR δ 0.92 (t, J = 7.3 Hz, 3 H), 1.07 (t, J = 7.3 Hz, 3 H), 1.12 (d, J = 6.3 Hz, 3 H), 1.57 (m, 2 H), 1.92−2.07 (m, 2 H), 2.07 (dq, J = 14.2 Hz, J = 7.3 Hz, 1 H), 2.24 (dq, J = 14.2 Hz, J = 7.3 Hz, 1 H), 2.61 (d, J = 11.4 Hz, 3 H), 3.29 (dq, J = 6.3 Hz, J = 8.9 Hz, 1 H), 4.85 (dd, J = 8.9 Hz, J = 2.8 Hz, 1 H), 7.33−7.42 (m, 5 H); ^{31}P{^{1}H} NMR δ 16.76 (s); ^{13}C{^{1}H} NMR δ 8.5 (s), 13.8 (s), 15.5 (d, J = 10.1 Hz), 17.6 (s), 28.5 (d, J = 3.1 Hz), 31.7 (s), 40.3 (d, J = 4.9 Hz), 61.7 (d, J = 11.9 Hz), 80.0 (d, J = 8.4 Hz), 85.6 (s), 118.9 (d, J = 7.9 Hz), 127.0 (s), 128.7 (s), 129.2 (s), 136.7 (d, J = 7.2 Hz); IR 1270, 1185, 985 cm^{-1}. Anal. Calcd for $C_{17}H_{25}N_2O_3P$: C, 60.70; H, 7.49; N, 8.33. Found: C, 60.72; H, 7.43; N, 8.15.

(1′*S*,2*S*,4*S*,5*S*)-2-(1′-Cyano-1′-benzylbutoxy)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (5h): yield 55%; mp 90−91 °C; ^{1}H NMR δ 0.97 (t, J = 7.3 Hz, 3 H), 1.17 (d, J = 5.9 Hz, 3 H), 1.69 (m, 2 H), 1.94−2.13 (m, 2 H), 2.55 (d, J = 11.4 Hz, 3 H), 3.28 (dq, J = 5.9 Hz, J = 9.0 Hz, 1 H), 3.37 (d, J = 13.9 Hz, 1 H), 3.55 (d, J = 13.9 Hz, 1 H), 4.89 (dd, J = 9.0 Hz, J = 2.2 Hz, 1 H), 7.27−7.43 (m, 10 H); ^{31}P{^{1}H} NMR δ 16.79 (s); ^{13}C{^{1}H} NMR 13.7 (s), 15.4 (d, J = 10.2 Hz), 17.7 (s), 28.3 (d, J = 3.4 Hz), 40.7 (d, J = 4.4 Hz), 44.6 (s), 61.7 (d, J = 11.9 Hz), 79.0 (d, J = 8.7 Hz), 85.7 (s), 118.8 (d, J = 6.4 Hz), 127.0 (s), 127.7 (s), 128.5 (s), 128.7 (s), 129.2 (s), 130.9 (s), 133.5 (s), 136.5 (d, J = 6.4 Hz); IR 1270, 1185, 965 cm^{-1}. Anal. Calcd for $C_{22}H_{27}N_2O_3P$: C, 66.32; H, 6.83; N, 7.03. Found: C, 66.13; H, 7.12; N, 7.08.

(1′*S*,2*S*,4*S*,5*S*)-2-(1′-Cyano-4′-phenyl-1′-propylbutoxy)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (5i): yield 56%; oil: ^{1}H NMR δ 0.97 (t, J = 7.6 Hz, 3 H), 1.19 (d, J = 6.0 Hz, 3 H), 1.59 (m, 2 H), 1.93 (m, 2 H), 1.93−2.12 (m, 2 H), 2.12−2.27 (m, 2 H), 2.64 (d, J = 11.4 Hz, 3 H), 2.68 (m, 2 H), 3.32 (dq, J = 6.0 Hz, J = 8.8 Hz, 1 H), 4.90 (dd, J = 8.8 Hz, J = 2.5 Hz, 1 H), 7.14−7.39 (m, 10 H); ^{31}P{^{1}H} NMR δ 16.78 (s); ^{13}C{^{1}H} NMR δ 13.7 (C^1, s), 15.5 (d, J = 9.8 Hz), 17.6 (s), 26.0 (s), 28.5 (d, J = 2.8 Hz), 35.3 (s), 38.1 (s), 40.8 (d, J = 4.9 Hz), 61.7 (d, J = 11.7 Hz), 79.1 (d, J = 8.6 Hz), 85.6 (s), 118.9 (d, J = 7.2 Hz), 126.0 (s), 127.0 (s), 128.3 (s), 128.4 (s), 128.8 (s), 129.3 (s), 136.7 (d, J = 6.3 Hz), 141.3 (s); IR 1270, 1185, 970 cm^{-1}. Anal. Calcd for $C_{24}H_{31}N_2O_3P$: C, 67.59; H, 7.33; N, 6.57. Found: C, 67.78; H, 7.39; N, 6.76.

General Procedure for the Cleavage of 5a−i to Ketone Cyanohydrins 6a−i. Under a nitrogen atmosphere the cyanohydrin phosphates were dissolved in freshly dried THF (ca. 25 mg/mL), then titanium chloride triisopropoxide (1.0 M solution in hexane, 4 equiv) was added at room temperature. The mixture was stirred for 4 h at room temperature, water was added under a nitrogen atmosphere, and the two-layer system was vigorously stirred for another 4 h at room temperature. After phase separation, drying over magnesium sulfate, and evaporation of the solvent, the free tertiary cyanohydrins can be chromatographed over silica gel, but cleavage to the parent ketone must be considered. The crude product can also be used for further syntheses. As already described by us,[17] **1** can be reobtained from the aqueous layer by acid hydrolysis.

(*R*)-2-Hydroxy-2-methyl-3-pentenonitrile (6a): yield 56%; ^{1}H NMR δ 1.63 (s, 3 H), 1.77 (dd, J = 6.6 Hz, J = 1.7 Hz, 3 H), 4.10 (s, 1 H), 5.55 (dq, J = 15.4 Hz, J = 1.7 Hz, 1 H), 6.08 (dq, J = 15.4 Hz, J = 6.6 Hz, 1 H); ^{13}C{^{1}H} NMR δ 17.3 (s), 28.5 (s), 68.1 (s), 121.2 (s), 128.2 (s), 131.4 (s); MS *m*/*e* (rel intensity) 111 (12, M$^+$), 96 (100), 84 (11), 78 (41), 69 (60), 42 (43).

(*R*)-2-Hydroxy-2-ethyl-3-pentenonitrile (6b): yield 60%; ^{1}H NMR δ 0.99 (t, J = 7.6 Hz, 3 H), 1.73 (dd, J = 6.6 Hz, J = 1.7 Hz, 3 H), 1.74 (dq, J = 13.9 Hz, J = 7.6 Hz, 1 H), 1.86 (dq, J = 13.9 Hz, J = 7.6 Hz, 1 H), 2.43 (s, 1 H), 5.47 (dq, J = 15.5 Hz, J = 1.7 Hz, 1 H), 6.14 (dq, J = 6.6 Hz, J = 15.5 Hz, 1 H); ^{13}C{^{1}H} NMR δ 8.4 (s), 17.4 (s), 30.3 (s), 73.2 (s), 120.0 (s), 129.9 (s), 130.2 (s); MS *m*/*e* (rel intensity) 125 (14, M$^+$), 110 (8), 98 (15), 96 (66), 83 (19), 78 (30), 69 (43), 56 (43), 41 (100).

(*R*)-2-Hydroxy-2-benzyl-3-pentenonitrile (6c): yield 64%; ^{1}H NMR δ 1.75 (dd, J = 6.6 Hz, J = 1.7 Hz, 3 H), 3.05 (d, J = 13.7 Hz, 1 H), 3.08 (d, J = 13.7 Hz, 1 H), 3.25 (s, 1 H), 5.55 (dq, J = 15.4 Hz, J = 1.7 Hz, 1 H), 6.07 (dq, J = 15.4 Hz, J = 6.6 Hz, 1 H), 7.26−7.41 (m, 5 H); ^{13}C{^{1}H} NMR δ 17.4 (s), 47.2 (s), 72.3 (s), 119.8 (s), 127.8 (s), 128.5 (s), 129.4 (s), 130.0 (s), 130.7 (s), 133.4 (s); MS *m*/*e* (rel intensity) 187 (21, M$^+$), 160 (16), 96 (24), 91 (100), 77 (15), 69 (50), 65 (30), 51 (26), 42 (14).

(*R*)-2-Hydroxy-5-phenyl-2-prop-1′-enyl-4-pentenonitrile (6d): yield 59%; ^{1}H NMR δ 1.77 (dd, J = 6.6 Hz, J =1.7 Hz, 3 H), 2.70 (dd, J = 14.0 Hz, J = 7.9 Hz, 1 H), 2.74 (dd, J = 14.0 Hz, J = 6.8 Hz, 1 H), 3.68 (s, 1 H), 5.56 (dq, J = 15.5 Hz, J = 1.7 Hz, 1 H), 6.16 (dq, J = 15.5 Hz, J = 6.6 Hz, 1 H), 6.23 (ddd, J = 15.8 Hz, J = 7.9 Hz, J = 6.8 Hz, 1 H), 6.58 (d, J = 15.8 Hz), 1 H), 7.20−7.47 (m, 5 H); ^{13}C{^{1}H} NMR δ 17.5 (s), 44.9 (s), 71.6 (s), 120.0 (s), 121.3 (s), 126.5 (s), 127.9 (s), 128.6 (s), 129.4 (s), 130.1 (s), 136.3 (s), 136.5 (s); MS *m*/*e* (rel intensity) 213 (15, M$^+$), 186 (20), 117 (100), 96 (22), 91 (56), 77 (46), 69 (72), 65 (69), 51 (61), 42 (22).

(*R*)-2-Hydroxy-2-prop-2′-enyl-3-pentenonitril (6e): yield 62%; ^{1}H NMR δ 1.78 (dd, J = 6.6 Hz, J = 1.7 Hz, 3 H), 2.56 (dt, J = 7.2 Hz, J = 1.1 Hz, 2 H), 4.09 (s, 1 H), 5.23−5.31 (m, 2 H), 5.51 (dq, J = 15.4 Hz, J = 1.7 Hz, 1 H), 5.86 (ddt, J = 16.8 Hz, J = 10.5 Hz, J = 7.2 Hz, 1 H), 6.11 (dq, J = 15.4 Hz, J = 6.6 Hz, 1 H); ^{13}C{^{1}H} NMR δ 17.4 (s), 45.5 (s), 71.4 (s), 120.0 (s), 121.2 (s), 129.6 (s), 129.7 (s), 130.5 (s); MS *m*/*e* (rel intensity) 137 (4, M$^+$), 110 (4), 96 (100), 83 (15), 69 (72), 54 (43), 42 (94).

(*R*)-2-Hydroxy-2-methylpentanonitrile (6f): yield 56%; ^{1}H NMR δ 1.00 (t, J = 7.3 Hz, 3 H), 1.56 (m, 2 H), 1.60 (s, 3 H), 1.75 (m, 2 H), 3.02 (s, 1 H); ^{13}C NMR 13.8 (s), 17.6 (s), 27.6 (s), 43.7 (s), 68.6 (s), 122.0 (s); MS *m*/*e* (rel intensity) 98 (21, M$^+$ − CH$_3$), 94 (10), 86 (9), 80 (28), 71 (56), 58 (10), 53 (18), 43 (100), 41 (90); the [MNH$_4$]$^+$ ion was detected via CI-MS.

(*R*)-2-Ethyl-2-hydroxypentanonitrile (6g): yield 50%; ^{1}H NMR δ 0.94 (t, J = 7.3 Hz, 3 H), 1.06 (t, J = 7.3 Hz, 3 H), 1.50 (m, 2 H), 1.67 (m, 2 H), 1.74 (m, 2 H), 2.27 (s, 1 H); ^{13}C{^{1}H} NMR δ 8.2 (s), 11.4 (s), 18.8 (s), 33.3 (s), 41.8 (s), 72.9 (s), 121.1 (s); MS *m*/*e* (rel intensity) 108 (3), 100 (8, M$^+$ − HCN), 98 (41), 85 (53), 80 (37), 70 (59), 57 (65), 53 (22), 43 (84), 41 (100); the [MNH$_4$]$^+$ ion was detected via CI-MS.

(*S*)-2-Benzyl-2-hydroxypentanonitrile (6h): yield 50%; ^{1}H NMR δ 0.95 (t, J = 7.3 Hz, 3 H), 1.61 (m, 2 H), 1.76 (m, 2 H), 2.33 (s, 1 H), 2.87 (d, J = 13.9 Hz, 1 H), 3.03 (d, J = 13.9 Hz, 1 H), 7.33−7.41 (m, 5 H); ^{13}C{^{1}H} NMR δ 13.9 (s), 17.6 (s), 42.2 (s), 46.4 (s), 72.1 (s), 120.7 (s), 128.1 (s), 129.0 (s), 130.5 (s), 133.3 (s); MS *m*/*e* (rel intensity) 189 (40, M$^+$), 162 (25), 91 (100), 77 (13), 71 (56), 65 (47), 51 (20), 43 (82), 41 (63).

(*S*)-2-Hydroxy-5-phenyl-2-propylpentanonitrile (6i): yield 53%; ^{1}H NMR δ 0.91 (t, J = 7.3 Hz, 3 H), 1.49 (m, 4 H), 1.67 (m, 4 H), 1.83 (m, 2 H), 2.24 (s, 1 H), 7.15−7.31 (m, 5 H); ^{13}C{^{1}H} NMR δ 13.0 (s), 16.5 (s), 24.9 (s), 34.8 (s), 39.1 (s), 41.8 (s), 72.1 (s), 121.8 (s), 126.8 (s), 129.0 (s), 129.2 (s), 142.0 (s); MS *m*/*e* (rel intensity) 217 (3, M$^+$), 190 (39), 175 (51), 147 (32), 129 (17), 119 (22), 104 (100), 99 (9), 91 (70), 86 (25), 77 (29), 71 (35), 65 (41), 58 (48), 51 (20), 43 (73), 41 (80).

General Procedure for the Hydrogenation of Tertiary Olefinic Cyanohydrins 6a−d. The olefinic cyanohydrins were dissolved in ethanol (ca. 25 mg/mL) and stirred with a catalytic amount of palladium on carbon under a hydrogen atmosphere for 36 h at room temperature. Filtration and evaporation yielded the crude aliphatic cyanohydrins **6f−i** (95%).

General Procedure for the Preparation of the α-Hydroxy Acids 8a,b. The cyanohydrins were stirred with concd HCl (2.5 mL/mmol cyanohydrin) for 16 h, then heated under reflux for 5 h. After extraction with diethyl ether, the collected organic layers were dried (MgSO$_4$) and evaporated. The

residue can be recrystallized from *n*-hexane. For the GC−MS experiment, the acids were silylated with *O*,*N*-bis(trimethylsilyl)trifluoroacetamide.

(*R*)-2-Hydroxy-2-methylpentanoic acid (8a): yield 70%; ^{1}H NMR δ 0.86 (t, J = 7.3 Hz, 3 H), 1.20−1.42 (m, 2 H), 1.41 (s, 3 H), 1.61−1.74 (m, 2 H), 6.4 (s (broad), 1 H); ^{13}C{^{1}H} NMR δ 13.2 (s), 16.1 (s), 25.3 (s), 41.7 (s), 74.7 (s), 182.9 (s); IR 3400 (w), 1720, 1375, 1170 cm^{-1}; MS of silylated compound *m*/*e* (rel intensity) 261 (46, $M^+ - CH_3$), 233 (61), 171 (8), 159 (100), 147 (77), 143 (13), 133 (27), 73 (75), 45 (25).

(*R*)-2-Ethyl-2-hydroxypentanoic acid (8b): yield 70%; ^{1}H NMR δ 0.85 (t, J = 7.3 Hz, 3 H), 0.86 (t, J = 7.3 Hz, 3 H), 1.16 (m, 2 H), 1.40−1.80 (m, 4 H), 3.6 (s (broad), 1 H); ^{13}C{^{1}H} NMR δ 6.9 (s), 13.3 (s), 16.1 (s), 31.6 (s), 40.7 (s), 78.0 (s), 181.1 (s); IR 3400 (w), 1720, 1375, 1170 cm^{-1}; MS of silylated compound *m*/*e* (rel intensity) 275 (32, $M^+ - CH_3$), 261 (20), 247 (53), 185 (15), 173 (100), 157 (10), 147 (73), 133 (32), 73 (88), 57 (34), 45 (51).

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Supporting Information Available: Experimental and spectral data of **4a** and **4b** (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfiche version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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