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Industrial Synthesis of the Key Precursor in the Synthesis of the Anti-Influenza Drug Oseltamivir Phosphate (Ro 64-0796/002, GS-4104-02): Ethyl (3*R*,4*S*,5*S*)-4,5-epoxy-3-(1-ethyl-propoxy)-cyclohex-1-ene-1-carboxylate

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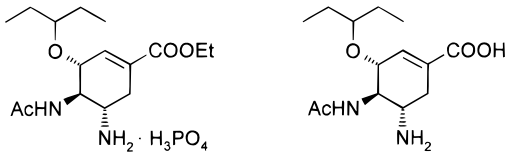
Abstract:

Starting from (−)-quinic acid, the title compound was synthesized in seven chemical steps and an overall yield of 35−38%. The route of the improved Gilead synthesis was not changed. However, significant improvements in each step led to a doubled overall yield, a 30% reduction in the number of unit operations, and an excellent quality (≥99%) of the resulting epoxide. A highly regioselective method for the dehydration of a quinic acid to a shikimic acid derivative and for the reduction of a cyclic ketal was found. Alternatively, the title compound was synthesized in six chemical steps and 63−65% yield from commercially available (−)-shikimic acid. Compared to the optimized quinic acid route, the production time was reduced by about 50%. The quality of epoxide produced from either natural product was equivalent. Therefore (−)-shikimic acid is the preferred raw material. The absolute configuration of the epoxide was determined by X-ray single crystal structure analysis and it was demonstrated that the epoxide was stereoisomerically pure.

Introduction

Oseltamivir phosphate **1**, discovered by Kim et al. from Gilead Sciences,[1] is the prodrug of the potent neuraminidase inhibitor **2** and targeted for use as an orally active antiviral compound for prevention and treatment of influenza infections (Figure 1).

On the basis of the discovery synthesis, Rohloff et al. had developed a conceptionally elegant synthesis of **1** from (−)-quinic acid **3** (Scheme 1).[2] This synthesis was satisfactory for the production of kilogram quantities of **1** for initial toxicological and phase I clinical studies. However, the demand for drug substance increased substantially as it entered phase II and III clinical trials. To enable large-scale production of epoxide **10**, each step of the synthesis required further improvement. Special focus was directed to the dehydration reaction to form the shikimic acid derivative **7** and the reductive ketal opening to form hydroxyether **9**. Furthermore, the development of an industrial synthesis of epoxide **10** from (−)-shikimic acid **23** (Scheme 6) is described.



1 Oseltamivir phosphate Ro 64-0796/002 (GS-4104-02)

2 Ro 64-0802 (GS-4071)

Figure 1.

Results and Discussion

Quinic Acid Route. Originally, the conversion of (−)-quinic acid **3** to lactone **4** was carried out with 2,2-dimethoxypropane in refluxing acetone followed by an extractive workup (Scheme 1).[2] We found that under these conditions the reaction did not go to completion and obtained a black-green reaction mixture which contained about 20% methyl ester **12**, 8% bis-acetonide **13**, and many other unknown by-products (Scheme 2). Furthermore, during extractive workup a substantial amount of the by-products **12** and **13** were lost to the aqueous layer and therefore no longer available for the ethanolysis reaction.

The reaction proceeded faster (90 min) and much cleaner in EtOAc when the generated MeOH and acetone were continuously removed from the reaction mixture by azeotropic distillation (Scheme 2). As a result, the reverse reaction (methanolysis of **11** to **3**) was prevented, and only 2% of bis-acetonide **13** and 6% of methyl ester **12** were formed. The first step of the reaction, which occurs even at ambient temperature, is the formation of acetonide **11** which lactonizes to **4** upon heating. Apart from **12** and **13**, the crude product (>90% **4)** contained only traces of other impurities and could be used in the next step without extractive workup. Skipping of the extraction also prevented the removal of **12** and **13**, which were both converted to ethyl ester **5** in the ethanolysis reaction.

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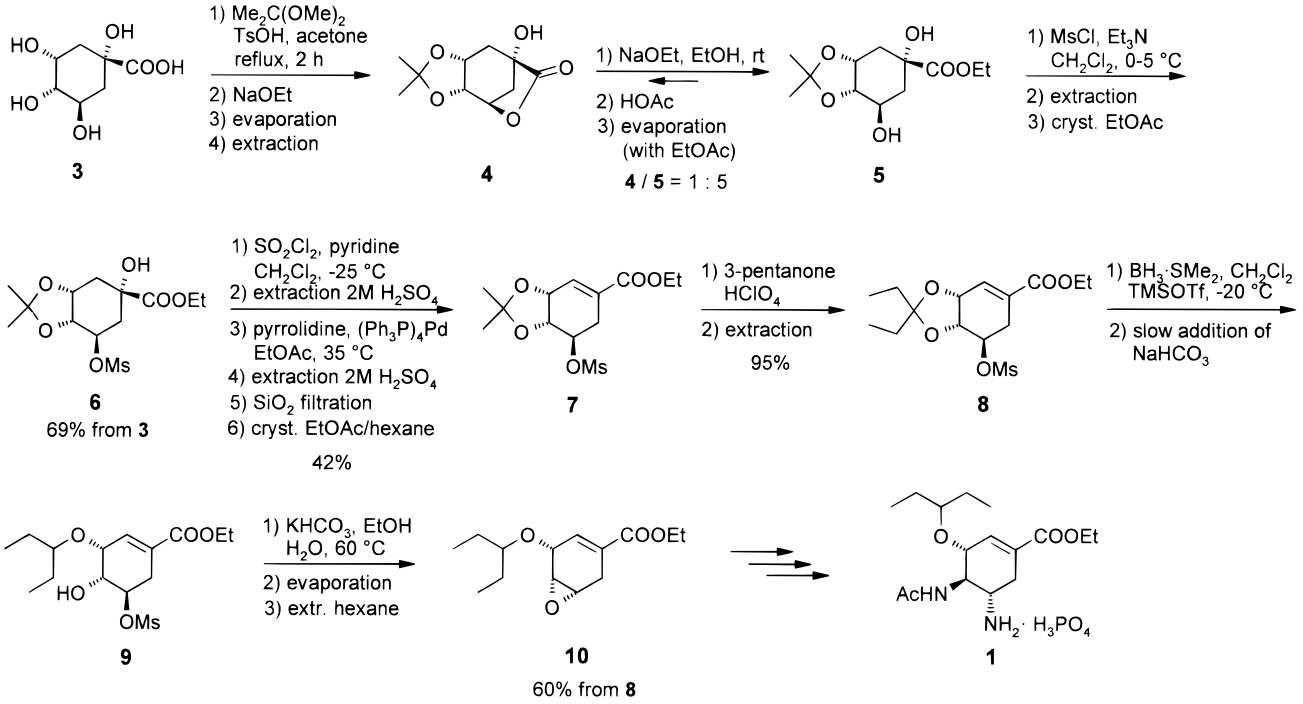
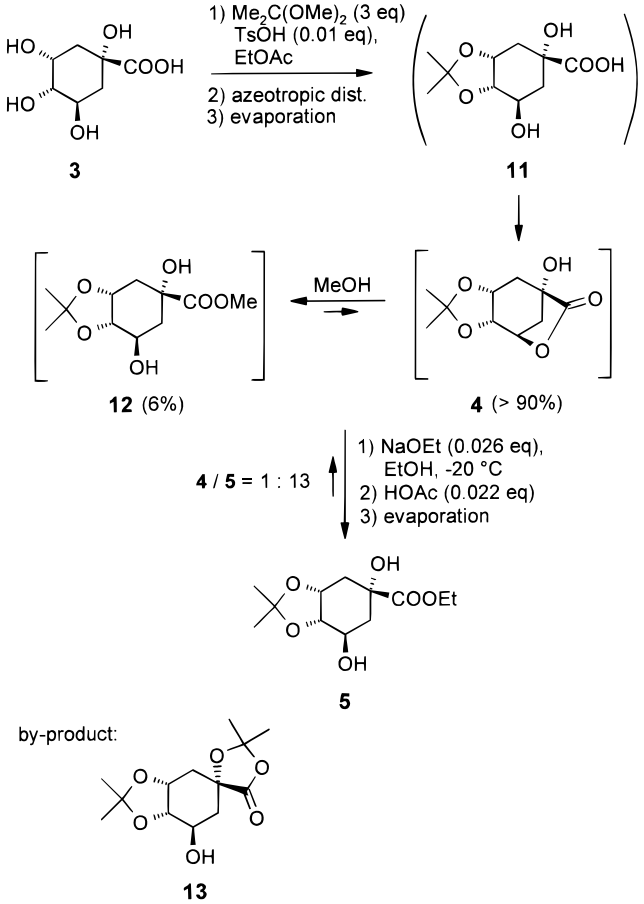
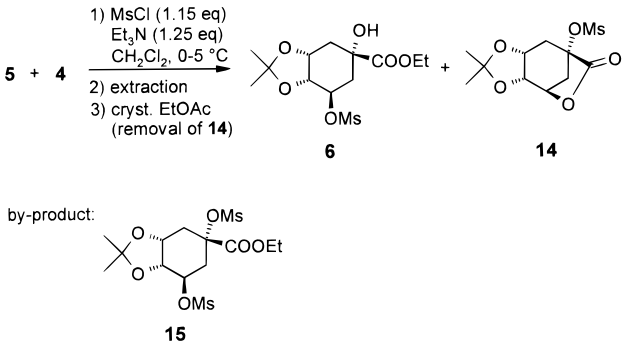
Scheme 1. **Synthesis of epoxide 10 according to Rohloff et al.[2]**



Scheme 2. **Synthesis of ethyl ester 5**



Scheme 3. **Mesylation of 5**

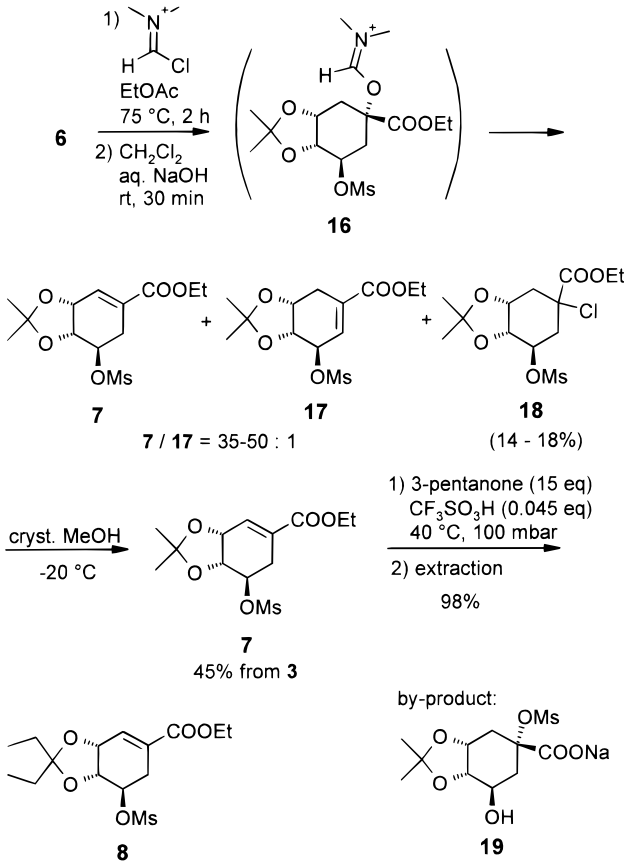


The acid catalyst (0.01 equiv TsOH) in the mixture of **4**, **12**, and **13** was neutralized with NaOEt and ethanolysis effected by addition of a small excess of NaOEt in EtOH. At ambient temperature, a 5:1 mixture of ethyl ester **5** and lactone **4** was obtained.[2] We found that at −20 °C, the equilibrium shifted to a 13:1 ratio in favor of the desired ethyl ester **5**. To stabilize the ratio, NaOEt was neutralized with HOAc at −20 °C and EtOH was evaporated at room temperature. Residual EtOH was removed by azeotropic distillation with EtOAc. The crude product was taken on directly to the mesylation reaction.

The modified production process of **5** from **3** resulted in less than half the number of unit operations, a substantially improved yield of 90−93%, and a much better impurity profile.

Complete mesylation of the 5-hydroxy group of ethyl ester **5** and the 1-hydroxy group of lactone **4** was accomplished with a slight excess of MsCl (1.15 equiv) in the presence of NEt_3 (1.25 equiv) in CH_2Cl_2 (Scheme 3). Under these conditions less than 3% dimesylate **15** was formed. The occasional formation of emulsions during extractive workup was suppressed by adjustment of the pH to 7.5−7.8 with HCl. Most of the mesyllactone **14** was removed by crystallization from EtOAc, the rest by a hydrolytic workup in the following step.

Scheme 4. **Elimination reaction and transketalization**



According to Rohloff et al., hydroxymesylate **6** was dehydrated to the shikimic acid derivative **7** with SO_2Cl_2/pyridine in CH_2Cl_2 at −20 °C (Scheme 1).[2] The strongly exothermic reaction gave a 4:1:1 mixture of the desired 1,2-olefin **7**, the regioisomeric 1,6-olefin **17** and the chloro compound **18** (Scheme 4). The allylic mesylate **17** was reacted with pyrrolidine under $(PPh_3)_4Pd$ catalysis to the corresponding pyrrolidine derivative which was removed by extraction with aqueous H_2SO_4.[2] Due to its complexity, the high catalyst cost, and the low yield, this procedure was deemed inappropriate for large-scale production.

A number of alternative dehydrating reactions were examined. $POCl_3$/pyridine[3] gave a slightly better ratio of **7** and **17** (6:1). However, 25% of the chloro compound **18** and other by-products were also formed. With Tf_2O in pyridine/MeCN a 2:1 mixture of **7** and **17** was obtained. A better selectivity in the elimination reaction was achieved in aprotic dipolar solvents (MeCN, *N*-methyl pyrrolidone, and DMF). SO_2Cl_2/DBU in MeCN at −15 °C resulted in a 80:5:3 mixture of **7**/**17**/**18**. However, the isolated yield of **7** was only 43%.

A breakthrough concerning selectivity and yield was achieved with Vilsmeier's salt which was prepared either in situ from DMF and $POCl_3$, $(COCl)_2$, or $COCl_2$ or purchased as (chloromethylene)dimethyliminium chloride.[4] The reaction proceeds via the imidate ester **16**, which upon heating very selectively eliminates DMF to yield the 1,2-olefin **7** and only trace amounts of the 1,6-olefin **17** (ratio of **7**/**17** = 35−50:1). To the best of our knowledge this is the most selective and straightforward method to synthesize a shikimic acid derivative from quinic acid.[5] Vilsmeier's salt has frequently been used for the dehydration of oximes to nitriles.[6] However, only a few examples have been reported in which the dehydration of alcohols to olefins was observed.[7]

As a side reaction 14−18% of the chloro compound **18** formed. Attempts were made to avoid the formation of **18**. However, all experiments with chloride-free Vilsmeier's salts (Tf_2O/DMF, oxalyl bromide/DMF) failed, emphasizing the importance of Cl^- as a base in this elimination reaction.

The mesyllactone **14** from the previous step remained unchanged under the reaction conditions. Upon workup, it was hydrolyzed with ice cold NaOH to the corresponding hydroxyacid **19** and extracted into the aqueous layer. The chloro compound **18** and the 1,6-olefin **17** remained in the mother liquor when **7** was crystallized from MeOH. Transesterification of the ethyl ester **7** to the corresponding methyl ester was not observed during crystallization. The desired product **7** was isolated in 65−68% yield and assayed to >98%. Crystallization of **7** from EtOH gave a lower yield and an inferior impurity profile.

For the transketalization of **7** to **8**, the potentially hazardous catalyst $HClO_4$[2] was replaced by CF_3SO_3H. Continuous distillation of acetone at 400 °C/100−150 mbar provided the pentylideneketal **8** almost quantitatively. To prevent ketal hydrolysis upon workup, the reaction mixture was neutralized with Et_3N. Residual 3-pentanone was removed to <0.5% by azeotropic distillation with cyclohexane.

The reductive opening of pentylideneketal **8**, devised by Rohloff et al., is an elegant way to introduce the 3-pentyl ether moiety into the molecule (Scheme 1).[2] $BH_3{\cdot}SMe_2$ and TMSOTf in CH_2Cl_2 were employed, a combination of reagents recently published by Hunter,[8] and afforded a 10:1:1 mixture of the isomeric hydroxyethers **9** and **20** and the diol **21** (Scheme 5). It was found that the reductive ketal opening was initiated only after addition of aqueous $NaHCO_3$ precluding reaction monitoring by HPLC. Furthermore the regioselectivity of the reaction deteriorated with time.[2]

For large-scale production of the epoxide **10**, $BH_3{\cdot}SMe_2$ and TMSOTf were considered unsuitable and a more robust and possibly also more selective method was sought. A screening with different reducing agents with or without (Lewis) acids was carried out. $BH_3{\cdot}THF$,[9] $NaBH_4$/CF_3COOH,[10] $NaCNBH_3/BF_3{\cdot}OEt_2$,[11] DIBAH,[12] and Et_3SiH/

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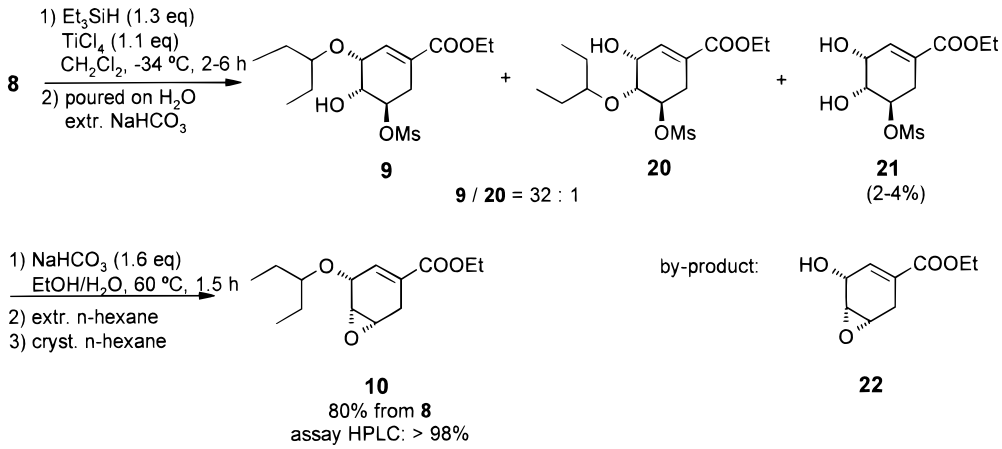
Scheme 5. **Reductive ketal opening and epoxide formation**



Nafion-H[13] gave unsatisfactory results. However, a very selective reduction was observed with the reagent combination $Et_3SiH/TiCl_4$[11,14,15] in CH_2Cl_2 (Scheme 5). At −34 °C, a 32:1 mixture of hydroxyether **9** and isomer **20** was obtained along with 2−4% diol **21**. For complete conversion, a small excess of $TiCl_4$ was necessary. CH_2Cl_2 appeared to be the only suitable solvent. No reaction was observed in *t*-BuOMe, THF, EtOAc or toluene. The reaction was preferentially carried out at −32 to −36 °C. At higher temperatures (−20 or 0 °C), a substantial amount of diol **21** was formed, and therefore epoxide **10** was isolated in lower yields. At −78 °C, no reaction occurred. The reaction was quenched with an ice/H_2O mixture. The titanium salts remained dissolved in the aqueous layer (pH < 0) and were precipitated as TiO_2 by the adjustment of the pH to 7.0 with 28% aqueous NaOH. Residual CH_2Cl_2 was stripped off, and the fine TiO_2 was separated on a filter press.

The organic layer was concentrated and the crude hydroxy ether **9** was converted to **10** with $NaHCO_3$ in EtOH/H_2O at 60 °C. Epoxide **10** was extracted with hexane at 35 °C and crystallized by lowering the temperature to −20 °C. The product was isolated as a white, crystalline solid in 80% yield and had an assay of typically 99%. Diol **21** was partially removed during the extractive workup of the reductive ketal opening reaction. The remainder (1−2%) cyclized to hydroxyepoxide **22** upon treatment with $NaHCO_3$ and was extracted into the H_2O/EtOH layer. The isomeric ether **20** did not react under the basic conditions and was removed by crystallization. Another by-product of the reductive ketal opening, Et_3SiOH, was extracted into the hexane layer and was removed during the crystallization of epoxide **10**.

Attempts to replace the fairly expensive Et_3SiH by other reducing agents failed. Poly(methylhydrosiloxane)[16] also reduced ketal **8** selectively to hydroxyether **9**. Unfortunately the reaction did not go to completion, and emulsions were obtained in the aqueous workup. Complete conversion of **8** to **9** with 1,1,3,3-tetramethyl-disiloxane required 1.0 equiv of the reagent which indicates that only one of the two hydrides was transferred in the reaction. Compared to that for Et_3SiH, the reaction proceeded more sluggishly (16 h at −15 °C) and 5−10% diol **21** was formed.

Shikimic Acid Route. (−)-Shikimic acid **23** (Scheme 6) represents an ideal alternative raw material for the synthesis of epoxide **10** due to the fact that the double bond is already present in the correct position. This of course bypasses the regioselective dehydration of **6** to **7** which is, despite the considerably improved protocol, still a moderately yielding step. As suppliers were identified which were able to manufacture **23** on a large scale, either by fermentation or by extraction of star anise or ginkgo leaves, an efficient synthesis of ketal **8** from this natural product was developed. Depending on the source, batches of (−)-shikimic acid had assays ranging from 85 to 99% and very different impurity profiles. Thus, a process had to be developed able to cope with variable quality. We evaluated two routes: the direct conversion to pentylideneketal **8** and the route via acetonide **7**. The acetonide route was preferred to the pentylideneketal route, although longer by one step. Acetonide **7** is a highly crystalline compound which can be purified efficiently. In contrast, the intermediates of the pentylidene route **25** and **8** are oils and had to be carried through in crude form. Hence, purification was only possible at the stage of epoxide **10**. The resulting epoxide **10** often did not meet the quality requirements and had to be reprocessed. Furthermore, the overall yield decreased from 65 to 45%. Therefore, the direct route through intermediate **25** was dropped.

(−)-Shikimic acid **23** was esterified under acidic conditions. With H_2SO_4 (0.05 equiv) or TsOH (0.1 equiv) in boiling EtOH the reaction proceeded slowly and even after 20 h ∼5% starting material remained unreacted. Better results

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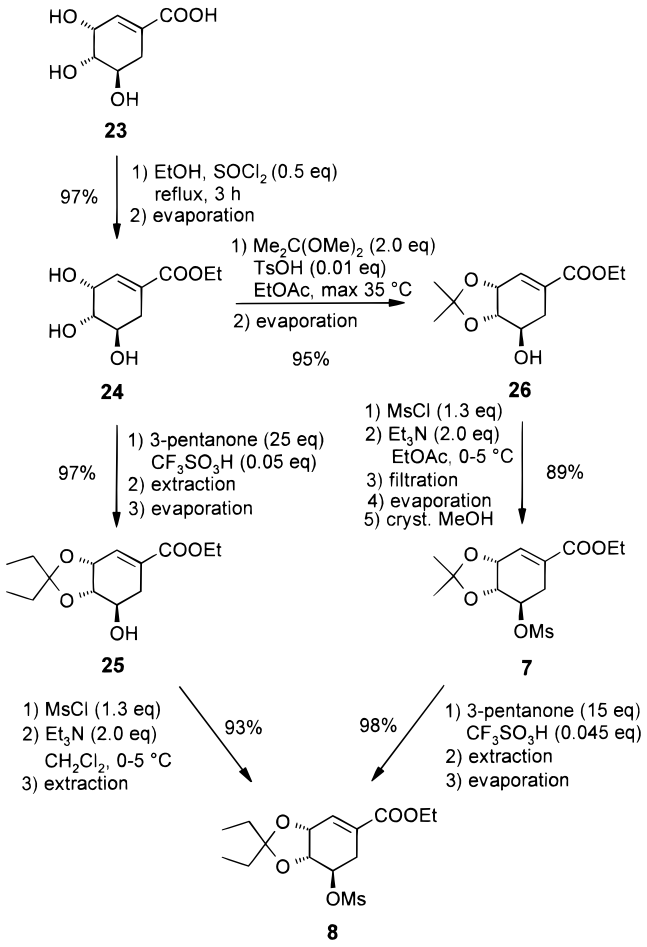
Scheme 6. **Synthesis of pentylidene ketal 8 from shikimic acid 23**



were achieved with EtOH/$SOCl_2$. After 3 h at boiling temperature, <2% of **23** was detected. The solvent was exchanged from EtOH to EtOAc and crude ethyl shikimate **24** was treated with 2,2-dimethoxypropane in the presence of TsOH to give ketal **26**. MeOH was removed by azeotropic distillation at 35 °C under reduced pressure.

Mesylation of **26** was accomplished in EtOAc. The normal aqueous workup was deemed unsuitable for technical scale due to the formation of emulsions, which were difficult to break. A practical solution for this problem was found whereby the crude reaction mixture was filtered on a basket centrifuge to remove $Et_3N{\cdot}HCl$ and insolubles. The filtrate was concentrated and the residual crude product crystallized from MeOH and yielded **7** in 82% yield with an assay of 97−99%.

Mesylate **7** was converted to epoxide **10** as described above. It was isolated with an overall yield of 63−65% from shikimic acid **23** and had an assay of ≥99%.

Impurity Profile. The impurity profiles of epoxide **10**, produced either from (−)-quinic acid or (−)-shikimic acid were equivalent. No impurities related to these raw materials or to the different synthetic routes were found in crystallized epoxide at levels above 0.1%; hence a single set of specifications was defined for **10**.

The only significant impurities detected in the isolated material, were the precursors pentylideneketal **8** and hydroxyether **9**, hydroxyether-isomer **20**, the isopropylether **27**, the 2-butylether epimers **28**, the 2-pentylether epimers **29**, and the methyl ester **30** (Figure 2).

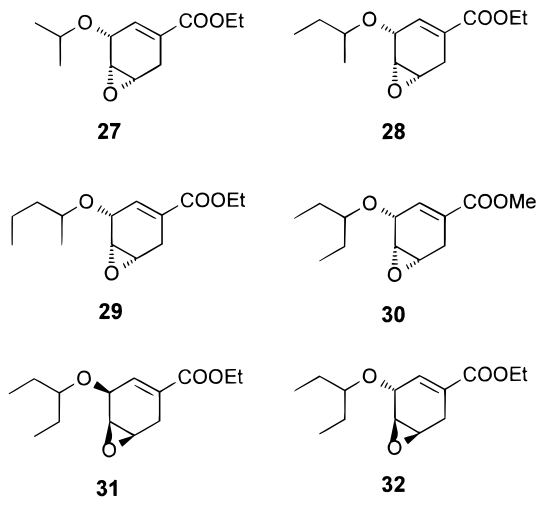


Figure 2. **Impurities in epoxide 10.**

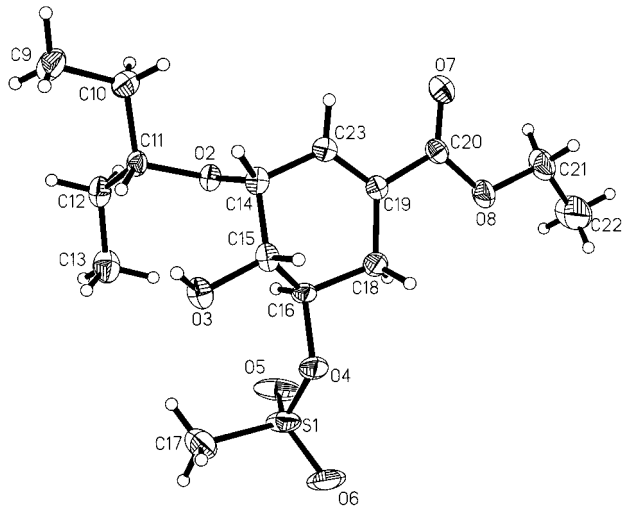


Figure 3. **Monoview of compound 9. Atoms are drawn with anisotropic displacement parameters at 30% probability level with arbitrary numbering of the non-hydrogen atoms. The absolute configuration is (3*R*,4*R*,5*R*).**

Isopropylether **27** is the reaction product of residual acetonide **7** which was not converted to pentylideneketal **8** in the transketalization step. The epimers of **28** arise from trace amounts of butanone in commercial 3-pentanone. Methyl ester **30** was derived from the methyl ester of **7** which itself results from transesterification reactions at various stages of the synthesis. Only minute amounts of **30** were detected in the crystallized epoxide. The 2-pentylethers **29** formed during the reductive ketal opening and do not result from the corresponding ketals since no 2-pentanone was detected in 3-pentanone. Currently no mechanistic explanation for the formation of **29** is available.

Some of these impurities **27**, **28**, **29**, and **30** undergo functional group transformations in analogy to epoxide **10** and were detectable as their corresponding derivatives in the drug substance **1**. To control their levels, appropriate specifi-

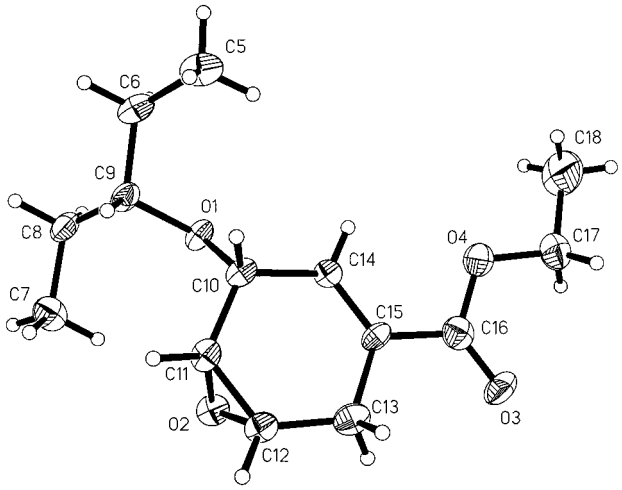


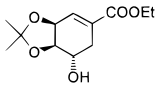
Figure 4. **Monoview of compound 10. Atoms are drawn with anisotropic displacement parameters at 30% probability level with arbitrary numbering of the non-hydrogen atoms. The absolute configuration is (3*R*,4*S*,5*S*).**

cations were set for each intermediate in the synthesis and for the raw material 3-pentanone.

The expected high stereoisomeric purity of epoxide **10** was confirmed using appropriate analytical methods. The absence of the enantiomer **31**[17] was verified by chiral HPLC, whereas the absence of the *trans*-epoxide **32**[18] (and its enantiomer) was confirmed by achiral reversed phase HPLC.

X-ray Crystallography, Absolute Configuration of 10. By X-ray analysis the absolute configuration of compound **9** (Figure 3) was reliably determined by refinement of the absolute structures. The parameter for the absolute configuration gave Flack-values of zero for the (3*R*,4*R*,5*R*) configuration corresponding to the correct assignment of the absolute configuration to the refined structure.[19] As the configuration of the ethylpropoxy-bearing carbon (3*R*) does not change during the epoxide formation (see Scheme 5), the absolute configuration of compound **10** (Figure 4) can be deduced from the absolute configuration of compound **9** and the relative configuration of the three chiral centers as emerged from the X-ray analysis of compound **10**. The absolute configuration of compound **10** is (3*R*,4*S*,5*S*).

(17) L-Mannose was converted to (+)-ethyl 3,4-*O*-isopropylideneshikimate **33** according to Fleet, G. W. J.; Shing, T. K. M.; Warr, S. M. *J. Chem. Soc. Perkin Trans. I* **1984**, 905. **33** was converted to **31** as described above.



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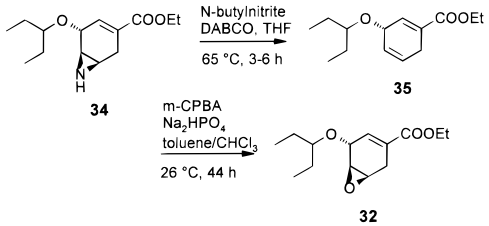
(18) The diastereomer **32** was synthesized from aziridine **34**, an advanced intermediate of the synthesis of **1**,[2] by deamination and stereoselective epoxidation of the resulting 1,4-diene **35**.



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Conclusion

The seven-step Gilead synthesis of epoxide **10** from (−)-quinic acid was significantly improved. A highly selective method for the dehydration of the quinic acid derivative **6** to the shikimic acid derivative **7** and for the reduction of the cyclic ketal **8** was found. The overall yield was increased from 17 to 35−38%, the number of unit operations was reduced by about 30%, and the resulting epoxide was of excellent quality (≥99%).

Alternatively, epoxide **10** has been synthesized in six steps and 63−65% yield from commercially available (−)-shikimic acid. Compared to that for the optimized quinic acid route, the cycle time was halved.

The quality of epoxide **10** produced from either natural product was equivalent. The absolute configuration of **10** was determined by X-ray single crystal structure analysis, and it was demonstrated that **10** was stereoisomerically pure.

Both syntheses were used on production scale (50−250 kg batches). At several stages of the process the evaporation of the solvent led to solid residues. This was neither a problem in the miniplant runs nor on production scale.

The epoxide **10** produced was used for the manufacture of drug substance **1** needed for phase II and III clinical trials as well as for the launch of Oseltamivir phosphate.

Experimental Section

General. Reagents and solvents were used as received from commercial suppliers. (−)-Shikimic acid **23** (assay 85−99%), obtained by fermentation or from star anise or ginkgo leaves, and (−)-quinic acid **3** (assay >98%), isolated from chinchona bark, were used. Both materials are commercially available from various suppliers. All reactions were carried out in standard miniplant equipment consisting of a 35-L glass-lined Büchi reactor with variable speed agitator, −50 to 150 °C jacket temperature range, a separate 100-L extraction vessel, and a 20-mbar vacuum to 1050 mbar pressure rating. The equipment was connected to a gas scrubber charged with 10% aqueous sodium hydroxide solution. Solids were separated on a 40-cm ∅ basket centrifuge from GFT-Trenntechnik. All equipment was inspected visually for cleanliness and integrity before use. All reactions were carried out under a nitrogen atmosphere. Nitrogen was also routinely used to break vacuums for safety reasons.

^{1}H NMR were recorded using tetramethylsilane as an internal standard. Spectra are given in ppm (δ) and coupling constants, *J*, are reported in hertz. Peaks in IR spectra are reported in cm^{-1} with the following relative intensities: s (strong, 0−33% transmittance), m (medium, 34−66%). Low-resolution EI mass spectra were obtained with an ionization voltage of 70 eV. Data are reported in the form of *m*/*z* (intensity relative to base = 100). Analytical HPLC was performed on a Hewlett Packard 1050 or 1100 system with UV detection at a wavelength of 210 nm using a LiChrospher 100 RP18 endcapped (5 μm) 250 × 4 mm column (Merck) and gradient elution with H_2O/MeCN. Chiral HPLC was performed on a Chiracel OD column (Daicel). GC analysis was performed on a Hewlett Packard 5890 or 6890 system equipped with split injection and FID. A DB-1

column of 30-m length, 0.25-μm film thickness, and ID 0.32-mm column (J&W) was used for all compounds with helium as carrier gas (75 kPa). The samples were derivatized with a 1:1 mixture of MSTFA and pyridine at room temperature.

Quinic Acid Route. (1*R*,2*R*,6*R*,8*S*)-8-Hydroxy-4,4-dimethyl-3,5,10-trioxa-tricyclo[6.2.1.0]-2,6-undecan-9-one (3,4-*O*-isopropylidene-1,5-quinic Acid Lactone) (4). (−)-Quinic acid ((1S_n,3*R*,4S_n,5*R*) tetrahydroxycyclohexanecarboxylic acid[20]) **3** (3.00 kg, GC assay 99.7% w/w, 15.6 mol) was suspended in EtOAc (20.0 L). TsOH·H_2O (29.8 g, 0.156 mol) and 2,2-dimethoxypropane (4.9 kg, 47 mol) were added, and the mixture was heated to 70−78 °C with a jacket temperature of 90 °C. Solvent (a mixture of EtOAc, 2,2-dimethoxypropane, MeOH, and acetone) was removed by distillation for 1 h. During distillation the temperature in the gas phase rose from 55 to 65 °C. In total 10 L of solvent were distilled off. Then the reaction mixture was cooled to 35 °C in 30 min and concentrated at reduced pressure (initially 140 mbar, later reduced to 20 mbar). The residual brownish solid, lactone **4**, was dissolved in EtOH (24.0 L) and used in the next step.

Ethyl (3a*R*,5*R*,7*R*,7a*S*)-5,7-dihydroxy-2,2-dimethyl-hexahydro-benzo[1,3]dioxole-5-carboxylate (Ethyl 3,4-*O*-Isopropylidene-1,5-quinate) (5). To the stirred solution of crude lactone **4** in EtOH was added NaOEt in EtOH (134 g, assay 21% w/w, 0.41 mol) in 5 min. The mixture was stirred at 20 °C for l h, cooled to −20 °C in 2 h, and stirred overnight at this temperature. The reaction mixture was neutralized at −20 °C with HOAc (21.1 g, 0.35 mol) and warmed up to 15−20 °C in 0.5 h. GC analysis of the reaction mixture showed 89% of ethyl ester **5** and 7% of lactone **4**. EtOH was distilled off at this temperature at a vacuum of 20−50 mbar. The residue was taken up in EtOAc (9.1 L), and the solution was concentrated at a jacket temperature of ≤35 °C and 20−50 mbar. The residual brownish solid, a mixture of ethyl ester **5** and lactone **4** (ratio 13:1), was dissolved in CH_2Cl_2 (12.0 L) and used in the next step.

Ethyl (3a*R*,5*S*,7*R*,7a*R*)-5-Hydroxy-7-methanesulfonyloxy-2,2-dimethyl-hexahydrobenzo[1,3] dioxole-5-carboxylate (Ethyl 3,4-*O*-Isopropylidene-5-*O*-methanesulfonyl Quinate) (6). To the cold (0−5 °C) solution of crude **5** (13.4 mol) in CH_2Cl_2, MsCl (1.76 kg, 15.5 mol) was added. Et_3N (1.68 kg, 16.6 mol) was added at a rate that the temperature of the reaction mixture did not exceed 5 °C. The addition of Et_3N was completed after 70 min, and stirring at 5 °C was continued for another 60 min. Then GC analysis of the reaction mixture indicated <0.5% ethyl ester **5**. The reaction mixture was diluted with water (3.2 L), and the pH was adjusted to 7.5−7.8 by addition of 0.5% aqueous HCl. After phase separation, the organic layer was washed with H_2O (2 × 9.6 L), and the combined aqueous layers were re-extracted with CH_2Cl_2 (4.8 L). The combined organic layers were concentrated at 30 °C under reduced pressure (initially 400 mbar, later reduced to 20 mbar). Residual CH_2Cl_2 was removed by co-evaporation with EtOAc (12.8 L) at reduced pressure (100 mbar, 30 °C). The residual oil contained mesylate **6** and mesyllactone **14** in a ratio of 13:1. It was dissolved in EtOAc (4.0 L) and the solution was stirred at 0 °C over night. The precipitated mesyllactone **14** was removed by centrifugation and washed with EtOAc (1.5 L). The combined, brown organic layers (containing mesylate **6** and still 2−3% mesyllactone **14**) were directly used in the next step.

Ethyl (3a*R*,7*R*,7a*R*)-2,2-Dimethyl-7-methanesulfonyloxy-3a,6,7,7a-tetrahydrobenzo[1,3]dioxole-5-carboxylate (Ethyl 3,4-*O*-Isopropylidene-5-*O*-(methansulfonyl) Shikimate) (7). The solution of crude **6** in EtOAc (total volume 10 L) was added at rt to a suspension of (chloromethylene)dimethyliminium chloride (2.0 kg, 15.6 mol) in EtOAc (5.5 L) in 10 min. After a slightly exothermic reaction, an orange-red suspension formed. The suspension was warmed up to 70−78 °C (above 60 °C a red-brown solution was obtained) in 30−40 min. Stirring at this temperature was continued for 2 h. Subsequent GC analysis of the reaction mixture indicated <0.5% iminoester **16** (detected as the corresponding formate). The reaction mixture was cooled to 45 °C in 20 min and concentrated under reduced pressure (100 mbar) at this temperature. The residual, brown oil was taken up in CH_2Cl_2 (9.4 L), and the solution was added to a cold (−5 °C) solution of aqueous NaOH (28%, 4.4 kg) and H_2O (18.0 L) at a rate that the temperature did not exceed 0 °C. The addition took 40 min at a jacket temperature of −10 to −20 °C. The resulting mixture was stirred for 30 min while the temperature was raised to 20−25 °C and kept stirring for another 30 min at this temperature. After phase separation, H_2O (4.7 L) was added to the separated organic layer, and the pH of the mixture was adjusted to 8.5−9.0 with HCl (2 N, 0.57 kg). The organic layer was washed with H_2O (4.7 L), separated, and collected. EtOAc (0.7 L) was added, and the solution was concentrated at 100−200 mbar and 45 °C jacket temperature. The partially crystalline residue was suspended in CH_3OH (2.0 L) and the suspension was stirred for 5 min. Solvent was again removed by distillation at 100 mbar. The crystalline residue was dissolved in CH_3OH (3.2 L) at 60−65 °C and the dark brown solution was cooled to −20 °C in 3 h. At a temperature of 40−45 °C crystallization was induced by seeding of **7** (10 g). The thick suspension was stirred at −20 °C for 1 h. The product was collected by centrifugation and washed with CH_3OH (2 × 2.2 L, −15 °C). It was dried to constant weight (35 °C, 20 mbar, 6 h) to yield 2.25 kg of mesylate **7** (HPLC assay 99.0% w/w, 6.95 mol, 45% yield from **3**) as a beige solid.

Ethyl (3a*R*,7*R*,7a*R*)-2,2-diethyl-7-methanesulfonyloxy-3a,6,7,7a-tetrahydrobenzo[1,3]dioxole-5-carboxylate (Ethyl 3,4-*O*-Isopentylidene-5-*O*-(methansulfonyl) Shikimate) (8). A solution of acetonide **7** (7.50 kg, HPLC assay 97.7% w/w, 22.9 mol) and CF_3SO_3H (0.153 kg, 1.02 mol) in 3-pentanone (12.0 L) was heated to boiling temperature (40 °C) under partial vacuum of 100−150 mbar. Within 1 h a mixture of acetone and 3-pentanone (1.5 L) was removed by distillation. The vacuum was then adjusted to 50 mbar, and distillation was continued for another 4 h. During this time, 3-pentanone was added continuously at a rate (4.5 L/h) such that the volume in the reactor remained constant. The reaction mixture was cooled to rt in 15 min. GC analysis

showed 98.2% **8** and 0.2% **7**. The reaction mixture was neutralized with Et_3N (0.216 kg; 2.13 mol) and concentrated at ≤35 °C under reduced pressure (20 mbar). Residual 3-pentanone (ca. 3%) in the crude product was removed by azeotropic distillation with cyclohexane (2 × 9.0 L) at 150−50 mbar and 30 °C. The remaining oil was dissolved in CH_2Cl_2 (6.0 L), and the solution was extracted with aqueous $NaHCO_3$ (7.5%, 13.5 kg). The organic layer was washed with H_2O (8.1 L) and concentrated under reduced pressure (200−50 mbar, 30 °C) to afford pentylideneketal **8** as a yellow oil in 98% yield (7.97 kg, HPLC assay 98.7% w/w, 22.6 mol). **8** can be stored as a 40% solution in CH_2Cl_2 at 5 °C.

Ethyl (3*R*,4*R*,5*R*)-3-(1-Ethyl-propoxy)-4-hydroxy-5-methanesulfonyloxy-cyclohex-1-ene-1-carboxylate (9). To a cold (−32 to −36 °C) solution of pentylidene ketal **8** (2.63 kg, 7.55 mol) in CH_2Cl_2 (21.0 L, H_2O content 0.02%), Et_3SiH (1.18 kg, 10.2 mol) was added. A solution of $TiCl_4$ (1.60 kg, 8.47 mol) in CH_2Cl_2 (1.95 L) was added at a rate such that the temperature of the reaction mixture did not exceed −32 °C. The addition of $TiCl_4$ was completed after 90 min. Stirring at −36 to −32 °C was then continued for another 2 h. To monitor the reaction progress, a 30-mL sample of the reaction mixture was drawn and quenched as described below. HPLC analysis of the organic layer indicated that all of the starting material **8** had been consumed (0.20%). The reaction mixture was rapidly added to a stirred ice/H_2O mixture (9.4 kg, 17.0 L) and the connecting lines were washed with CH_2Cl_2 (2.5 L). The resulting biphasic mixture had a temperature of −3 °C and was warmed to 5 °C applying a maximum jacket temperature of 35 °C. The organic layer was washed with aqueous $NaHCO_3$ (7.5%, 18.4 kg) and concentrated under reduced pressure (400−200 mbar, 35 °C). Hydroxyether **9**, a beige solid, was dissolved in EtOH (10.6 L) and used in the next step. *Optional crystallization*: Traces of CH_2Cl_2 were evaporated at reduced pressure (50 mbar, 35 °C), the dry crystalline residue was suspended in hexane (6.9 L), and the solvent was evaporated. The solid was dissolved in EtOAc (1.25 L) at 30 °C, and hexane (19.3 L) was added to the solution over 60 min. Crystallization set in spontaneously after about 5 L hexane had been added. The suspension was cooled to −20 °C in 2 h and stirred for 1 h at this temperature. The product was collected by centrifugation and washed once with cold (−20 °C) hexane (5.75 L). It was dried (35 °C, 20 mbar, 4 h) to constant weight to yield 2.32 kg hydroxyether **9** (HPLC assay 98% w/w, 6.49 mol, 87% yield) as an off-white solid.

Ethyl (3*R*,4*S*,5*S*)-4,5-Epoxy-3-(1-ethyl-propoxy)-cyclohex-1-ene-1-carboxylate (10). To the stirred solution of crude hydroxyether **9** in EtOH was added aqueous $NaHCO_3$ (7.5%, 14.0 kg). The reaction mixture was heated to 60−65 °C in 60 min, and stirring at this temperature was continued for 1.5 h. After this time HPLC showed that all of the starting material had been consumed (**9** < 0.10%). The reaction mixture was cooled to 35 °C in 30 min and extracted with *n*-hexane (4 × 17.3 L). The combined organic layers were washed once with H_2O (10.2 L) at 35 °C and concentrated under reduced pressure (200 mbar, 35 °C) to a residual volume of 28 L. The pale yellow solution was cooled to −18 °C in 3 h. At 15 °C, the product crystallized spontaneously. The suspension was stirred at −18 °C for 2 h. The product was collected by centrifugation and washed with cold (−15 °C) *n*-hexane (2.2 L). It was dried (30 °C, 20 mbar, 4 h) to constant weight to yield 1.55 kg **10** (6.03 mol, HPLC assay 98.9% w/w, 80 % yield) as a fluffy white solid.

Shikimic Acid Route. Ethyl (3*R*,4*S*,5*R*)-3,4,5-Trihydroxy-cyclohex-1-ene-carboxylate (Ethyl Shikimate) (24). To a stirred suspension of (−)-shikimic acid ((3*R*,4*S*,5*R*)-3,4,5-trihydroxy-cyclohex-1-ene-carboxylic acid) **23** (2.00 kg, GC assay 91.6% m/m, 10.5 mol) in EtOH (8.0 L) was added $SOCl_2$ (0.61 kg, 5.13 mol) in 30 min, followed by toluene (0.8 L) to rinse the lines. During the addition of $SOCl_2$ the temperature rose from rt to 35 °C. Upon completion of the addition, the reaction mixture was heated to boiling temperature for 3 h. After about 1 h, all of the shikimic acid had dissolved, and a dark brown solution resulted. The reaction mixture was cooled to 40 °C in 45 min and concentrated under reduced pressure (100 mbar) at this temperature. GC analysis of the reaction mixture showed 1.7% of **23** and 90.7% of **24**. Ethyl shikimate **24** was obtained as viscous, brown oil (2.2−2.7 L), containing approximately 20% of EtOH. It was used in the next step without further purification.

For spectroscopic characterization a sample of **24** was prepared by reacting **23** (GC assay 98%) with EtOH in the presence of H_2SO_4 (0.05 equiv) at boiling temperature for 23 h. Crude **24** was recrystallized from *t*-BuOMe. Data for **24**: ^{1}H NMR (250 MHz, d_6-DMSO) 1.22 (t, J = 7.1, 3H), 2.05, 2.42 (2dm, J = 17.8, 2H), 3.58 (m, 1H), 3.85 (m, 1H), 4.12 (q, J = 7.1, 2H), 4.22 (m, 1H), 4.64 (d, J = 4.2, 1H), 4.83 (d, J = 4.2, 1H), 4.85 (s, 1H), 6.62 (s, 1H); IR (nujol) 3351 (s), 3194 (s), 2924 (s), 2871 (s), 1722 (s), 1658 (m), 1464 (m), 1371 (m), 1237 (s), 1093 (s); MS (EI) 202 (M^+, 2.2), 185 (4.3), 173 (7.2), 156 (32), 143 (37), 138 (23), 110 (20), 97 (100). Anal. Calcd for $C_9H_{14}O_5$ (202.206): C, 53.46; H, 6.98. Found: C, 53.18; H 7.03.

Ethyl (3a*R*,7*R*,7a*S*)-2,2-Dimethyl-7-hydroxy-3a,6,7,7a-tetrahydro-benzo[1,3]dioxole-5-carboxylate (Ethyl 3,4-*O*-Isopropylidene Shikimate) (26). To the crude ethyl shikimate **24**, EtOAc (13.6 L), 2,2-dimethoxypropane (1.070 kg, 10.3 mol) and $TsOH\cdot H_2O$ (0.020 kg, 0.105 mol) were added. At a vacuum of 150−200 mbar the reaction mixture was heated to boiling temperature (30−35 °C) applying a jacket temperature of 50 °C. The solvents (a mixture of EtOAc, 2,2-dimethoxypropane, MeOH and EtOH) were removed by distillation, and after about 2 h the initial volume was reduced by half. A second equivalent of 2,2-dimethoxypropane (1.070 kg, 10.3 mol) was added and the distillation at 30−35 °C was continued for further 2 h. The reaction mixture was then evaporated to dryness at 20 mbar. Acetonide **26** was obtained as a dark brown oil (assay by GC: 86.1% area) and was used in the next step without further purification. For spectroscopic characterization a sample of **26** was purified by column chromatography on SiO_2 using CH_2Cl_2 as eluent. Data for **26**: ^{1}H NMR (250 MHz, $CDCl_3$) 1.30 (t, J = 7.2,

3H), 1.41 (s, 3H), 1.46 (s, 3H), 2.23 (m, 1H), 2.62 (s, −OH), 2.82 (m, 1H), 3.89 (m, 1H), 4.09 (m, 1H), 4.22 (q, $J = 7.2$, 2H), 4.76 (m, 1H), 6.093 (m, 1H); IR (nujol) 3452 (s), 2964 (s), 2870 (s), 1712 (s), 1650 (m), 1476 (m) 1458 (m) 1383 (s), 1330 (m), 1261 (s), 1246 (s), 1209 (m), 1173 (s), 1137 (m), 1105 (m), 1098 (s), 1042 (s); MS (EI) 242 (M^+, 0.7), 227 (90), 197 (12), 167 (15), 139 (100), 121 (19), 110 (19), 95 (87), 43 (79). Anal. Calcd for $Cl_2H_{18}O_5$ (242.271): C, 59.49; H 7.49. Found: C, 59.34; H 7.35.

Ethyl (3a*R*,7*R*,7a*R*)-2,2-Dimethyl-7-methanesulfonyloxy-3a,6,7,7a-tetrahydrobenzo[1,3]dioxole-5-carboxylate (Ethyl 3,4-*O*-Isopropylidene-5-*O*-(methansulfonyl) Shikimate) (7). To the cold solution of crude acetonide **26** in EtOAc (15.2 L), MsCl (1.52 kg, 13.3 mol) was added. Then, Et_3N (2.32 kg, 22.9 mol) was added at a rate such that the temperature of the reaction mixture reached 20 °C at the end of the dosage. The mixture was stirred at 20 °C for further 30 min. GC analysis of the reaction mixture showed 0.13% of **26** and 85.7% of **7** after this time. The precipitate which had formed during the addition of Et_3N (Et_3N·HCl and insolubles) was removed by centrifugation and washed with EtOAc (3 × 2.5 L). The combined organic solutions were evaporated to dryness at ≤30 °C and 100 mbar. The partially crystalline residue was suspended in MeOH (3.6 L), and the suspension was stirred for 5 min. Solvent was again removed by distillation at 100 mbar, and the residue was dissolved in MeOH (12.0 L) at 45−50 °C. The solution was cooled to −20 °C at a rate of 0.33 °C/min. At a temperature of 30−35 °C, crystallization was induced by seeding (10 g). The suspension was stirred at −20 °C for 2 h. The product was collected by centrifugation and washed with MeOH (3.6 L, −20 °C). It was dried to constant weight (35 °C, 20 mbar, 6 h) to yield 2.78 kg mesylate **7** (HPLC assay 99.7% w/w, 8.65 mol, 82%) as a beige solid.

X-ray Crystallography. Crystals of hydroxyether **9** were obtained from EtOAc without agitation. Epoxide **10** was crystallized from *n*-hexane/*t*-BuOMe. All measurements were made at −90 °C on a Siemens P4 diffractometer with graphite-monochromated Cu Kα radiation from a rotating anode generator. The structures were solved using direct methods (SHELX-97[21]) and refined against F^2 by full-matrix least-squares methods.[21] Calculation of the absolute configuration was performed by least-squares refinement of the absolute-structures.[19] The data for the crystal structure analysis and refinement are given in Table 1.

Crystallographic data (excluding structure factors) for the structures of compounds **9** and **10** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication Nos. CCDC120350 and CCDC120351, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (deposit@ccdc.cam.ac.uk).

Table 1.

	epoxide **10**	hydroxyether **9**
wavelength, Å	1.54178	1.54178
crystal system	orthorhombic	orthorhombic
space group	P2(1)2(1)2(1)	P2(1)2(1)2(1)
unit cell dimensions, Å		
a	4.385	5.337
b	9.568	16.686
c	33.516	20.443
volume, $Å^3$	1406.2	1820.5
Z	4	4
density (calculated), g/cm^3	1.201	1.279
absorption coefficient, mm^{-1}	0.708	1.860
F(000)	552	752
crystal size	0.2 × 0.08 × 0.04 mm	0.3 × 0.2 × 0.15 mm
θ range data collection, deg	2.64−54.98	3.42−56.48
reflections collected	1415	4553
independent reflections	1225	2315
data/restraints/parameters	1220/0/164	2315/0/209
final *R* indices [$I > 2\sigma(I)$]	R1 = 0.0971, wR2 = 0.2536	R1 = 0.0482, wR2 = 0.1220
R indices (all data)	R1 = 0.1268, wR2 = 0.3108	R1 = 0.0525, wR2 = 0.1310
absolute structure parameter		−0.05(3)
extinction coefficient	0.001	0.0054
largest diff. peak and hole, $e·Å^{-3}$	0.360 and −0.380	0.210 and −0.313

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