Practical Total Synthesis of the Anti-Influenza Drug GS-4104

John C. Rohloff,* Kenneth M. Kent, Michael J. Postich, Mark W. Becker, Harlan H. Chapman, Daphne E. Kelly, Willard Lew,† Michael S. Louie, Lawrence R. McGee,† Ernest J. Prisbe, Lisa M. Schultze, Richard H. Yu, and Lijun Zhang†

Gilead Sciences Inc., Process Chemistry, 353 Lakeside Drive, Foster City, California 94404

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Introduction

The lipophilic sialic acid analogue GS-4071 (**1**) is a potent inhibitor of viral neuraminidase (Figure 1).[1] The ethyl ester pro-drug GS-4104 (**2**) has potential as an orally active agent for the treatment and prevention of influenza infections.[2] To supply an accelerated program of clinical and toxicological studies, a practical kilogram-scale preparation of **2** was needed. The key structural feature in **2**, in terms of both pharmacological activity and synthetic challenge, was the 3-pentyl ether group. The discovery synthesis of **2**·HCl by Kim et al. constructed this 3-pentyl ether by acid-catalyzed opening of the tritylaziridine **5** (methyl ester) with 3-pentanol (Scheme 1).[1a] The tritylaziridine **5** was prepared stereospecifically from either (−)-quinic acid (**3**) or (−)-shikimic acid (**4**), but both sequences required double inversion and repeated protection/deprotection of the (*R*)-3-hydroxyl group. The generality of the tritylaziridine opening for a wide variety of alcohols and other nucleophiles[1c] facilitated the rapid creation of structural diversity in the discovery route, but identification of the lead compound **2** allowed for the design of a more efficient approach.

This paper describes the development of a new 12-step synthesis of **2** utilizing a novel and efficient reductive ketal opening to construct the 3-pentyl ether. This new process is highly amenable to kilogram-scale synthesis in that it features only three isolated crystalline intermediates and requires no chromatography.

Results and Discussion

The first route that was examined to construct the 3-pentyl ether involved direct alkylation of the (*R*)-3-hydroxyl group in the known shikimic acid derivative **7**[1a] with base and 3-iodopentane or similar electrophiles (Scheme 2). This approach was not efficient, presumably due to the sterically crowded nature of both reactants. Aromatization occurred under forcing conditions.

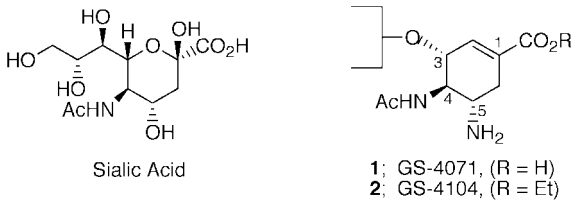

Figure 1.

It was next proposed that construction of the 3-pentyl ether group could be accomplished by reductive opening of a quinic or shikimic acid-derived 3,4-pentylidene ketal **9** (Scheme 3). In a test of the concept, 3,4-pentylidene ketal **9** was prepared in three steps and 80% yield from natural (−)-shikimic acid **4**. Treatment of **9** with trimethylsilyl trifluoromethanesulfonate and borane·methyl sulfide complex in dichloromethane, under modified Hunter conditions,[3] gratifyingly afforded a 10:1:1 mixture of isomeric pentyl ethers **10a**:**10b** and diol **10c** in 75% yield. The highest regioselectivity (∼10:1) for the ketal opening was obtained by immediately treating the freshly prepared reaction mixture at −20 °C with small portions of aqueous sodium bicarbonate. The reductive ketal opening was found to be initiated by addition of the first portion of the quench. Overnight reaction at −20 °C, followed by quenching, gave **10a**:**10b** in a <2:1 ratio. Separation of the **10a**:**10b**:**10c** mixture was not possible through fractional crystallization or chromatography, but heating the crude mixture in aqueous ethanol in the presence of potassium bicarbonate selectively converted **10a** into the alkane-soluble epoxide **11**. Heptane extraction gave crystalline epoxide **11** in 60% overall yield from ketal **9**.

Due to the limited commercial availability of (−)-shikimic acid **4**,[4] an efficient preparation of ketal **9** from readily available (−)-quinic acid **3**[5] was developed (Scheme 4). The quinic lactone acetonide **12a** was prepared in 90% yield from **3** by modification of the method of Shing,[1a,6] and this was converted to an 1:5 equilibrium mixture of lactone:hydroxy ester **12a**:**13a** in anhydrous ethanol (1 M) containing catalytic sodium ethoxide. Separation of the **12a**:**13a** mixture by fractional crystallization was found to be inefficient on the kilogram scale, and instead, the crude **12a**:**13a** mixture was treated with methanesulfonyl chloride (1.1 equivalents) in methylene chloride in the presence of triethylamine to chemoselectively afford the monomesylates **12b**:**13b** in an unchanged ratio of 1:5. The undesired, but highly crystalline, lactone mesylate **12b** was readily removed by

* To whom correspondence should be addressed. Tel.: (650) 572-6673. Fax: (650) 572-6572. E-mail: John_Rohloff@gilead.com.
† Medicinal Chemistry, Gilead Sciences Inc.

(1) (a) Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681. (b) Kim, C. U. *Book of Abstracts*, 214th ACS National Meeting, Las Vegas, NV, Sep 7−11, 1997; American Chemical Society: Washington, DC, 1997; MEDI-137. (c) Williams, M. A.; Lew, W.; Mendel, D. B.; Tai, C. Y.; Escarpe, P. A.; Laver, W. G.; Stevens, R. C.; Kim, C. U. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1837. (d) Lew, W.; Williams, M. A.; Mendel, D. B.; Escarpe, P. A.; Kim, C. U. *Ibid.* **1997**, *7*, 1843. (e) Zhang, L.; Williams, M. A.; Mendel, D. B.; Escarpe, P. A.; Kim, C. U. *Ibid.* **1997**, *7*, 1847.

(2) (a) Cundy, K. C.; Eisenberg, E.; Bidgood, A.; Li, W.-X.; Mendel, D.; Francis, R. J.; Angus, D.; Sharp, S. R.; Lee, W. A. *Abstracts of 37th ICAAC*, Toronto, Canada, Sep 28−Oct 1, 1997, H-135. (b) Hayden, F. G.; Treanor, J. J.; Lobo, M.; Miller, M.; Mills, R. E. Efficacy and Tolerability of Oral GS4104 for Early Treatment of Experimental Influenza A Virus Infection. *Ibid.* Program Addendum (Late Breaker Session).

(3) Hunter, R.; Bartels, B. *J. Org. Chem.* **1993**, *58*, 6756.

(4) (a) Review: Campbell, M. M.; Sainsbury, M.; Searle, P. A. *Synthesis* **1993**, 179. (b) Dell., K. A.; Frost, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 11581. (c) Evans, D. A.; Barnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 57.

(5) Hanessian, S.; Pan, J.; Carnell, A.; Bouchard, H.; Lesage, L. *J. Org. Chem.* **1997**, *62*, 465 and ref 13 cited therein.

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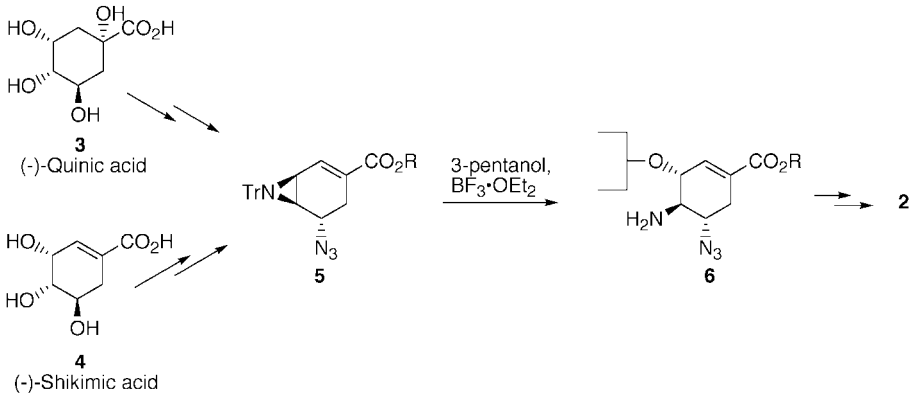
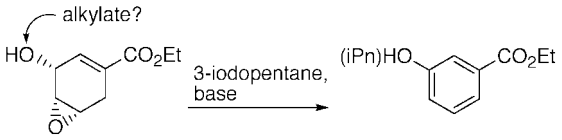
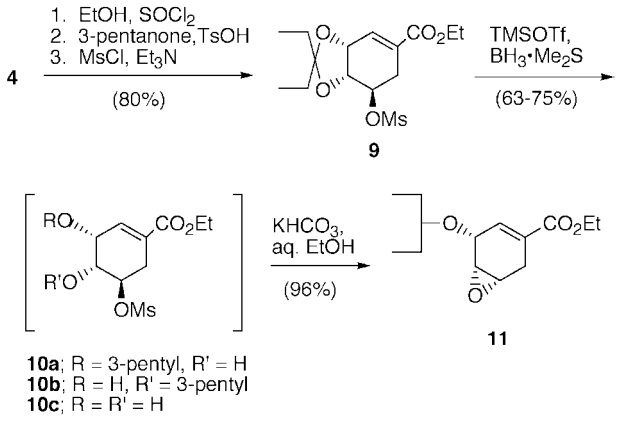
Scheme 1



Scheme 2



Scheme 3



filtration of an ethyl acetate slurry of the **12b**:**13b** mixture. Upon evaporation of the filtrate, crude oily **13b** was isolated in 69% overall yield from (−)-quinic acid **3**.

Dehydration of **13b** to form the unsaturated "shikimic" ring system was accomplished with sulfuryl chloride and pyridine in methylene chloride at −20 °C.[7] A mixture of 1,2- and 1,6-olefin regioisomers **14**:**15** (ratio 4:1) was obtained in 60% yield along with 10−15% of the oily α-chloro compound **16**. Due to the high crystallinity of both olefin isomers, a high-throughput fractional crystallization could not be accomplished. Instead, it was found that treatment of the crude **14**:**15**:**16** mixture with pyrrolidine and catalytic tetrakis(triphenylphosphine)-palladium(0) in ethyl acetate led to selective conversion of the undesired 1,6-olefin (*allylic* mesylate) **15** into the pyrrolidine substitution product **17**.[8] This 1,6-olefin adduct was readily removed by aqueous sulfuric acid extraction. The pure 1,2-olefin isomer **14** was then isolable by crystallization from ethyl acetate/hexane in 30% overall yield from **3**.

In order complete the link to the (−)-shikimic acid route, the quinic acid-derived acetonide **14** was transketalized using catalytic perchloric acid[9] in 3-pentanone at ambient temperature with continuous vacuum distillation of acetone. The oily 3,4-pentylidene ketal **9** was isolated in nearly quantitative yield and was identical in all respects to the ketal **9** prepared from (−)-shikimic acid **4**. A more concise route based on initial formation of the 3,4-pentylidene ketal analogues of **12a**, **13a**, and **13b** from (−)-quinic acid **3** was found to be impractical for scale-up due to the lack of crystallinity in the 3,4-pentylidene series.

Stereospecific conversion of the (4*R*,5*S*)-epoxide in **11** into the desired (4*R*,5*S*)-diamine moiety was accomplished using azide chemistry,[10] by analogy to the procedure of Kim (Scheme 5).[1a] Epoxide **11** was heated at 70 °C with sodium azide and ammonium chloride in aqueous ethanol to afford an oily 10:1 mixture of isomeric azido alcohols **18a**:**18b**. Intramolecular reductive cyclization[11] of the crude **18a**,**b** mixture with trimethylphosphine in anhydrous acetonitrile at 35 °C cleanly afforded a single aziridine **19**, of ca. 70% purity.[12] Triphenylphosphine, in the presence of catalytic triethylamine hydrochloride (5 mol %), also gave satisfactory results in the reductive cyclization but required a more complex workup to remove the byproduct, triphenylphosphine oxide. Aziridine opening proceeded smoothly at 80 °C with sodium azide and ammonium chloride in dimethylformamide (DMF) affording the azidoamine **6** (ethyl ester), which was directly acylated under Schotten−Baumann conditions with acetic anhydride. The resulting azidoacetamide **20** (mp 137−8 °C) was isolated, after recrystallization, in 37% overall yield from epoxide **11**. Due to its stability and high crystallinity, the azidoacetamide **20** has proven to be an excellent final intermediate for drug substance synthesis.

To complete the synthesis, azide reduction with substrate **20** was accomplished using catalytic hydrogenation with Raney nickel in ethanol (1 atm H_2) at 35 °C.[13] After removal of the catalyst by filtration, 85% phosphoric acid

(7) Cleophax, J.; Leboul, J.; Mercier, D.; Gaudemer, A.; Gero, S. D. *Bull. Soc. Chim. Fr.* **1973**, *11*, 2992.

(8) (a) Trost, B. M.; Kelnan, E. *J. Am. Chem. Soc.* **1978**, *100*, 7779. (b) Genet, J. P.; Balabane, M.; Backvall, J. E.; Nystrom, J. E. *Tetrahedron Lett.* **1983**, *24*, 2745.

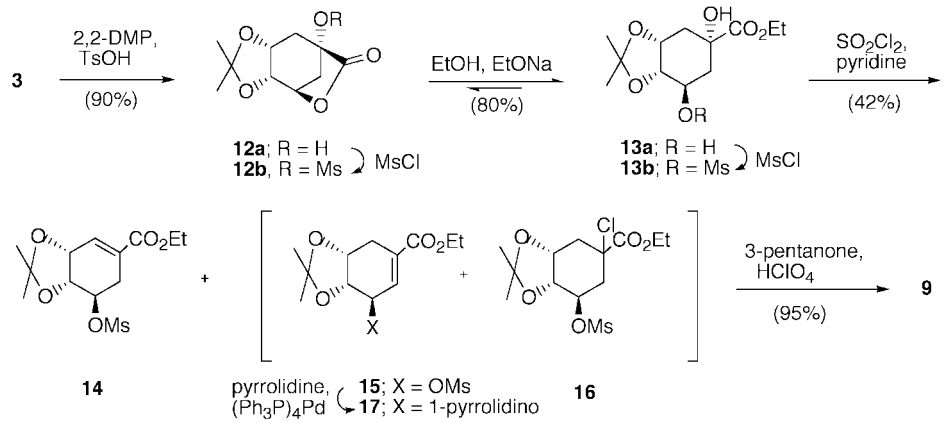
(9) (a) Lewbart, M. L.; Schneider, J. J. *J. Org. Chem.* **1969**, *34*, 3505. (b) Zderic, J. A.; Moffatt, J. G.; Kau, D.; Gerzon, K.; Fitzgibbon, W. E. *J. Med. Chem.* **1965**, *8*, 275.

(10) Review: Biffin, M. E. C.; Miller, L.; Paul, D. B. In *The Chemistry of the Azido Group*; Patai, S., Ed.; Wiley Interscience Publishers: London, 1971, pp 58−177.

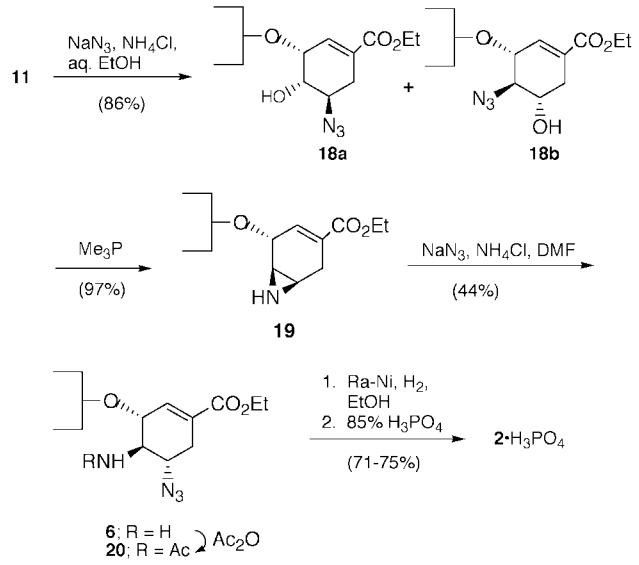
(11) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353 and refs 276−282 cited therein.

(12) Trimethylphosphine is available from the Aldrich Chemical Co., 1001 West Saint Paul Ave., Milwaukee, WI 53233, or it can be prepared as described: Reier, F.-W.; Wolfram, P.; Schumann, H. German Offen. DE 3612629 A1, 1987.

Scheme 4



Scheme 5



(1 equiv) was added. The salt **2**·H_3PO_4 crystallized[14] as feathery needles, and it was isolated in 71% yield from **20**.

In summary, a new synthesis of the promising anti-influenza drug GS-4104 monophosphate (**2**·H_3PO_4) has been completed. Processing efficiency has been achieved by having no chromatography and only three isolated crystalline intermediates: **14**, **11**, and **20**. Notable transformations include regioselective reductive ketal opening to construct the key 3-pentyl ether group in **10a**, selective decomposition of allylic mesylate **15** under palladium catalysis, and the one-step reductive cyclization of azido alcohols **18a**,**b** into aziridine **19**. Overall, **2** was prepared in 12 steps and 4.4% yield from (−)-quinic acid (average 77.2% yield/step) and (formally) in 10 steps and 21% yield from (−)-shikimic acid. Kilogram quantities of drug substance have been prepared by this route in standard pilot plant equipment.

Experimental Section

General Methods. All solvents and reagents were obtained commercially and were used without purification. Melting points were obtained on a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ. High-resolution mass spectra were performed by the Mass Spectrometry Lab, University of California, Berkeley. Column chromatography was carried out using 70−230 mesh silica gel. ^{1}H NMR spectra were recorded at 300 MHz unless otherwise indicated. ^{13}C NMR spectra were recorded at 75 MHz with proton decoupling, unless otherwise indicated. All steps were carried out under cGMP conditions in standard pilot plant/kilolab equipment consisting of: 120 and 200 L glass-lined Pfaudler reactors, a 20 L Buchi Rotovapor and various 12−50 L round-bottom and cylindrical flasks.

3,4-*O*-Isopropylidene-1,5-quinic Lactone (12a). A mixture of (1*R*,3*R*,4*R*,5*R*)-(−)-quinic acid **3** (20.00 kg, 104.1 mol, $[\alpha]_D = -44°$ (c 1, water)), *p*-toluenesulfonic acid monohydrate (200 g, 1.05 mol), 2,2-dimethoxypropane (38.00 kg, 364.9 mol), and acetone (80 kg) was heated to reflux for 2 h. The reaction was cooled to 50 °C and neutralized by the addition of 21% sodium ethoxide in denatured ethanol (340 g, 1.05 mol). Most of the ethanol was removed by distillation in vacuo (50 °C, 75 mmHg), and the gummy residue was dissolved in ethyl acetate (108 kg). This mixture was washed with water (30 kg), and the water was back-extracted with ethyl acetate (13 kg). The organic layers were combined and washed with 5% aqueous sodium bicarbonate (13.5 kg, 8.0 mol). The ethyl acetate and other volatile components were removed by distillation in vacuo (60 °C, 75 mmHg). The resulting pale yellow, semisolid residue **12a** was used without purification in the next step: FT IR (KBr) 1775 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.76 (1 H, dd, J = 2.5, 6.2 Hz), 4.56−4.50 (1 H, m), 4.36−4.32 (1 H, m), 2.83 (1 H, s), 2.68 (1 H, d, J = 12.7 Hz), 2.44−2.30 (2 H, m), 2.21 (1 H, dd, J = 3.0, 14.7 Hz), 1.55 (3 H, s), 1.36 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 179.0, 109.7, 75.4, 72.0, 71.5, 71.4, 38.0, 34.2, 26.9, 24.2. An analytical sample of **12a** was prepared by column chromatography (30% EtOAc/70% hexanes, R_f 0.3) and then crystallized from ethyl acetate: mp 140.5−142 °C. Anal. Calcd for $C_{10}H_{14}O_5$ (214.2): C, 56.07; H, 6.59. Found: C, 56.1; H, 6.68. A minor byproduct (R_f 0.25, 8% yield) was isolated during chromatography of **12a**. The byproduct was a colorless oil. Spectral data were consistent with the bis-acetonide **21** (Figure 2): FT IR (film) 1787 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.50−4.44 (1 H, m), 4.04−3.97 (2 H, m), 2.34−2.22 (3 H, m), 2.10−2.07 (1 H, m), 1.98−1.88 (1 H, m), 1.62 (3 H, s), 1.60 (3 H, s), 1.52 (3 H, s), 1.36 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 176.5, 112.0, 109.4, 80.7, 78.9, 71.8, 66.2, 36.9, 34.2, 27.8, 27.4, 26.0, 24.4; HRMS calcd for $C_{13}H_{21}O_6$ [MH$^+$] 273.1338, found 273.1331.

Ethyl (−)-3,4-*O*-Isopropylidenequinate (13a). A suspension of the crude lactone **12a** (22.3 kg, 104.1 mol) in absolute ethanol (70.4 kg) under a nitrogen atmosphere was treated with

(13) (a) Prisbe, E. J.; Verheyden, J. P. H.; Montgomery, W. W.; Strosberg, A. M. *J. Med. Chem.* **1986**, *29*, 239. (b) Trimethylphosphine in moist THF also reduced azide **20** in good yield: Knapp, S.; Shieh, W.-C.; Jaramillo, C.; Trilles, R. V.; Nanden, S. R. *J. Org. Chem.* **1994**, *59*, 946. (c) Satisfactory results with low purity **20** were obtained with Lindlar catalyst: Corey, E. J.; Nicolaou, K. C.; Balanson, R. D.; Machida, Y. *Synthesis* **1975**, 590.

(14) The hydrochloride salt **2**·HCl was a solid, but not crystalline in our hands. Screening of pharmaceutically acceptable acids (Berge, S. M.; Bighley, L. D.; Monkhouse, D. C. *J. Pharm. Sci.* **1977**, *66*, 1) revealed two that gave crystalline salts: citric (mp 123−6 °C, acetone) and phosphoric (mp 203−4 °C, ethanol). Both salts were 1:1 stoichiometry.

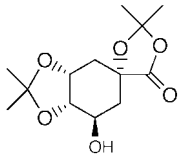


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Figure 2.

21% sodium ethoxide in denatured ethanol (340 g, 1.05 mol), and the resulting solution was stirred for 2 h. The sodium ethoxide was quenched by the addition of glacial acetic acid (72 g, 1.2 mol), and the volatile components were removed by distillation in vacuo (50 °C, 25 mmHg). The residue was coevaporated with ethyl acetate (36 kg) in vacuo (50 °C, 25 mmHg) to leave a mixture of **12a**:**13a** (ratio 1:5) as a pale yellow paste (23.3 kg). This crude mixture was used directly in the next step. An analytical sample of **13a** was prepared by column chromatography (50% EtOAc/ 50% hexanes, R_f 0.5): mp 89−91 °C; FT IR (film) 1731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.52−4.47 (1 H, m), 4.28 (2 H, q, J = 7.1 Hz), 4.21−4.13 (1 H, m), 4.03−3.99 (1 H, m), 3.43 (1 H, s), 2.68 (1 H, bs), 2.28−2.26 (2 H, m), 2.08 (1 H, dd, J = 4.3, 13.7 Hz), 1.89 (1 H, dd, J = 10.8, 13.7 Hz), 1.57 (3 H, s), 1.40 (3 H, s), 1.34 (3 H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 175.0, 109.0, 80.1, 73.6, 73.3, 67.9, 62.0, 38.9, 34.6, 28.1, 25.6, 13.9. Anal. Calcd for $C_{12}H_{20}O_6$ (260.2): C, 55.37; H, 7.74. Found: C, 55.22; H, 7.71.

Ethyl (−)-3,4-*O*-Isopropylidene-5-*O*-(methanesulfonyl)-quinate (13b). A mixture of **12a**:**13a** (ratio 1:5) (23.3 kg) and methanesulfonyl chloride (12.4 kg, 108.3 mol) in dichloromethane (122 kg) was cooled to 0−5 °C and treated dropwise with triethylamine (12.6 kg, 124.5 mol) over 1.5 h. Water (57.8 kg) was added, followed by 37% hydrochloric acid (1.2 kg, 1.2 mol). The yellow organic layer was separated and washed with water (12 kg). The volatile components were removed by distillation in vacuo (50 °C, 440 mmHg). The semisolid residue was suspended in ethyl acetate (14 kg), heated to 60 °C for 1 h, and then cooled to −15 °C for 1 h. The colorless crystalline byproduct, mesyl lactone **12b**, was removed by filtration and washed with ethyl acetate (14 kg). The combined filtrate and wash were concentrated in vacuo (65 °C, 25 mmHg) to afford **13b** as an orange oil (24.2 kg, 68.6% yield from **3**). TLC analysis indicated a purity of 90−95%: FT IR (film) 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.14−5.05 (1 H, m), 4.56−4.51 (1 H, m), 4.34−4.24 (2 H, m), 4.18−4.13 (1 H, m), 3.42 (1 H, bs), 3.17 (3 H, s), 2.37−2.27 (3 H, m), 2.02 (1 H, t, J = 3.1 Hz), 1.63 (3 H, s), 1.40 (3 H, s), 1.33 (3 H, t, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 173.8, 109.6, 80.3, 76.4, 73.7, 73.6, 62.3, 38.4, 38.3, 34.0, 27.9, 25.7, 13.9; HRMS calcd for $C_{13}H_{23}O_8S$ [MH^+] 339.1113, found 339.1117.

For mesyl lactone **12b**: mp 178.5−181 °C; FT IR (KBr) 1794, 1356 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.84−4.81 (1 H, m), 4.58−4.52 (1 H, m), 4.35−4.32 (1 H, m), 3.30 (3 H, s), 3.14−3.07 (1 H, m), 2.85 (1 H, d, J = 13.0 Hz), 2.57 (1 H, ddd, J = 2.7, 8.5, 16.7 Hz), 2.41 (1 H, dd, J = 3.7, 16.7 Hz), 1.54 (3 H, s), 1.35 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 179.7, 109.6, 82.6, 75.0, 71.0, 70.1, 40.1, 35.9, 32.1, 26.0, 23.8. Anal. Calcd for $C_{11}H_{16}O_7S$ (292.31): C, 45.20; H, 5.52. Found: C, 45.46; H, 5.53.

Ethyl 3,4-*O*-Isopropylidene-5-*O*-(methanesulfonyl)shikimate (14). A solution of mesylate **13b** (24.2 kg, 71.64 mol) and pyridine (34.0 kg, 430 mol) in dichloromethane (92 kg) was cooled to between −20 and −30 °C and treated dropwise with sulfuryl chloride (14.5 kg, 107.4 mol) over 3.5 h. Excess sulfuryl chloride was decomposed by dropwise addition of ethyl alcohol (5.7 kg) over 1 h. The mixture was warmed to 0−5 °C and washed with 2 M sulfuric acid (69 kg, 131 mol). (*Caution; exothermic, temperature must be maintained below 20 °C).* The aqueous layer was back-extracted with dichloromethane (29 kg), and the organic layers were combined and washed with water (34 kg), followed by 5% aqueous sodium bicarbonate (33.9 kg, 20.2 mol). The volatile components were removed by distillation (50 °C, 200 mmHg) to afford an oily residue composed of a mixture of **14**:**15**:**16** (ratio 4:1:1). The mixture was dissolved in ethyl acetate (51 kg) and treated with pyrrolidine (5.33 kg, 74.9 mol) and tetrakis(triphenylphosphine)palladium(0) (165 g, 0.14 mol) at 35 °C for 3.5 h. The 1,6-olefin **15** was converted into the pyrrolidine substitution product **17**. The murky brown mixture was extracted three times with 2 M sulfuric acid (3 × 47 kg) to remove **17** and unreacted pyrrolidine. The organic layer was filtered through a silica gel pad (Merck SG 60, 70−230 mesh, 24 kg) to remove catalyst residues, and the pad was eluted with ethyl acetate (102 kg). The eluent was washed with 5% aqueous sodium bicarbonate (24.2 kg, 14.3 mol), and the volatiles were removed by distillation in vacuo (60 °C, 50 mmHg). The semisolid residue was recrystallized from refluxing ethyl acetate (14.3 kg) and hexanes (13.0 kg) with vigorous stirring. After cooling at 0−5 °C for 12 h, the product **14** was isolated by filtration and washed with a cold (0−5 °C) solution of ethyl acetate (0.72 kg) in hexanes (4.2 kg). Drying in vacuo afforded the 1,2-olefin **14** as an off-white solid (10.08 kg, 30.2% yield from quinic acid **3**: mp 101−2 °C; FT IR (KBr) 1717, 1350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.99−6.96 (1 H, m), 4.84−4.76 (2 H, m), 4.29 (1 H, dd, J = 6.5, 7.7 Hz), 4.25 (2 H, q, J = 7.1 Hz), 3.14 (3 H, s), 3.02 (1 H, dd, J = 5.1, 17.4 Hz), 2.56−2.46 (1 H, m), 1.50 (3 H, s), 1.43 (3 H, s), 1.32 (3 H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 165.2, 133.3, 130.2, 110.4, 79.1, 75.0, 72.3, 61.3, 38.6, 28.5, 27.7, 25.6, 14.1. Anal. Calcd for $C_{13}H_{20}O_7S$ (320.5): C, 48.74; H, 6.29. Found: C, 48.86; H, 6.43.

For 1,6-olefin **15**: ^1H NMR ($CDCl_3$) δ 6.93−6.91 (1 H, m, vinyl).

Ethyl 3,4-*O*-Isopentylidene-5-*O*-(methanesulfonyl)shikimate (9). A mixture of acetonide **14** (10.00 kg, 31.23 mol) and 3-pentanone (27.0 kg, 313.5 mol) was treated with 70% perchloric acid (63 g, 0.439 mol). After 0.5 h, the mixture was warmed to 40 °C, and 3-pentanone/acetone (ca. 10 kg) was removed by distillation in vacuo (40 °C, 50 mmHg). Fresh 3-pentanone (13 kg, 150.9 mol) was charged to the mixture, and the distillation (40 °C, 25 mmHg) was continued for 4−20 h, until conversion of **14** to **9** was complete by TLC analysis (Merck SG 60, 50% EtOAc/50% hexanes). The resulting yellow slurry was filtered through a 1 μm polypropylene filter cartridge and rinsed through with toluene (18 kg). The filtrate was washed with 5% aqueous sodium bicarbonate (1.4 kg, 0.83 mol), followed by water (19 kg). The volatile components were removed by distillation in vacuo (50 °C, 25 mmHg). The residue was coevaporated with toluene (9.5 kg) in vacuo (50 °C, 25 mmHg), which afforded pentylidene ketal **9** as a yellow oil (10.33 kg, 95% yield): FT IR (film) 1717, 1350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00−6.99 (1 H, m), 4.88−4.81 (2 H, m), 4.34 (1 H, t, J = 7.1 Hz), 4.26 (2 H, q, J = 7.3 Hz), 3.15 (3 H, s), 3.01 (1 H, dd, J = 4.9, 17.5 Hz), 2.58−2.48 (1 H, m), 1.74 (2 H, q, J = 7.4 Hz), 1.69 (2 H, q, J = 7.4 Hz), 1.34 (3 H, t, J = 7.3 Hz), 0.94 (3 H, t, J = 7.4 Hz), 0.93 (3 H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 165.3, 134.0, 129.3, 114.4, 79.1, 74.8, 72.2, 61.3, 38.7, 29.6, 28.9, 28.0, 14.1, 8.5, 7.9; HRMS calcd for $C_{15}H_{25}O_7S$ [MH^+] 349.1321, found 349.1319.

Ethyl 3-*O*-(1-Ethylpropyl)-5-*O*-(methanesulfonyl)shikimate (10a). A solution of pentylidene ketal **9** (10.3 kg, 29.6 mol) in dichloromethane (125 kg) was cooled to between −10 and −20 °C and treated with borane·dimethyl sulfide complex (2.47 kg, 32.6 mol), followed by trimethylsilyl trifluoromethanesulfonate (4.80 kg, 21.6 mol) over 0.5 h. After being stirred for 0.2 h, the reaction was treated in portions with 6.8% aqueous sodium bicarbonate (38.7 kg, 31.3 mol) over 3−6 h. The initial portions were added slowly, ca. 30 mL/10 min over the first 2 h. (*Caution: Exothermic; temperature must be maintained below 15 °C, recool between portions; sulfide stench, scrub effluent gas with bleach; flammable hydrogen gas generated; dilute with nitrogen*). The mixture was warmed to 20−25 °C and stirred for 6−18 h while purging with nitrogen to remove residual hydrogen. The biphasic mixture was then filtered through a 1 μm polypropylene filter. The organic layer was separated and concentrated by distillation (50 °C, 760 mmHg, *Caution: sulfide stench*) to afford an oily mixture of **10a**:**10b**:**10c** (ratio 10:1:1) (ca. 8 kg, 75% yield). The mixture was used without purification in the following step. For **10a**: FT IR (film) 1717, 1694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.89−6.86 (1 H, m), 5.03−4.96 (1 H, m), 4.28−4.21 (3 H, m), 3.99−3.92 (1 H, m), 3.47 (1 H, h, J = 5.9 Hz), 3.13 (3 H, s, OMs), 3.07−2.99 (1 H, m), 2.83 (1 H, bs), 2.59−2.50 (1 H, m), 1.65−1.51 (4 H, m), 1.32 (3 H, t, J = 7.1 Hz), 0.96 (3 H, t, J = 7.4 Hz), 0.92 (3 H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 165.6, 134.9, 129.3, 82.2, 78.0, 71.2, 68.6, 61.1, 38.6, 29.3, 26.4, 26.1, 14.1, 9.6, 9.4. HRMS calcd for $C_{15}H_{27}O_7S$ [MH^+] 351.1478, found 351.1472.

For **10b**: ^{1}H NMR ($CDCl_3$) δ 6.89−6.86 (1 H, m), 3.85 (1 H, m), 3.07 (s, OMs).

Ethyl (3*R*,4*R*,5*S*)-4,5-Epoxy-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate (11). A solution of the crude **10a**:**10b**:**10c** mixture (16.4 kg, ratio 10:1:1) in absolute ethanol (55.7 kg) was treated with potassium hydrogen carbonate (7.3 kg, 72.9 mol) in water (45.9 kg), and the mixture was warmed to 55−65 °C, affording a clear solution. After 1 h, most of the ethanol (ca. 43 kg) was removed by distillation in vacuo (55 °C, 75 mmHg). Water (8.2 kg) was added to dissolve the salty residue, and the mixture was extracted twice with hexanes (52 kg, then 35 kg). The organic extracts were combined, washed with water (2 × 4.6 kg), and concentrated in vacuo (60 °C, 175 mmHg). The residue was coevaporated with ethyl alcohol (14.9 kg) in vacuo (65 °C, 75 mmHg) which afforded epoxide **11** as a yellow oil that crystallized on standing (9.6 kg, 96.7% yield, based on contained **10a** in the starting mixture). TLC analysis indicated a purity of 90−95% and this material was typically used directly in the next step. An analytical sample was recrystallized from aqueous ethanol to afford **11** as long white needles: mp 57−8 °C; FT IR (KBr) 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.76−6.73 (1 H, m), 4.42−4.39 (1 H, m), 4.26−4.18 (2 H, m), 3.55−3.46 (3 H, m), 3.13−3.05 (1 H, m), 2.49−2.40 (1 H, m), 1.67−1.57 (4 H, m), 1.30 (3 H, t, J = 7.1 Hz), 1.01 (3 H, t, J = 7.3 Hz), 0.98 (3 H, t, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 166.1, 135.3, 126.7, 81.5, 71.3, 60.7, 53.3, 50.7, 26.7, 26.5, 24.5,14.2, 9.7, 9.6. Anal. Calcd for $C_{14}H_{22}O_4$ (254.3): C, 66.12; H, 8.72. Found: C, 65.94; H, 8.91.

Ethyl (3*R*,4*S*,5*R*)-5-Azido-3-(1-ethylpropoxy)-4-hydroxycyclohexene-1-carboxylate (18a). *Caution: This procedure should only be attempted by technically qualified persons who are fully familiar with the safe handling of sodium azide and ammonium azide. These reagents are highly toxic and potentially explosive.* A solution of epoxide **11** (1.0 kg, 3.93 mol) in ethanol (1.54 kg) and water (0.5 kg) was treated with ammonium chloride (0.231 kg, 4.31 mol) and sodium azide (0.280 kg, 4.31 mol) and the resulting mixture was heated to 70−75 °C. *(Caution: do not exceed an internal temperature of 78 °C).* When TLC analysis (Merck SG 60, 50% EtOAc/50% hexanes) indicated that **11** was consumed (12−18 h), the mixture was cooled to ambient temperature and treated with 5% aqueous sodium bicarbonate (1.23 kg, 0.73 mol). Most of the ethanol was removed by distillation in vacuo (50 °C, 25 mmHg). The aqueous residue was extracted with ethyl acetate (1.58 kg, then 0.81 kg), and the combined extracts were washed with brine (1.5 kg) and dried over anhydrous sodium sulfate (0.79 kg). Filtration and concentration in vacuo (50 °C, 25 mmHg) afforded a ca. 10:1 mixture of isomeric azido alcohols **18a**:**18b** as a brown oil (1.0 kg, 85.5% yield). An analytical sample of **18a** was prepared by column chromatography (20% EtOAc/ 80% hexanes) as a pale yellow oil: FT IR (film) 2100, 1717 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.88−6.86 (1 H, m), 4.25 (2 H, q, J = 7.0 Hz), 4.17−4.14 (1 H, m), 3.94−3.87 (1 H, m), 3.83−3.78 (1 H, m), 3.47 (1 H, p, J = 5.7 Hz), 2.91−2.82 (1 H, m), 2.75 (1 H, bs), 2.33−2.24 (1 H, m), 1.66−1.52 (4 H, m), 1.33 (3 H, t, J = 7.0 Hz), 0.97 (3 H, t, J = 7.4 Hz), 0.93 (3 H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 165.9, 135.0, 130.1, 81.9, 71.0, 70.2, 61.0, 58.9, 28.2, 26.4, 26.1, 14.2, 9.6, 9.5; HRMS calcd for $C_{14}H_{23}N_3O_4$ [M$^+$] 297.1689, found 297.1685.

Ethyl (3*R*,4*S*,5*R*)-4,5-Imino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate (19). A ca. 10:1 mixture of azido alcohols **18a**:**18b** (2.00 kg, 6.73 mol) was dissolved in anhydrous acetonitrile (2.1 kg) and dried by azeotropic distillation of acetonitrile in vacuo (50 °C, 100 mmHg). When the water content was determined to be <0.1% by Karl Fischer titration, the solution was cooled and diluted to a total volume of 5 L with anhydrous acetonitrile. A solution of trimethylphosphine (0.52 kg, 6.83 mol) in anhydrous acetonitrile (4.7 kg) was added dropwise over 2 h, while maintaining a temperature <38 °C. *(Caution: trimethylphosphine stench!)* The mixture was concentrated in vacuo (50 °C, 50 mmHg), and the residue was partitioned between ethyl acetate (6 kg) and water (3.4 kg). The organic layer was washed with water (3.4 kg) and concentrated in vacuo (50 °C, 50 mmHg), which afforded aziridine **19** as a brown oil (1.66 kg, 97.3% crude yield). An analytical sample of **19** was prepared by column chromatography (45% EtOAc/45% hexanes/10% MeOH, R_f 0.5) as a pale yellow oil: FT IR (film) 1711, 1656 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.78−6.75 (1 H, m), 4.33−4.28 (1 H, m), 4.16 (2 H, q, J = 7.2 Hz), 3.38 (1 H, p, J = 5.8 Hz), 2.83−2.76 (1 H, m), 2.64−2.55 (1 H, m), 2.52−2.49 (1 H, m), 2.42−2.40 (1 H, m), 1.60−1.48 (4 H, m), 1.25 (3 H, t, J = 7.2 Hz), 0.94 (3 H, t, J = 7.4 Hz), 0.89 (3 H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 166.6, 132.9, 127.6, 82.0, 70.0, 60.5, 31.5, 28.2, 26.7, 26.6, 24.2, 14.1, 9.8, 9.5; HRMS calcd for $C_{14}H_{24}NO_3$ [MH$^+$] 254.1756, found 254.1759.

Ethyl (3*R*,4*R*,5*S*)-4-Amino-5-azido-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate (6). *Caution: This procedure should only be attempted by technically qualified persons who are fully familiar with the safe handling of sodium azide and ammonium azide. These reagents are highly toxic and potentially explosive.* A mixture of crude aziridine **19** (1.66 kg, 6.55 mol), dimethylformamide (3.3 kg), ammonium chloride (0.35 kg, 6.53 mol), and sodium azide (0.43 kg, 6.61 mol) was stirred and heated at 70−80 °C under a nitrogen atmosphere. *(Caution: do not exceed an internal temperature of 80 °C).* After **19** was consumed (12−18 h) by TLC analysis (Merck SG 60, diethyl ether), the reaction mixture was cooled to ambient temperature and treated with 5% aqueous sodium bicarbonate (1.97 kg, 1.17 mol). The product **6** was extracted with hexanes (4 × 1.8 kg). Concentration of the combined extracts in vacuo (50 °C, 75 mmHg) afforded the azidoamine **6** as a brown oil (ca. 1.95 kg) that was used directly in the next step. An analytical sample of **6** was prepared by column chromatography (20% EtOAc/80% hexanes, R_f 0.35) as a pale tan oil: FT IR (film) 2089, 1711 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.79−6.77 (1 H, m), 4.20 (2 H, q, J = 7.2 Hz), 3.89−3.83 (1 H, m), 3.48−3.39 (1 H, m), 3.37 (1 H, p, J = 5.8 Hz), 2.89−2.82 (2 H, m), 2.33−2.21 (1 H, m), 1.79 (2 H, bs), 1.65−1.40 (4 H, m), 1.28 (3 H, t, J = 7.2 Hz), 0.91 (6 H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 165.7, 137.3, 128.0, 81.0, 78.0, 61.5, 60.8, 55.9, 29.7, 26.3, 25.5, 14.0, 9.6, 9.2; HRMS calcd for $C_{14}H_{25}N_4O_3$ [MH$^+$] 297.1927, found 297.1926.

Ethyl (3*R*,4*R*,5*S*)-4-Acetamido-5-azido-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate (20). A solution of crude azidoamine **6** (1.95 kg, 6.56 mol) in hexanes (6 kg) and dichloromethane (3.8 kg) was treated portionwise with 7.8% aqueous sodium bicarbonate (12.4 kg, 11.51 mol) and acetic anhydride (0.56 kg, 5.48 mol) over 1 h. *(Caution: Frothing).* The aqueous layer was discarded, and the organic layer was concentrated in vacuo (40 °C, 50 mmHg). The residue was crystallized from hot ethyl acetate (0.51 kg) and hexanes (1.8 kg). After cooling to 0−5 °C for 3−24 h, the solid was isolated by filtration and washed with cold (0−5 °C) 19% ethyl acetate in hexanes (2 kg). Drying in vacuo at 25−40 °C afforded azidoacetamide **20** as a light brown solid (1.12 kg). Recrystallization from ethyl acetate (2.53 kg) and butyl ether (10.7 kg) afforded pure **20** as off-white needles (0.98 kg, 44.2% yield from **19**): mp 137−138 °C; FT IR (KBr) 2100, 1717, 1656 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.81 (1 H, dd, J = 2.2, 2.3 Hz), 6.01 (1 H, d, J = 7.4 Hz), 4.60−4.57 (1 H, m), 4.34−4.27 (1 H, m), 4.23 (2 H, q, J = 7.1 Hz), 3.40−3.31 (2 H, m), 2.88 (1 H, dd, J = 5.7, 17.1 Hz), 2.31−2.19 (1 H, m), 2.06 (3 H, s), 1.59−1.47 (4 H, m), 1.32 (3 H, t, J = 7.1 Hz), 0.93 (3 H, t, J = 7.3 Hz), 0.92 (3 H, t, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 171.1, 165.8, 137.9, 128.1, 82.0, 73.4, 61.0, 58.0, 57.2, 30.5, 26.2, 25.6, 23.5, 14.2, 9.6, 9.3. Anal. Calcd for $C_{16}H_{26}N_4O_4$: C, 56.79; H, 7.74; N, 16.56. Found: C, 56.55; H, 7.65; N, 16.68.

Ethyl (3*R*,4*R*,5*S*)-4-Acetamido-5-azido-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate Phosphate [1:1] (2·H_3PO_4). A mixture of azidoacetamide **20** (0.33 kg, 0.98 mol) and Raney nickel (107 g) in absolute ethanol (5.2 kg) was vigorously stirred for 10−16 h while hydrogen (1 atm) was bubbled through the mixture. After the starting azidoacetamide **20** was consumed by TLC analysis (Merck SG 60, EtOAc), excess hydrogen was removed by purging with nitrogen. The reaction mixture was filtered through a 0.45 μm polypropylene filter cartridge, rinsed forward with ethanol (1.0 kg), and concentrated in vacuo (45 °C, 20 mmHg) to afford free base **2** as a tan oil (ca. 0.32 kg) that solidified on standing. The free base was dissolved in absolute ethanol (2.1 kg) and added in one portion to a 55−65 °C solution of 85% phosphoric acid (108 g, 0.94 mol) in absolute ethanol (4 kg). Crystallization commenced within minutes. After cooling to 0 °C over 3−24 h with slow agitation, the precipitate was collected by filtration and washed with acetone (3 kg) to afford **2·H_3PO_4** as long white needles (0.285 kg, 71% yield): $[\alpha]_D$ = −39.9° (*c* 1, water); mp 203−4 °C; FT IR (KBr) 3500, 1719, 1661 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 6.87 (1 H, s), 4.78 (bs, HOD),

4.34 (1 H, d, J = 8.5 Hz), 4.29−4.25 (2 H, m), 4.07 (1 H, dd, J = 8.5, 11.6 Hz), 3.63−3.54 (2 H, m), 2.97 (1 H, dd, J = 5.5, 17.1 Hz), 2.54 (1 H, m), 2.10 (3 H, s), 1.62−1.55 (3 H, m), 1.53−1.45 (1 H, m), 1.31 (3 H, t, J = 7.3 Hz), 0.90 (3 H, t, J = 7.3 Hz), 0.86 (3 H, t, J = 7.3 Hz); ^{13}C NMR (125 MHz, D_2O) δ 178.1, 170.3, 140.8, 130.5, 87.1, 78.0, 65.2, 55.6, 52.0, 31.1, 28.3, 27.9, 25.2, 16.2, 11.4, 11.3; ^{31}P NMR (202 MHz, D_2O) δ 0.5 (s, PO_4). FAB MS (NBA) 313, 243, 225, 208, 166. FAB HRMS (NBA) calcd for $C_{16}H_{29}O_4N_2$ [MH^+] 313.2127, found 313.2126. Anal. Calcd for $C_{16}H_{31}O_8N_2P$ (410.4): C, 46.83; H, 7.61; N, 6.83; P, 7.55. Found: C, 46.58; H, 7.86; N, 6.80; P, 7.47.

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