New, Azide-Free Transformation of Epoxides into 1,2-Diamino Compounds: Synthesis of the Anti-Influenza Neuraminidase Inhibitor Oseltamivir Phosphate (Tamiflu)

Martin Karpf* and René Trussardi

F. Hoffmann-La Roche Ltd., Pharmaceuticals Division, Non-Clinical Development, Chemical Process Research, Grenzacherstrasse 124, CH-4070, Basel, Switzerland

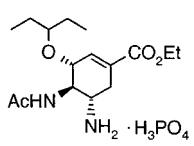
martin.karpf@roche.com

Received October 27, 2000

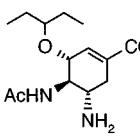
A new, azide-free transformation of the key precursor epoxide **6** to the influenza neuraminidase inhibitor prodrug oseltamivir phosphate (**1**, Tamiflu) is described. This sequence represents a new and efficient transformation of an epoxide into a 1,2-diamino compound devoid of potentially toxic and hazardous azide reagents and intermediates and avoids reduction and hydrogenation conditions. Using catalytic $MgBr_2 \cdot OEt_2$ as a new, inexpensive Lewis acid, the introduction of the first amino function was accomplished by opening of the oxirane ring with allylamine followed by Pd/C-catalyzed deallylation to the amino alcohol **16**. The introduction of the second amino group was then accomplished via an efficient reaction cascade involving a domino sequence preferably utilizing a transient imino protection. Selective acetylation of the resulting diamine **17** was achieved under acidic conditions providing the crystalline 4-acetamido-5-*N*-allylamino-derivative **18**, which upon deallylation over Pd/C and phosphate salt formation afforded drug substance **1**. The overall yield of this route from **6** of 35−38% exceeds the yield of the azide-based process (27−29%) and does not require any chromatographic purification.

Introduction

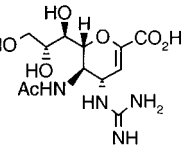
Oseltamivir phosphate,[1] (**1**, Tamiflu, Ro 64-0796, GS 4104) is the prodrug of the potent and selective competitive inhibitor[2] **2** of influenza A and B neuraminidase, comparing well with the inhibitory activities of Zanamivir[3] (**3**, Relenza, GG 167). In contrast to the heterocyclic analogue **3**, the carbocyclic ester **1** can be orally administered for the treatment and prevention of influenza infections. The drug discovery synthesis[2] of **1** starting from (−)-quinic acid **4** and proceeding through the *N*-tritylaziridine **5** was projected to attain various derivatives with different ether side chains introduced by aziridine ring opening. For larger scale preparation of **1**, a practical 12-step synthesis[4] was specifically designed on the basis of the access to the key precursor epoxide **6** obtained from **4** or (−)-shikimic acid **7**. The synthesis of **6** was further developed[5] in order to allow the manufacture of **1** on a commercial scale.



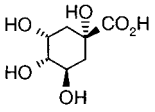
1
Oseltamivir Phosphate
Tamiflu™
GS-4104-02
Ro 64-0796/002



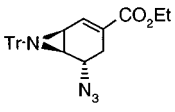
2
GS-4071
Ro 64-0802



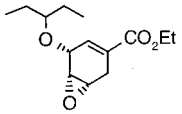
3
Zanamivir
Relenza™
GG 167



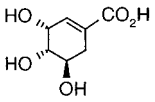
4
(-)-quinic acid



5



6



7
(-)-shikimic acid

The synthesis[4] of **1** from **6** proceeds through the intermediates shown in Scheme 1 in an overall yield of 27−29% and involves potentially toxic and hazardous azide reagents, intermediates and reaction conditions. Although the use of azide chemistry on an industrial scale is well documented,[6] the potential hazards related to its application prompted us to evaluate an azide-free syn-

(1) Kim, C. U.; Lew, W.; Williams, M. A.; Wu, H.; Zhang, L.; N.; Chen, X.; Escarpe, P. A.; Mendel, D. B.; Laver, W. G.; Stevens, R. C. *J. Med. Chem.* **1998**, *41*, 2451.

(2) Kim, C. U.; Lew, W.; Williams C. U.; Liu, H.; Zhang, l.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, W. G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681.

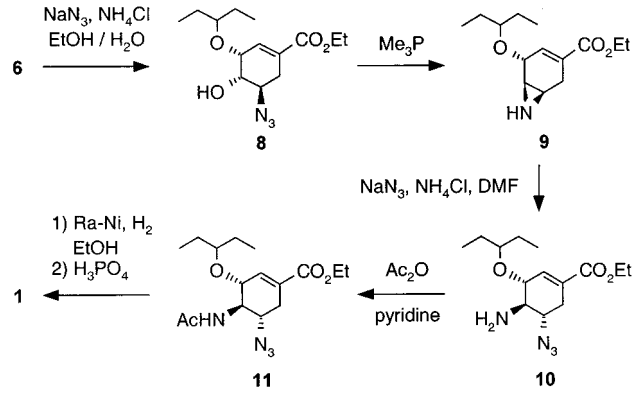
(3) (a) von Itzstein, M.; Wu, W.-Y.; Jin, B. *Carbohydr. Res.* **1994**, *259*, 301. (b) von Itzstein, M.; Wu, W.-Y.; Kok, G. B.; Pegg, M. S.; Dyason, J. C.; Jin, B.; Phan T. V.; Smythe, M. L.; White, H. F.; Oliver, S. W.; Colman, P. M.; Varghese, J. N.; Ryan, D. M.; Wood, J. M.; Bethell, R. C.; Hothman, V. J.; Cameron, J. M.; Penn, C. R. *Nature (London)* **1993**, *363*, 418. (c) von Itzstein, M.; Taylor, N. R. *J. Med. Chem.* **1994**, *37*, 616.

(4) Rohloff, J. C.; Kent K. M.; Postich, M. J.; Becker, M. W.; Chapman, H. H. Kelly, D. E.; Lew, W.; Louie, M. S.; McGee, L. R.; Prisbe, E. J.; Schultze, L. M.; Yu, R. H.; Zhang. L. *J. Org. Chem.* **1998,** *63*, 4545.

(5) Federspiel, M.; Fischer, R.; Hennig, M.; Mair, H. J.; Oberhauser, T.; Rimmler, G.; Albiez, T.; Bruhin, J.; Estermann, H.; Gandert, C.; Göckel, V.; Götzö, S.; Hoffmann, U.; Huber, G.; Janatsch, G.; Lauper, S.; Röckel-Stäbler, O.; Trussardi, R.; Zwahlen, A. G. *Org. Process Res. Dev.* **1999**, *3*, 266.

10.1021/jo005702l CCC: $20.00
Published on Web 02/24/2001

Scheme 1

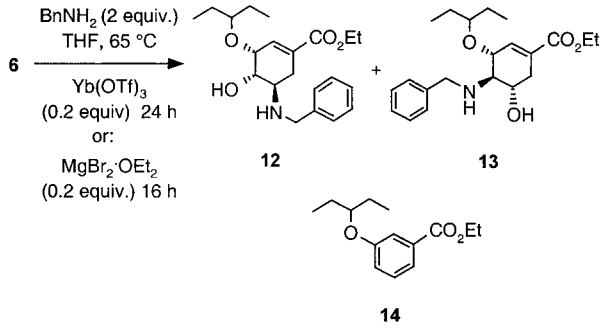


thesis in order to establish an independent, safe, and efficient alternative route amenable to a risk-free large-scale industrial production of **1**.

Results and Discussion

For an efficient azide-free transformation of **6**, a suitable nonazide nitrogen nucleophile and appropriate conditions had to be found, which are compatible with the functional groups present and the pronounced tendency of such highly functionalized cyclohexene derivatives toward aromatization. For the epoxide ring opening of **6**, a substantial number of parallel experiments were performed using several amines and related nitrogen nucleophiles under various noncatalytic and catalytic conditions.[7] All experiments resulted in either no or incomplete conversion accompanied by substantial aromatization leading to variable amounts of **14**[4] along with nonidentified byproducts. The first positive results were achieved using 2 equiv of benzylamine and 0.2 equiv of ytterbium trifluoromethanesulfonate ($Yb(OTf)_3$),[8] providing the amino alcohol **12** after reflux in THF for 24 h together with its regioisomer **13** (∼15%) in 93% yield as shown in Scheme 2. Since $Yb(OTf)_3$ is a high molecular weight, expensive, and therefore barely technical catalyst, an extensive search for a more practicable promoter for the oxirane ring opening led to the discovery and

Scheme 2



implementation of magnesium bromide etherate ($MgBr_2 \cdot OEt_2$) for this purpose,[9] affording the same product mixture in only 16 h.

Since selective hydrogenolysis of **12** to the amino alcohol **16** without affecting the conjugated cyclohexene double bond was not achievable, a search for an amine suitable for the overall transformation **6** → **16** was started. This investigation finally led to the selection of allylamine as the reagent of choice not only for the $MgBr_2 \cdot OEt_2$-catalyzed epoxide ring opening reaction to **15** and the subsequent Pd/C-catalyzed deallylation to **16** but also for the short, selective and effective introduction of the second amino function present in **17**. The details of this new and efficient reaction sequence, summarized in Scheme 3 and finally leading to the drug substance **1** in good overall yield, will be discussed below.

The epoxide ring-opening reaction of **6** using allylamine (2 equiv) and $MgBr_2 \cdot OEt_2$ (0.2 equiv) in various solvents led to the 5-*N*-allylamino derivative **15** accompanied by the regioisomer **19** (**15**/**19** ∼ 10:1 to 13:1) but only to trace amounts of the aromatic derivative **14** (about 1% or less). Whereas the reaction in THF at 65 °C for 12 h yielded 90% of **15** and **19** after hydrolytic workup, a nearly quantitative yield (97%) was obtained in a 9:1 mixture of *t*-BuOMe/MeCN at 55 °C for 16 h. The reaction also proceeded well in various other solvents[10] but the use of

(6) (a) Peer, M. *Inf. Chim.* **1997**, *393*, 98. (b) Van Brussel, W. *Belg. Spec. Chem.* **1996**, *16*(4), 142. (c) Stohlmeier, M., Thewalt, K. *Chem. Ind. Dig.* **1993**, *6*(2), 124.

(7) A reaction substructure search on commercially available reaction databases revealed a large number of reactions involving the transformation of epoxides to 2-amino alcohols under a variety of reaction conditions. For typical conditions and additional references, see: (a) Rampalli S.; Chaudhari, S. S.; Akamanchi, K. G. *Synthesis* **2000**, 78. (b) Sekar, G.; Singh, V. K. *J. Org. Chem.* **1999**, *64*, 287. (c) Augé, J.; Leroy, F. *Tetrahedron Lett.* **1996**, *37*, 7715. (d) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361. (e) Carré, M. C.; Houmounou, J. P.; Caubere, P. *Tetrahedron Lett.* **1985**, *26*, 3107 and references therein.

(8) Chini, M.; Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **1994**, *35*, 433.

(9) To our knowledge, the only use of magnesium bromide in an epoxide opening process leading to *β*-amino alcohols involves the transformation of 2,3-epoxyamines to 3-hydroxyazetidines interpreted by initial bromination of the epoxide and subsequent intramolecular bromide substitution: Karikomi, M.; Arai, K.; Toda T. *Tetrahedron Lett.* **1997**, *38*, 6059. In our case an analogous successive substitution process can be ruled out based on the configuration of the products obtained. *Note added in proof:* A reviewer has drawn our attention to a very recent report describing the $MgBr_2$ promoted opening of an epoxide: Kauffman, G. S.; Harris, D.; Dorow, R. L.; Stone, B. R. P.; Parsons, R. L.; Pesti, J. A.; Magnus, N. A.; Fortunak, J. M.; Confalone, P. N.; Nugent, W. A. *Org. Lett.* **2000**, *2*, 3119. The 2-fold molar excess of the Lewis acid applied to induce epoxide opening parallels our observations of lower activity of $MgBr_2$ compared to the catalytic activity of $MgBr_2 \cdot OEt_2$ as summarized in footnote 11.

(10) High yields of **15** and **19** were also obtained in MeCN (95% at 65 °C/15 h, 94% at 82 °C/5 h) or in *t*-BuOMe (91% at 111 °C/∼5 bar/1 h), in toluene (93% at 110 °C/3 h), in *i*-PrOAc (92% at 88 °C/5 h) and in $(i\text{-Pr})_2O$ (91% at 110 °C/∼5 bar/3 h) but in EtOAc (78 °C/3 h) the yield dropped to 81%.

(11) Essentially no reaction ensued using $CaCl_2$ or $ZnCl_2$ and partial aromatization was observed with $FeCl_2$ or $NiCl_2$. Various amounts of product **15** and aromatization product **14** were formed using $MgBr_2 \cdot 6H_2O$, anhydr $MgBr_2$, anhydr. MgI_2, LiOTf, LiBr or $Zn(OTf)_2$ but starting material **6** was still present even after 15−20 h at reflux. The formation of polar byproducts was observed using LiCl whereas $BF_3 \cdot OEt_2$ and $Sc(OTf)_3$ led to extensive decomposition. $TiCl_4$ led to the formation of the corresponding chlorohydrin.

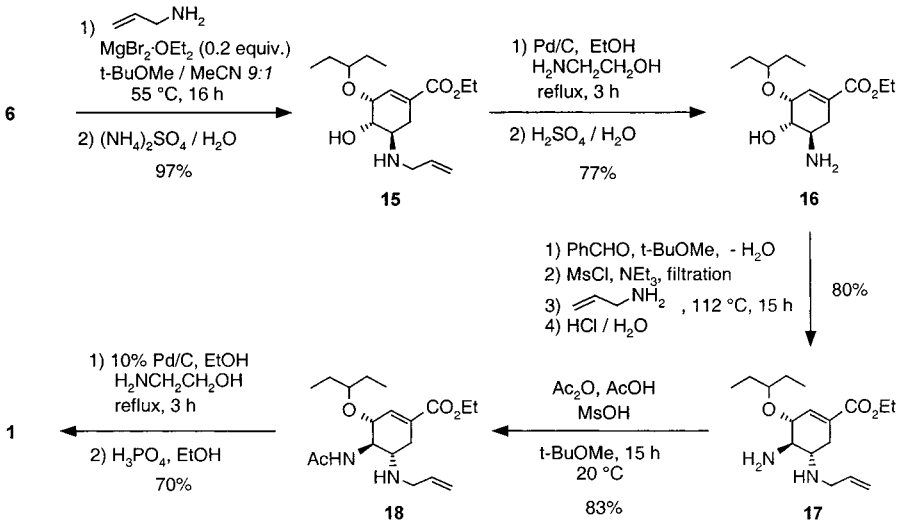
(12) Afarinkia, K.; Cadogan, J. I. G.; Rees, C. W. *Synlett* **1990**, *7*, 415.

(13) Murahashi, S. I.; Yoshimura, N.; Tsumiyama, M.; Kojima, T. *J. Am. Chem. Soc.* **1983**, *105*, 5002.

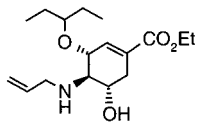
(14) Guibé, F. *Tetrahedron* **1998**, *54*, 2967 and references therein.

(15) Several aromatic (i.e., furfural, 2-pyridinecarboxaldehyde, 4-methoxy-, 3-nitrobenzaldehyde) and aliphatic aldehydes (propionaldehyde, pivalaldehyde, 2-methylpentenal, 2-ethylbutyraldehyde, chloral (hydrate), ethyl glyoxylate (50% in toluene)) as well as some ketones (cyclopentanone, cyclohexanone and 1,1-dimethoxyacetone) were tested as carbonyl components for imine formation with **16**. However none of these substrates revealed a clear advantage compared to the use of benzaldehyde with regard to relevant parameters (yield, reaction time, commercial availability, price, toxicity, ease of removal after activation of the 4-hydroxy group etc.). In contrast to the imines generated from aromatic aldehydes the imines from aliphatic aldehydes revealed a tendency towards condensation and/or oxazolidine formation, thus impeding their efficient use as N-protecting groups. Attempts towards the direct conversion of the crude product of the deallylation step **15** → **16** containing the imine **23** via mesylation and allylation led only to low yields of **17**.

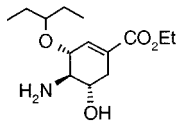
Scheme 3



water immiscible solvents is preferred allowing a very simple workup procedure, namely stirring of the reaction mixture with 1 M aqueous ammonium sulfate or chloride in order to remove the magnesium salts. An exploratory screening[11] of potential alternative catalysts for the epoxide opening reaction using allylamine in THF revealed a clear preference for $MgBr_2 \cdot OEt_2$ regarding reaction time, workup procedure, and yield.

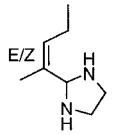


19

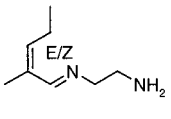


20

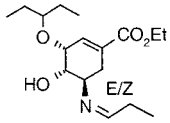
The deallylation of **15** to **16** was achieved in 77% yield with Pd/C in EtOH[12] in the presence of ethanolamine at reflux for 3 h followed by acidic workup. The product contained about 4% of the isomer **20** derived from **19** present in the epoxide ring opening product. The addition of ethylenediamine or ethanolamine to the reaction mixture was shown to initiate and to promote the deallylation process considerably. Although the role of these auxiliaries is not fully understood, evidence for their role as propionaldehyde scavengers was obtained by GC/MS analysis of reactions mixtures with ethylenediamine, revealing peaks interpretable as the propionaldehyde derived condensation products **21** and **22**. The same analysis indicated the presence of the (unstable) imine **23** or the corresponding enamine, the products of the Pd-catalyzed double bond isomerization process and the potential precursors of the condensation product **24**, which was isolated as a minor byproduct. The structure of **24** was confirmed by independent synthesis from **16** and 2-methyl-2-pentenal. The use of ethylenediamine as an additive led to the formation of about 7−10% of the *N*-propylamino derivative **25**, indicating the activity of ethylenediamine as a potential hydrogen source in the system. The amount of **25** was effectively reduced to a level of about 1−2% by using ethanolamine instead.



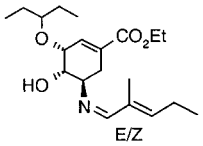
21



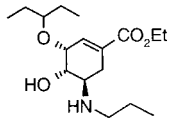
22



23



24



25

While numerous catalytic methods are described for the removal of N-allylic protecting groups including homogeneous palladium π-allyl methodology,[14] the straightforward method applied here was clearly advantageous regarding practicality and efficiency.

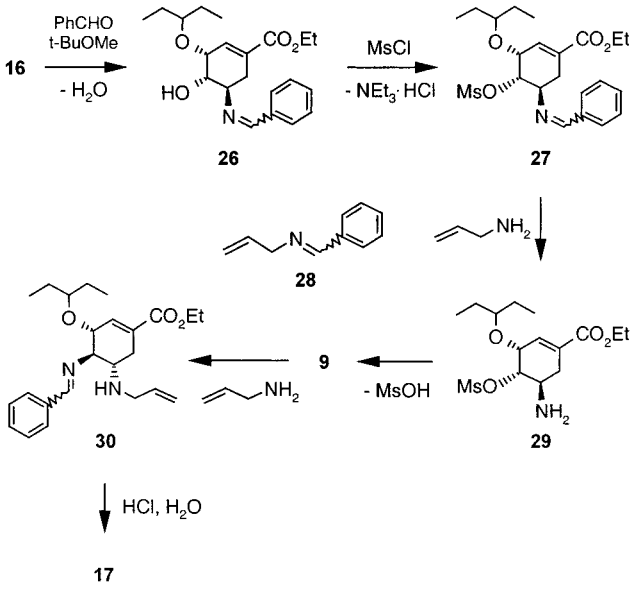
The direct conversion of **16** to **17** with concomitant introduction of the second amino function was achieved without isolation of the intermediates. The sequence shown in Scheme 4 started with the protection of the 5-amino group by formation of the benzaldehyde imine **26** through azeotropic removal of water in *t*-BuOMe directly followed by mesylation. After filtration of $NEt_3 \cdot HCl$, the *t*-BuOMe solution of **27** was treated for 15 h with 4 equiv of allylamine in an autoclave at 112 °C at 3.5−4.5 bar resulting in an 80% yield of **17** after acidic hydrolysis. This sequence requiring just one filtration and workup constitutes a new, straightforward and practical conversion of an amino alcohol into a vicinal diamine employing readily available and safe reagents. The efficiency of this transformation is mainly due to the reversible protection of the amino group as the benzaldehyde imine.[15]

The unexpected presence of **30** as the final product of the reaction sequence before hydrolysis rose the question concerning the actual intermediates in the process. Analytical tracking showed the temporary formation and disappearance of both the imine **28**[16] and of the aziridine **9**. Therefore, we assume that the domino sequence starts with the trans imination reaction of **27** with allylamine

(16) De Kimpe, N.; De Smaele, D.; Sakonyi, Z. *J. Org. Chem.* **1997**, *62*, 2448.

(17) The appearance of **28** and **9** in the reaction mixture together with the observation that secondary amines (dimethylamine, diallylamine) are unreactive towards **27** provide sufficient evidence against the postulation of a mechanistic alternative, namely a direct conversion of **27** to **30** via extrusion of mesylate forming a benzylidene-aziridinium type intermediate opened in 5-position by allylamine.

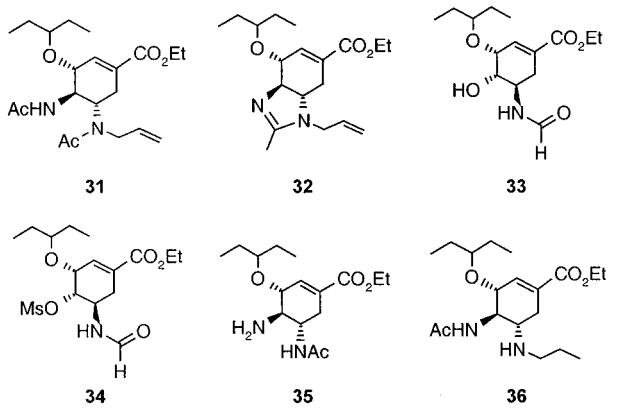
Scheme 4



to form **28** and the aminomesylate **29**. The fast ring closure to the aziridine **9** however prevents **29** to be detected in the reaction mixture. The subsequent aziridine ring opening catalyzed by methanesulfonic acid liberated in the aziridine ring closure step, led initially to the diamine **17** which by trans imination with **28** — present in the reaction mixture — forms the imino derivative **30**.[17] The reaction sequence was found to proceed also in other aprotic solvents (e.g., EtOAc, toluene) but the best results concerning overall yield, simplicity of implementation, and purity of the product **17** were obtained in *t*-BuOMe.

The acetylation of **17** using 1 equiv of acetic anhydride and NEt_3 in EtOAc yielded a mixture of the desired product **18**, about 20% of the 4,5-diacetyl derivative **31** and about 20% of starting material **17**. However, selective acetylation at the 4-amino group was achieved under acidic conditions with 1 equiv of acetic anhydride in 10 equiv of acetic acid and 1 equiv of $MeSO_3H$ in EtOAc at room temperature. This selectivity is interpreted by effective protonation of the secondary 5-amino group under acidic conditions preventing its acetylation and reflects the substantial pK_a difference in **17** of more than 3 units (pK_a^1 4.2, pK_a^2 7.9, measured in 0.1 M aq KNO_3 containing 3% MeOH). The product **18** was obtained by extractive workup in pure, crystalline form (mp 109 °C, HPLC area >98%) and in an overall yield of about 50 to 54% based on **6**. Interestingly the use of an excess of Ac_2O under acidic conditions did not lead to **31** but to the imidazoline **32**.

Alternatively, a stepwise procedure for the transformation of **16** to **17** via the *N*-formyl derivatives **33** and **34** was elaborated. Formylation of the amino alcohol **16** with ethyl formate in an autoclave at 100 °C led to **33** followed by mesylation to form **34**. After deformylation ($MeSO_3H$, EtOH, reflux, 2.5 h), the aminomesylate **29** obtained was treated with allylamine in EtOAc in an autoclave at 112 °C to yield the 4-amino-5-*N*-allylamino-intermediate **17** via the nonisolated aziridine **9**. Selective acetylation then led to **18** in an overall yield of 57% based on **16**.



For the final transformation of the 4-acetamido intermediate **18** to the drug substance **1** the deallylation conditions had to be elaborated which prevented the 4,5-acetyl migration to form the isomer **35**.[18] An exploratory investigation of the main factors controlling the acetyl migration tendency in EtOH at reflux revealed accelerated interconversion under acidic conditions (e.g., AcOH. NEt_3·HCl, H_3PO_4) or in the presence of salts (e.g., NaOAc, $NaHCO_3$). To efficiently suppress acetyl migration it is therefore important to exclude any proton sources and salts.

Deallylation of **18** over 10% Pd/C in refluxing EtOH and ethanolamine followed by acidic hydrolysis provided the free base of the drug substance **1**. The use of ethanolamine instead of ethylenediamine as an auxiliary to promote the deallylation allowed to reduce the amount of **36** in the free base from initially 7−10% to about 1−1.5% and to simultaneously shorten the reaction time from about 12 to 3 h. After complete deallylation, filtration of the catalyst, acidic hydrolysis and extraction, the phosphate salt of **1** was formed[19] to yield drug substance **1** of high purity (99.7%) in a yield of 68−73% from **18** or about 35−38% overall from the epoxide **6**.

The reaction sequence described (Scheme 3) represents a new, unprecedented azide-free transformation of an epoxide into a 1,2-diamino compound avoiding reduction and hydrogenation conditions. Due to the efficient 5-step reaction cascade including a domino sequence involving transient imino-protection, the number of reaction steps performed as well as the overall yield of ∼35−38% compare favorably with the 27−29% yield of the corresponding five-step azide reaction sequence[4] (Scheme 1). Since no potentially hazardous azide reagents and intermediates are involved, the new synthesis is safer and amenable to industrial scale production.

Experimental Section

General Methods. Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. All reactions were carried out under argon atmosphere. Thin-layer chromatography (TLC) was performed on silica gel 60 F254 plates, 0.25 mm (Merck). Column chromatography on silica gel 60 (mesh 70−230, Merck) was used to provide reference samples for analytical purposes of products and byproducts. Qualitative HPLC was performed on a Merck-Hitachi L6200 system with UV detection at a wavelength of 210 nm using Symmetry C18 columns (250 × 4.6 mm, Waters) with gradient elution H_2O/MeCN containing 10% of a phosphate buffer at

(18) Oliya, R.; Yuan, L.-C.; Dahl, T. C.; Swaminathan, S.; Wang, K.-Y.; Lee, W. A. *Pharmaceut. Res.* **1998**, *15*, 1300.

(19) Mair, H. J. F. Hoffmann-La Roche Ltd., European Patent Application No. 99,124,223.1, Dec 3, 1999.

pH 3.0. For acid sensitive samples Phenomenex Luna C18 columns (30 × 4.6 mm, Phenomenex) were used with gradient elution H_2O/MeCN containing 10% of a borate buffer at pH 8.0. Quantitative HPLC analysis using 1,3-dinitrobenzene as internal standard was performed on a Hewlett-Packard 1050 system using Symmetry C18 columns (250 × 4.6 mm, Waters) with UV detection (diode array) and elution with H_2O/MeCN containing a phosphate buffer at pH 3.0 and dodecyl sulfate or Symmetry C8 columns (250 × 4.6 mm, Waters) with gradient elution H_2O/MeCN containing a phosphate buffer at pH 6.0. ^{1}H NMR spectra 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}. Low-resolution electron impact mass spectra (EI-MS) were obtained at an ionization voltage of 70 eV or by positive ion spray ionization (ISP-MS). Data are reported in the form of m/z (intensity relative to base = 100).

Ethyl (3*R*,4*S*,5*R*)-5-*N*-Benzylamino-3-(1-ethylpropoxy)-4-hydroxy-1-cyclohexene-1-carboxylate (12). To a stirred solution of **6** (5.08 g, 20 mmol) in THF (20 mL) was added $MgBr_2$·OEt_2 (1.03 g, 4.0 mmol) and benzylamine (4.4 mL, 40 mmol). The yellow suspension was heated to reflux for 12 h and evaporated in a rotary evaporator at 48 °C in vacuo. The remaining turbid oil was treated with EtOAc (20 mL) and extracted six times with 5 M aqueous NH_4Cl solution. The organic phase was separated, dried over Na_2SO_4, filtered, and evaporated in a rotary evaporator at 48 °C in vacuo to yield 6.88 g (95%) of **12** and **13** as a brown oil containing 15% of the isomer **13**. A reference sample of **13** was obtained from **20** as described below. **12**: IR (film) ν 2966, 2935, 2877, 1715, 1654, 1495, 1455, 1382, 1367, 1335, 1250, 1090, 976, 699 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40−7.19 (m, 5H), 6.89−6.82 (m, 1H), 4.21 (q, J = 7.3 Hz, 2H), 4.15−4.09 (m, 1H), 3.98 (d, J = 13.0 Hz, 1H), 3.75 (d, J = 13.0 Hz, 1H), 3.68−3.61 (m, 1H), 3.49−3.37 (m, 1H), 3.10−2.83 (m, 2H), 2.9−2.2 (s br, 2H), 2.16−2.00 (m, 1H), 1.63−1.43 (m, 4H), 1.30 (t, J = 7.0 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H), 0.87 (t, J = 7.3 Hz, 3H); EI-MS (m/z) 361 (M$^+$, 1), 343 (6), 330 (12), 290 (35), 274 (20), 260 (10), 149 (52), 120 (19), 106 (26), 91 (100). Anal. Calcd for $C_{21}H_{31}NO_4$: C, 69.78; H, 8.64; N, 3.87. Found: C, 69.61; H, 8.35; N, 3.96.

Ethyl (3*R*,4*R*,5*S*)-4-*N*-Benzylamino-3-(1-ethylpropoxy)-5-hydroxy-1-cyclohexene-1-carboxylate (13). A stirred solution of **20** (0.95 g, 3.5 mmol) and benzaldehyde (0.37 mL, 3.5 mmol) in *t*-BuOMe (10 mL) was heated to reflux for 2 h on a Dean-Stark condenser. After distillation of solvent (∼5 mL), *t*-BuOMe (5 mL) was added, and the solution was evaporated in a rotary evaporator at 48 °C in vacuo to dryness. The remaining white solid (1.11 g) was dissolved in EtOH (12.6 mL) and treated with $NaBH_4$ (133 mg, 3.5 mmol), and the slightly yellow solution was stirred at reflux for 24 h. The yellow solution was evaporated at 45 °C in vacuo, and the remaining yellow crystalline mass was dissolved in EtOAc (12.6 mL) and extracted with aqueous $NaHCO_3$ (12.6 mL). The organic phase was separated and dried over Na_2SO_4, filtered, and evaporated in a rotary evaporator at 48 °C in vacuo to yield 0.87 g of crude **13** (69%) which was purified by column chromatography using (i-Pr)$_2$O/*t*-BuOMe = 1:1 containing 0.5% aqueous NH_3 as the eluent: IR (film) ν 2964, 2936, 2876, 1714, 1653, 1496, 1454, 1365, 1238, 1118, 1049, 733, 698 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38−7.22 (m, 5H), 6.87−6.83 (m, 1H), 4.21 (q, J = 7.3 Hz, 2H), 4.08−4.02 (m, 1H), 4.06 (d, J = 12.7 Hz, 1H), 3.88 (d, J = 12.7 Hz, 1H), 3.77−3.67 (m, 2H), 3.46−3.38 (m, 1H), 2.87−2.73 (m, 2H), 2.37−2.26 (s, 1H), 1.68−1.45 (m, 5H), 1.30 (t, J = 7.0 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H); ISP-MS (m/z) 362.3 (M$^+$ + H). Anal. Calcd for $C_{21}H_{31}NO_4$: C, 69.78; H, 8.64; N, 3.87. Found: C, 70.14; H, 8.95; N, 3.62.

Ethyl (3*R*,4*S*,5*R*)-5-*N*-Allylamino-3-(1-ethylpropoxy)-4-hydroxy-1-cyclohexene-1-carboxylate (15) and Ethyl (3*R*,4*R*,5*S*)-4-*N*-Allylamino-3-(1-ethylpropoxy)-5-hydroxy-1-cyclohexene-1-carboxylate (19). To a stirred solution of **6** (254.3 g, purity 96.9%, 0.97 mol) in *t*-BuOMe (900 mL) and MeCN (100 mL) were added $MgBr_2$·OEt_2 (51.7 g, 0.20 mol) and allylamine (150 mL, 2.0 mol). The yellow suspension was heated to 55 °C, whereby complete dissolution occurred after about 1.5 h. The clear yellow solution was refluxed for 15 h, after which time qualitative HPLC analysis (pH 3) showed less than 1.0% (area) of the starting material **6**. The yellowish, turbid solution was cooled to about 30 °C and stirred vigorously with 1 M aqueous $(NH_4)_2SO_4$ for 15 min, whereby a clear two-phase mixture evolved after initial cloudiness. The organic phase was separated, filtered and evaporated in a rotary evaporator at 48 °C in vacuo to a volume of about 580 mL. The solid particles were filtered and the brown solution was evaporated at 48 °C in vacuo for 2 h to yield 312.8 g of crude **15** and **19** (containing 86.6% of **15** and 7.0% of **19** based on quantitative HPLC analysis (pH 3) corresponding to a 97% yield of **15** and **19** from **6**) as a brown-yellow oil that was used in the next step without further purification. Reference samples of **15** and **19** were obtained by column chromatography using *t*-BuOMe/EtOH = 9:1 containing 1% aq. NH_3 as the eluent. **15**: IR (film) ν 3540, 2967, 2936, 2877, 1716, 1657, 1463, 1244, 1094 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.90−6.83 (m, 1H), 6.01−5.83 (m, 1H), 5.27−5.06 (m, 2H), 4.21 (q, J = 7.0 Hz, 2H), 4.16−4.09 (m, 1H), 3.67−3.54 (m, 1H), 3.52−3.35 (m, 2H), 3.28−3.16, (m, 1H), 3.03−2.80 (m, 2H), 2.80−2.65 (s br, 1H), 2.06−1.92 (m, 1H), 1.69−1.44 (m, 5H), 1.30 (t, J = 7.0 Hz, 3H), 0.94 (t, J = 7.3 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H); ISP-MS (m/z) 312.5 (M$^+$ + H). Anal. Calcd for $C_{17}H_{29}NO_4$: C, 65.57; H, 9.39; N, 4.50. Found: C, 65.49; H, 9.36; N, 4.63. **19**: IR (film) ν 3422, 2966, 2936, 2877, 1717, 1653, 1464, 1246, 1056, 921 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.86−6.81 (m, 1H), 6.00−5.82 (m, 1H), 5.26−5.06 (m, 2H), 4.21 (q, J = 7.0 Hz, 2H), 4.03−3.94 (m, 1H), 3.73−3.61 (m, 1H), 3.56−3.30 (m, 3H), 2.88−2.75, (m, 1H), 2.74−2.64 (m, 1H), 2.39−2.24 (m, 1H), 1.69−1.44 (m, 6H), 1.29 (t, J = 7.0 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H); EI-MS (m/z) 312 (M$^+$, 2), 240 (2), 224 (4), 213 (8), 143 (13), 99 (100); HRMS (m/z) calcd for $C_{17}H_{29}NO_4$ + H$^+$ 312.2175, obsd 312.2176.

Ethyl (3*R*,4*S*,5*R*)-5-Amino-3-(1-ethylpropoxy)-4-hydroxy-1-cyclohexene-1-carboxylate (16) and Ethyl (3*R*,4*R*,5*S*)-4-Amino-3-(1-ethylpropoxy)-5-hydroxy-1-cyclohexene-1-carboxylate (20). To a stirred solution of **15** (312.8 g, containing 7% of the isomer **19**, purity 94.6% (**15** and **19**), 0.95 mol) and ethanolamine (66.2 mL, 1.10 mol) in EtOH (1560 mL) was added 10% Pd/C catalyst (31.3 g). The black suspension was heated to reflux for 3 h, cooled to 40 °C, and filtered, and the filter cake was washed with EtOH (100 mL). The combined filtrates were cooled to 0−5 °C and treated with intensive stirring with concentrated H_2SO_4 (59.0 mL, 1.10 mol), keeping the temperature below 30 °C. The resulting yellowish suspension was evaporated in a rotary evaporator at 48 °C in vacuo, and the remaining oily, yellow crystals (956 g) were dissolved in water and the orange solution was extracted with a mixture of *t*-BuOMe (500 mL) and hexane (500 mL). The organic phase was extracted with 0.5 M aqueous H_2SO_4 (260 mL), and the combined aqueous phases (pH = 2.3) were cooled to 10 °C and treated with stirring with 50% aqueous KOH (128 mL), keeping the temperature in the range of 5−20 °C until a pH of 9.5 was reached. The organic phase was separated, and the aqueous phase was extracted three times with *t*-BuOMe (1000 mL, twice 500 mL). The combined organic phases were dried over Na_2SO_4 (1000 g) and filtered, and the filter cake was washed with *t*-BuOMe (300 mL). The combined filtrates were evaporated in a rotary evaporator at 48 °C in vacuo and dried in vacuo for 2 h to yield 271.4 g of crude **16** and **20** (containing 69.1% of **16** and 4.0% of **20** based on quantitative HPLC analysis (pH 3) corresponding to a 77% yield of **16** and **20**) as a red oil which was used in the next step without further purification. A reference sample of **16** was obtained by column chromatography using CH_2Cl_2/EtOH = 95:5 containing 0.5% aqueous NH_3 as the eluent. A reference sample of **20** was prepared by reduction (PPh_3, THF, room temperature, 22 h) of the known[4] ethyl (3*R*,4*S*,5*R*)-4-azido-3-(1-ethylpropoxy)-5-hydroxy-1-cyclohexene-1-carboxylate followed by column chromatography using *t*-BuOMe/EtOH = 95:5 containing 1% aqueous NH_3 as the eluent. **16**: IR (film) ν 3585, 2966, 2935, 2877, 1715, 1651, 1483, 1247, 1100, 1063, 977 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.92−6.85 (m, 1H), 4.21 (q, J = 7.0 Hz,

2H), 4.12 (t, J = 4.3 Hz, 1H), 3.57−3.38 (m, 2H), 3.19−3.07, (m, 1H), 2.88−2.75 (m, 1H), 2.1−1.6 (m, 5H), 1.66−1.45 (m, 4H), 1.30 (t, J = 7.0 Hz, 3H), 0.94 (t, J = 7.3 Hz, 3H), 0.91 (t, J = 7.3 Hz, 3H); ISP-MS (m/z) 272.3 ($M^+ + H$). Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 61.91; H, 9.22; N, 5.10. **20**: IR (Nujol) ν 3201, 2957, 2922, 2853, 1712, 1654, 1577, 1458, 1375, 1244, 1056, 936 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.82−6.76 (m, 1H), 4.21 (q, J = 7.0 Hz, 2H), 3.84−3.74 (m, 1H), 3.67−3.53 (m, 1H), 3.44−3.32 (m, 1H), 2.91−2.72, (m, 2H), 2.7−1.7 (s br, ∼3H), 2.33−2.16 (m, 1H), 1.68−1.43 (m, 4H), 1.29 (t, J = 7.0 Hz, 3H), 0.94 (t, J = 7.3 Hz, 6H); EI-MS (m/z) 272 ($M^+ + H^+$, 4), 213 (21), 184 (11), 143 (100), 97 (59). Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 62.08; H, 9.24; N, 5.07.

Ethyl (3*R*,4*R*,5*S*)-5-*N*-Allylamino-4-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate (17). A stirred solution of **16** (271.4 g, containing 4% of the isomer **20**, purity 73.1% (**16** and **20**), 0.74 mol) and benzaldehyde (102.1 mL, 1.01 mol) in *t*-BuOMe (2710 mL) was heated to reflux for 2 h on a Dean-Stark condenser during which time about 9 mL of water separated. In the course of 30 min, 1350 mL of solvent were distilled and the red solution containing **26** (reaction monitoring by HPLC analysis (pH 8) was cooled to 0 to 5 °C, treated with triethylamine (167.3 mL, 1.18 mol), then dropwise with methanesulfonyl chloride (77.7 mL, 0.99 mol) keeping the temperature in the range of 0−5 °C in the course of 85 min during which time an orange precipitate formed. After the mixture was stirred for 45 min, methanesulfonyl chloride (15.6 mL, 0.18 mol) was added dropwise, the orange suspension was stirred for 25 min and filtered, and the filter cake was washed with *t*-BuOMe (300 mL). The combined filtrates containing **27** were treated with allylamine (300.5 mL, 4.0 mol), and the clear red solution was heated with stirring in a 3 L autoclave and 1 bar of Ar to 110−112 °C in the course of 45 min, stirred at this temperature for 15 h at a pressure of 3.5−4.5 bar, and cooled to 45 °C during 1 h. The red solution was evaporated in a rotary evaporator in vacuo at 48 °C and the remaining red gel (566 g) containing **17** and **30** was dissolved with intensive stirring in a two-phase mixture of 2 N aqueous HCl (1000 mL) and EtOAc (1000 mL). The organic phase was separated and extracted with 2 N aqueous HCl (1000 mL), and the combined aqueous phases were washed with EtOAc (500 mL), cooled to 10 °C, and treated with stirring with 50% aqueous KOH (256 mL) until pH 10 was reached keeping the temperature in the range of 10−20 °C. The organic phase was separated, the aqueous phase was extracted twice with *t*-BuOMe (1000 and 500 mL), and the combined extracts were evaporated in a rotary evaporator at 48 °C in vacuo to yield 277.9 g of crude **17** (containing 66.1% of **17** based on quantitative HPLC analysis (pH 3) corresponding to 80% of **17** from **16**) as a red-brown oil, which was used in the next step without further purification. A reference sample of **17** was obtained by column chromatography using *t*-BuOMe/EtOH = 95:5 containing 1% aqueous NH_3 as the eluent: IR (film) ν 3375, 3298, 2970, 2924, 2875, 1709, 1645, 1466, 1261, 1096, 1064 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.82−6.74 (m, 1H), 6.02−5.82 (m, 1H), 5.28−5.04 (m, 2H), 4.22 (q, J = 7.0 Hz, 2H), 3.87−3.77 (m, 1H), 3.51−3.33 (m, 2H), 3.31−3.15 (m, 1H), 2.92−2.68 (m, 2H), 2.67−2.53 (m, 1H), 2.06−1.89 (m, 1H), 1.85−1.40 (m, 7H), 1.30 (t, J = 7.0 Hz, 3H), 0.94 (t, J = 7.3 Hz, 6H); ISP-MS (m/z) 311.2 ($M^+ + H$). Anal. Calcd for $C_{17}H_{30}N_2O_3$: C, 65.77; H, 9.74; N, 9.02. Found: C, 65.60; H, 9.51; N, 8.98.

Ethyl (3*R*,4*R*,5*S*)-4-*N*-Acetylamino-5-*N*-allylamino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate (18). A red solution of **17** (278.0 g, purity 66.1%, 0.59 mol) in *t*-BuOMe (1400 mL) was cooled to 0−5 °C and treated with stirring with AcOH (512 mL, 9.0 mol), whereby the temperature rose to 23 °C. After the mixture was cooled to 0−5 °C, $MeSO_3H$ (58.1 mL, 0.90 mol) was added in the course of 27 min followed by dropwise addition of Ac_2O (84.7 mL, 0.90 mol) in the course of 40 min keeping the temperature in the range of 0−5 °C. The brown reaction mixture was stirred for 14 h at room temperature and then vigorously stirred with water (1400 mL), and the brown organic phase was extracted with 1 M aqueous $MeSO_3H$ (450 mL). The combined aqueous phases (pH ∼1.6) were treated with stirring with 50% aqueous KOH (694 mL) keeping the temperature in the range of 10−25 °C until pH ∼10 was reached. The brown, turbid mixture was extracted twice with *t*-BuOMe (1000 and 400 mL), and the combined organic extracts were stirred over charcoal (32 g) and filtered. The filter cake was washed with *t*-BuOMe (200 mL), and the combined filtrates were evaporated in a rotary evaporator in vacuo at 47 °C to yield brown-red, amorphous crystals (285.4 g) which were dissolved with stirring in a mixture of *t*-BuOMe (570 mL) and *n*-hexane (285 mL) at 50 °C. The brown solution was cooled to −20 to −25 °C with stirring in the course of 45 min and stirred for 5 h at this temperature whereby brown crystals precipitated. The suspension was filtered over a precooled (−20 °C) glass filter funnel, and the filter cake was washed with a precooled (−20 °C) mixture of *t*-BuOMe (285 mL) and *n*-hexane (143 mL) and dried in a rotary evaporator in vacuo at 48 °C to yield 200.33 g of crude **18** (containing 86.9% of **18** based on quantitative HPLC analysis (pH 3) corresponding to 83% of **18** from **17**) as beige crystals, which was used in the next step without further purification: mp 100−104 °C; IR (film) ν 3271, 3084, 2970, 2923, 1715, 1650, 1457, 1377, 1080, 1055 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.83−6.76 (m, 1H), 5.95−5.77 (m, 1H), 5.60−5.50 (m, 2H), 5.24−5.03 (m, 2H), 4.30−4.15 (m, 3H), 3.73−3.61 (m, 1H), 3.43−3.29 (m, 2H), 3.27−3.12 (m, 2H), 2.80−2.62 (m, 1H), 2.28−2.12 (m, 1H), 2.02 (s, 3H), 1.78−1.62 (s br, 1H), 1.60−1.42 (m, 4H), 1.30 (t, J = 7.0 Hz, 3H), 0.90 (t, J = 7.3 Hz, 6H); EI-MS (m/z) 352 (M^+, 4), 307 (4), 280 (4), 206 (100), 140 (50). Anal. Calcd for $C_{19}H_{32}N_2O_4$: C, 64.75; H, 9.15; N, 7.95. Found: C, 64.56; H, 9.13; N, 8.04.

Ethyl (3*R*,4*R*,5*S*)-4-*N*-Acetylamino-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate (1). A solution of **18** (176.2.0 g, purity 86.9%, 440 mmol) in EtOH (880 mL) was treated with ethanolamine (30.0 mL, 500 mmol) and 10% Pd/C catalyst (17.6 g). The black suspension was heated to reflux for 3 h, cooled to room temperature, and filtered. The filter cake was washed with EtOH (100 mL), and the combined filtrates were evaporated in a rotary evaporator at 75 bar in vacuo (<20 mbar) at 50 °C. The brown, oily residue (207.3 g) was treated with 2 N aqueous HCl (600 mL), and the brown solution was distilled in a rotary evaporator at 50 °C and 75 mbar for 5 min whereby vigorous gas evolution occurred (propionaldehyde). The solution was cooled to room temperature, washed with *t*-BuOMe (600 mL), and treated with stirring and cooling with 25% aqueous NH_3 (110 mL) keeping the temperature below room temperature until pH ∼9−10 was reached and a brown emulsion formed. The emulsion was extracted with EtOAc (3 × 600 mL), and the combined extracts were dried over Na_2SO_4 (200 g) and filtered. The filter cake was washed with EtOAc (200 mL), and the combined filtrates were evaporated in a rotary evaporator at 50 °C in vacuo (<20 mbar) to yield a brown oil (158.6 g) which was dissolved in EtOH (650 mL). The brown solution was added in the course of 1 min with stirring to a hot solution (50 °C) solution of 85% *o*-phosphoric acid (57.60 g, 0.50 mol) in EtOH (2500 mL). The resulting solution was cooled in the course of 1 h to 22 °C. At 40 °C seed crystals of **1** (about 10 mg) were added whereby crystallization started. The beige suspension was cooled in the course of 2 h to −20 to −25 °C and stirred at this temperature for 5 h. The suspension was filtered over a precooled (−20 °C) glass filter funnel for 2 h. The filter cake was first washed with EtOH (200 mL, precooled to −25 °C), then with acetone (twice 850 mL), then with *n*-hexane (twice 1000 mL), then dried for 3 h to yield 124.9 g (70%) of **1** as white crystals: mp 205−207 °C (lit.[4] mp 203−204 °C).

Ethyl 4-*N*-Acetylamino-3-(1-ethylpropoxy)-5-*N*-(2-methylpent-2-enylideneamino)-1-cyclohexene-1-carboxylate (24). A solution of **16** (543 mg, 2.0 mmol) and 2-methyl-2-pentenal (196 mg, 2.0 mmol) in toluene (5.4 mL) was heated to reflux on a Dean-Stark condenser for 2 h and evaporated to dryness at 45 °C in vacuo (<15 mbar) to yield 680 mg (97%) of **24** as a yellow oil: IR (film) ν 3549, 2964, 2935, 2876, 1714, 1643, 1628, 1462, 1376, 1240, 1099, 1054 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.89 (s, 1H), 6.91−6.84 (m, 1H), 5.94−5.83 (m, 1H), 4.27−4.14 (m, 3H), 3.87−3.78 (m, 1H), 3.62−3.51 (m, 1H),

3.50−3.40 (m, 1H), 2.76−2.62 (m, 1H), 2.38−2.17 (m, 4H), 1.82 (s, 3H), 1.64−1.48 (m, 4H), 1.29 (t, J = 7.0 Hz, 3H), 1.04 (t, J = 7.4 Hz, 3H),0.93 (t, J = 7.3 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H); ISP-MS (m/z) 352.4 (M^+ + H, 7), 280.2 (100). Anal. Calcd for $C_{20}H_{33}NO_4$: C, 68.34; H, 9.46; N, 3.99. Found: C, 68.36; H, 9.41; N, 3.99.

Ethyl (3*R*,4*S*,5*R*)-3-(1-Ethylpropoxy)-4-hydroxy-5-*N*-propylamino-1-cyclohexene-1-carboxylate (25). From the crude product **16** (6.0 g) of an experiment performed in analogy to the deallylation of **15** described above but using ethylenediamine instead of ethanolamine as the promoter the 5-*N*-propylamino derivative **25** (0.4 g) was separated by column chromatography on silica gel (170 g) using *t*-BuOMe containing 1% aqueous NH_3 as the eluent: IR (film) ν 3440, 2963, 2934, 2876, 1716, 1654, 1463, 1244, 1098 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.93−6.80 (m, 1H), 4.21 (q, J = 7.0 Hz, 2H), 4.16−4.09 (m, 1H), 3.63−3.52 (m, 1H), 3.46 (qui, J = 6.0 Hz, 1H), 2.98−2.66, (m, 4H), 2.59−2.45 (s, 1H), 2.07−1.88 (m, 1H), 1.73−1.40 (m, 6H), 1.30 (t, J = 7.0 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H); EI-MS (m/z) 313 (M^+, 4), 282 (26), 242 (56), 212 (54), 101 (100). Anal. Calcd for $C_{17}H_{31}NO_4$: C, 65.14; H, 9.97; N, 4.47. Found: C, 65.24; H, 9.84; N, 4.55.

Ethyl (3*R*,4*S*,5*R*)-5-*N*-Benzylideneamino-3-(1-ethylpropoxy)-4-hydroxy-1-cyclohexene-1-carboxylate (26). A solution of **16** (272 mg, 1.0 mmol) and benzaldehyde (117 mg, 1.1 mmol) in toluene (2.7 mL) was heated to 110 °C for 30 min and evaporated in a rotary evaporator to dryness at 45 °C in vacuo (<15 mbar) to yield 360 mg (100%) of **26** as a yellow oil: IR (film) ν 3540, 2966, 2934, 2876, 1714, 1644, 1451, 1244, 1101, 1055 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.81−7.68 (m, 2H), 7.47−7.33 (m, 3H), 6.95−6.88 (m, 1H), 4.33−4.23 (m, 1H), 4.22 (q, J = 7.0 Hz, 2H), 3.94−3.86 (m, 1H), 3.82−3.71 (m, 1H), 3.47 (qui, J = 5.8 Hz, 1H), 2.85−2.72 (m, 1H), 2.65−2.48 (s br, 1H), 2.47−2.33 (m, 1H), 1.68−1.48 (m, 4H), 1.29 (t, J = 7.0 Hz, 3H), 0.94 (t, J = 7.3 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H); ISP-MS (m/z) 360.3 (M^+ + H). Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.24; H, 8.06; N, 3.97.

Ethyl (3*R*,4*S*,5*R*)-5-*N*-Benzylideneamino-3-(1-ethylpropoxy)-4-methanesulfonyloxy-1-cyclohexene-1-carboxylate (27). To a solution of **26** (360 mg, 1.0 mmol) and triethylamine (153 μL, 1.1 mmol) in EtOAc (3.6 mL) cooled to 0−5 °C was added with stirring $MeSO_2Cl$ (87 μL, 1.1 mmol) and the mixture stirred for 1 h at room temperature. The white suspension was extracted with 1 M aqueous $NaHCO_3$ (3 mL), and the organic phase was separated and dried over Na_2SO_4, filtered, and evaporated to dryness in a rotary evaporator at 45 °C in vacuo (<15 mbar) to yield 410 mg (94%) of **27** as a yellow oil: IR (film) ν 2968, 2937, 2877, 1715, 1646, 1581, 1452, 1359, 1244, 1178, 987 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.77−7.66 (m, 2H), 7.47−7.36 (m, 3H), 6.95−6.88 (m, 1H), 4.83 (dd, J = 9.7, 4.0 Hz, 1H), 4.47−4.38 (m, 1H), 4.22 (q, J = 7.0 Hz, 2H), 4.08−3.95 (m, 1H), 3.56 (qui, J = 5.8 Hz, 1H), 2.93 (s, 3H), 2.88−2.74 (m, 1H), 2.60−2.45 (m, 1H), 1.68−1.47 (m, 4H), 1.29 (t, J = 7.0 Hz, 3H), 0.97 (t, J = 7.3 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H); ISP-MS (m/z) 438.3 (M^+ + H); HRMS (m/z) calcd for $C_{22}H_{31}NO_6S$ 438.1950, obsd 438.1951.

Ethyl (3*R*,4*S*,5*R*)-5-Amino-3-(1-ethylpropoxy)-4-methanesulfonyloxy-1-cyclohexene-1-carboxylate (29). A stirred orange solution of crude **34** (58.39 g, purity 67.8%, 105 mmol) in EtOH (290 mL) was treated with $MeSO_3H$ (10.7 mL, 165 mmol) and heated to reflux for 160 min. The red-brown reaction mixture was evaporated in a rotary evaporator at 45 °C in vacuo to dryness, and the remaining red-brown oil was dissolved in H_2O (260 mL) and extracted with *t*-BuOMe (260 mL). The organic phase was extracted with H_2O (52 mL), and the combined aqueous phases were cooled to 0−5 °C and treated dropwise with 50% aqueous KOH (13.7 mL) keeping the temperature below 10 °C until a pH of 9.4 was reached. The beige emulsion was extracted twice with EtOAc (260 and 70 mL), the combined extracts were dried over Na_2SO_4 (160 g), filtered, and evaporated in a rotary evaporator at 45 °C in vacuo to yield 45.66 g of crude **29** (containing 75.1% of **34** based on quantitative HPLC analysis (pH 3) corresponding to 93% of **29** from **34**) as a red oil, which was used in the next step without further purification. A reference sample of **29** was prepared analogously from a pure reference sample of **34**: IR (film) ν 3382, 2967, 2937, 2878, 1715, 1654, 1464, 1356, 1252, 1177, 1070, 966 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.89−6.77 (m, 1H), 4.52 (dd, J = 9.0, 3.7 Hz, 1H), 4.42−4.32 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.63−3.36 (m, 2H), 3.14 (s, 3H), 2.97−2.84 (m, 1H), 2.20−2.04 (m, 1H), 2.00−1.75 (s br, 2H), 1.73−1.46 (m, 5H), 1.30 (t, J = 7.3 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H); ISP-MS (m/z) 350.3 (M^++ H); HRMS (m/z) calcd for $C_{15}H_{28}NO_6S$ 350.1637, obsd 350.1626.

Ethyl (3*R*,4*R*,5*S*)-5-*N*-Allylamino-4-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate (17) from 29. A red solution of crude **29** (45.66 g, purity 75.1%, 98 mmol) in EtOAc (250 mL) was treated with allylamine (29.5 mL, 390 mmol) and heated with stirring in an autoclave and 1 bar of Ar to 112 °C in the course of 45 min, stirred at this temperature for 6 h at a pressure of 3.5 to 6.0 bar and cooled to room temperature during 50 min whereby a precipitate formed. The red suspension was vigorously stirred with 1 M aqueous $NaHCO_3$ (230 mL) for 20 min, the organic phase was separated, dried over Na_2SO_4 (100 g), filtered, and evaporated in a rotary evaporator at 45 °C in vacuo to yield 41.80 g of crude **17** (containing 55.0% of **17** based on quantitative HPLC analysis (pH 3) corresponding to 76% of **17** from **29**) as a red oil, which was used in the acetylation step as described above without further purification.

Ethyl (3*R*,4*R*,5*S*)-5-*N*-Allylamino-4-*N*-benzylideneamino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate (30). A solution of **17** (0.93 g, 3.0 mmol) and benzaldehyde (0.30 mL, 3.0 mmol) in $(i\text{-Pr})_2O$ (10 mL) was heated to reflux for 2 h and evaporated to dryness in a rotary evaporator at 45 °C in vacuo (<15 mbar) to yield 1.17 g (98%) of **30** as a yellow oil as a mixture of *E*/*Z* isomers: IR (film) ν 2965, 2937, 2876, 1715, 1644, 1462, 1241, 1098, 1060 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$,) δ 8.38 (s, ∼0.7H), 7.81−7.72 (m, ∼1.3H), 7.53−7.25 (m, ∼4H), 6.87−6.77 (m, 1H), 5.93−5.66 (m, 1H), 5.25−4.94 (m, 2H), 4.58 (s, ∼0.3H), 4.32−4.13 (m, ∼2.4H), 4.08−3.98 (m, ∼0.3H), 3.50−3.10 (m, ∼5H), 2.93−2.57 (m, ∼1.3H), 2.35−2.00 (m, ∼0.7H), 1.80−1.20 (m, ∼8H), 1.02−0.79 (m, ∼4H), 0.61 (t, J = 7.3 Hz, ∼2H); ISP-MS (m/z) 399.4 (M^+ + H). Anal. Calcd for $C_{24}H_{34}N_2O_3$: C, 72.33; H, 8.60; N, 7.03. Found: C, 72.33; H, 8.59; N, 7.12.

Ethyl (3*R*,4*R*,5*S*)-5-*N*-Acetyl-*N*-allylamino-4-*N*-benzylideneamino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate (31). To a solution of **18** (3.70 g, 11.9 mmol) in *t*-BuOMe (37 mL) was added with stirring at 0−5 °C NEt_3 (1.66 mL, 11.9 mmol) followed by dropwise addition of Ac_2O (1.13 mL, 11.9 mmol) in the course of 10 min. The yellowish solution was stirred at room temperature for 19 h and extracted with 1 M aqueous $NaHCO_3$ (37 mL), the organic phase separated and dried over Na_2SO_4 and filtered, and the filtrate was evaporated to dryness in a rotary evaporator at 50 °C in vacuo (<15 mbar) to yield a yellow oil (2.90 g) which was purified by column chromatography on silica gel (90 g) using EtOAc containing 1% aqueous NH_3 as the eluent to yield 1.83 g (44%) of **31** as a slightly yellowish oil: IR (film) ν 3311, 3084, 2966, 2937, 2877, 1716, 1650, 1629, 1555, 1417, 1249, 1130, 1079 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.83−6.72 (m, 1H), 6.18−6.02 (m, 1H), 5.76−5.57 (m, 1H), 5.21−5.08 (m, 2H), 4.98−4.65 (s *br*, 1H), 4.32−3.97 (m, 4H), 3.93−3.78 (m, 2H), 3.32 (qui, J = 5.7 Hz, 1H), 2.65−2.25 (m, 2H), 2.07 (s, 3H), 1.94 (s, 3H), 1.58−1.40 (m, 4H), 1.28 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H), 0.86 (t, J = 7.4 Hz, 3H); ISP-MS (m/z) 395.4 (M^+ + H). Anal. Calcd for $C_{21}H_{34}N_2O_5$: C, 63.94; H, 8.69; N, 7.10. Found: C, 63.87; H, 8.96; N, 6.71.

Ethyl (3a*R*,4*R*,7a*S*)-1-Allyl-2-methyl-4-(1-ethylpropoxy)-3a,4,7,7a-tetrahydrobenzimidazole-6-carboxylate (32). A yellow solution of **18** (1.76 g, 5.0 mmol) in EtOAc (16 mL) and a 50% solution of propane phosphonic acid anhydride in EtOAc (3.25 mL, 5.5 mmol) was heated with stirring to reflux for 7 h, cooled to room temperature, and extracted with 1 M aqueous Na_2CO_3 (16 mL). The organic phase was separated and dried over Na_2SO_4 and filtered, and the filtrate was evaporated to dryness in a rotary evaporator at 45 °C in vacuo (<5 mbar) to

yield a brown oil (1.55 g) which was purified by column chromatography on silica gel (90 g) and using *t*-BuOMe containing 1% aqueous NH_3 as the eluent to yield 1.23 g (74%) of **32** as a yellow oil: IR (film) ν 2966, 2936, 2876, 1715, 1679, 1658, 1601, 1370, 1236, 1103, 1062 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.83−6.76 (m, 1H), 5.76−5.57 (m, 1H), 5.22−5.08 (m, 2H), 4.21−4.05 (m, 3H), 3.74−3.58 (m, 3H), 3.16−3.01 (m, 1H), 2.92−2.76 (m, 1H), 2.75−2.62 (m, 1H), 2.24−2.05 (m, 1H), 1.97 (d, J = 1.8 Hz, 3H), 1.67−1.38 (m, 4H), 1.23 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H), 0.87 (t, J = 7.4 Hz, 3H); EI-MS (*m*/*z*) 335 (M^+ + H, 21), 334 (M^+, 10), 263 (100), 248 (52), 142 (64), 123 (53), 96 (88). Anal. Calcd for $C_{19}H_{30}N_2O_3$: C, 68.23; H, 9.04; N, 8.38. Found: C, 68.25; H, 9.09; N, 8.26.

Ethyl (3*R*,4*S*,5*R*)-5-*N*-Acetylamino-3-(1-ethylpropoxy)-4-hydroxy-1-cyclohexene-1-carboxylate (33). A stirred solution of crude **16** (40.70 g, containing ∼4% of the isomer **20**, purity 82.2% (**16** and **20**), 123 mmol) in ethyl formate (200 mL) was heated with stirring in an autoclave under 1 bar of Ar in the course of 35 min to 100 °C, stirred at this temperature for 6 h at a pressure of 4−5 bar and cooled to 45 °C during 1 h. The red solution was treated twice with toluene (2 × 150 mL) and evaporated in a rotary evaporator at 45 °C in vacuo to yield 46.24 g of crude **33** (containing 67.7% of **33** based on quantitative HPLC analysis (pH 3) corresponding to 85% of **33** from **16**) as a red oil, which was used in the next step without further purification. A reference sample of **33** (mixture of rotamers containing ∼2% toluene) was prepared from a pure reference sample of **16**: IR (film) ν 3295, 2967, 2937, 2878, 1715, 1673, 1536, 1463, 1385, 1247, 1100 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.26 (s, 1H), 6.95−6.85 (m, 1H), 5.77−5.65 (m, 1H), 4.35−4.04 (m, 4H), 3.81−3.55 (m, 1H), 3.52−3.38 (m, 1H), 3.18−3.04 (m, 1H), 2.75−2.35 (s br, 1H), 2.18−2.08 (m, 1H), 1.67−1.43 (m, 4H), 1.30 (t, J = 7.0 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H); EI-MS (*m*/*z*) 300 (M^+ + H, 4), 253 (52), 212 (55), 183 (100), 166 (90), 148 (82), 138 (74), 96 (59). Anal. Calcd for $C_{15}H_{25}NO_5$ + 1.79% toluene: C, 60.74; H, 8.42; N, 4.60. Found: C, 60.87; H, 8.47; N, 4.64.

Ethyl (3*R*,4*S*,5*R*)-3-(1-Ethylpropoxy)-5-*N*-formylamino-4-methanesulfonyloxy-1-cyclohexene-1-carboxylate (34). To a stirred orange solution of crude **33** (46.24 g, purity 67.7%, 105 mmol) in EtOAc (460 mL) and NEt_3 (23.7 mL, 170 mmol) was added dropwise at 0−5 °C $MeSO_3Cl$ (13.2 mL, 170 mmol) in the course of 30 min, during which time a white precipitate formed. After the mixture was stirred without cooling for 2 h, the white suspension was filtered, the filter cake was washed with EtOAc (45 mL), and the combined filtrates were extracted with 1 M aqueous $NaHCO_3$ (116 mL). The organic phase was separated and dried over Na_2SO_4 (130 g), filtered, and evaporated in a rotary evaporator at 45 °C in vacuo to yield 58.39 g of crude **34** (containing 67.8% of **34** based on quantitative HPLC analysis (pH 3) corresponding to 100% of **34** from **33**) as an orange-red oil, which was used in the next step without further purification. A reference sample of **34** (mixture of rotamers containing ∼6% of EtOAc) was prepared from a pure reference sample of **33**: IR (film) ν 3270, 2967, 2938, 2878, 1715, 1682, 1358, 1338, 1249, 1177 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.34−8.27 (m, 1H), 6.92−6.70 (m, 1H), 6.65−6.48 (m, 1H), 6.10−5.65 (s br, 1H), 4.86 (dd, J = 10.7, 3.7 Hz, 1H), 4.73−4.55 (m, 1H), 4.38−4.10 (m, 4H), 3.59−3.35 (m, 1H), 3.25−2.98 (m, 5H), 2.46−2.26 (m, 1H), 1.70−1.20 (m, 12H), 0.95 (t, J = 7.3 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H); EI-MS (*m*/*z*) 377 (M^+, 2), 290 (50), 244 (28), 194 (27), 166 (34), 148 (100), 142 (39), 96 (37). Anal. Calcd for $C_{16}H_{27}NO_7S$ + 5.77% EtOAc: C, 51.12; H, 7.32; N, 3.50; S, 8.00. Found: C, 51.10; H, 7.30; N, 3.55; S, 7.96.

Ethyl (3*R*,4*R*,5*S*)-4-*N*-Acetylamino-3-(1-ethylpropoxy)-5-*N*-propylamino-1-cyclohexene-1-carboxylate (36). This compound was separated by column chromatography as a byproduct of a deallylation experiment of **18** to **1** as described above using ethylenediamine as the promoter: IR (film) ν 3425, 3279, 2963, 2937, 1718, 1648, 1558, 1368, 1251, 1097, 1056 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.83−6.75 (m, 1H), 5.55−5.43 (m, 1H), 4.34−4.14 (m, 3H), 3.68−3.52 (m, 1H), 3.36 (qui, J = 5.6 Hz, 1H), 3.25−3.11 (m, 1H), 2.82−2.58 (m, 2H), 2.57−2.43 (m, 1H), 2.27−2.08 (m, 1H), 2.01 (s, 3H), 1.65−1.38 (m, 7H), 1.30 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.2 Hz, 9H); EI-MS (*m*/*z*) 355 (M^+ + H, 15), 282 (49), 208 (100), 142 (50), 100 (29). Anal. Calcd for $C_{19}H_{34}N_2O_4$: C, 64.38; H, 9.67; N, 7.90. Found: C, 64.18; H, 9.44; N, 8.00.

Acknowledgment. The authors thank Mr. Marc Duchene, Mr. Mischa Huber, Mr. Dieter Muri, and Mrs. Nathalie Sala for skillful experimental work and Mr. Marcel Althaus, Mr. Jean-Claude Jordan, and Mr. Vladimir Meduna for providing analytical support. We also thank the members of the Analytical Services of Hoffmann-La Roche Ltd., Basel, for efficiently and persistently providing and interpreting the physical data of all compounds described. The careful reading of the manuscript by Mark Rogers-Evans, Hans Hilpert, Thomas Oberhauser, and Ulrich Widmer is gratefully acknowledged.

JO005702L