ARTICLE

OBC
www.rsc.org/obc

New approaches to the industrial synthesis of HIV protease inhibitors

Yutaka Honda, Satoshi Katayama, Mitsuhiko Kojima, Takayuki Suzuki, Naomi Kishibata and Kunisuke Izawa *

AminoScience Laboratories, Ajinomoto Co., Inc., 1-1, Suzuki-cho, Kawasaki-ku, Kawasaki-shi 210-8681, Japan. E-mail: kunisuke_Izawa@ajinomoto.com; Fax: +81 (0) 44 211 7610; Tel: +81 (0) 44 244 7163

Received 18th March 2004, Accepted 26th May 2004
First published as an Advance Article on the web 23rd June 2004

Efficient and industrially applicable synthetic processes for precursors of HIV protease inhibitors (Amprenavir, Fosamprenavir) are described. These involve a novel and economical method for the preparation of a key intermediate, (3*S*)-hydroxytetrahydrofuran, from L-malic acid. Three new approaches to the assembly of Amprenavir are also discussed. Of these, a synthetic route in which an (*S*)-tetrahydrofuranyloxy carbonyl is attached to L-phenylalanine appears to be the most promising manufacturing process, in that it offers satisfactory stereoselectivity in fewer steps.

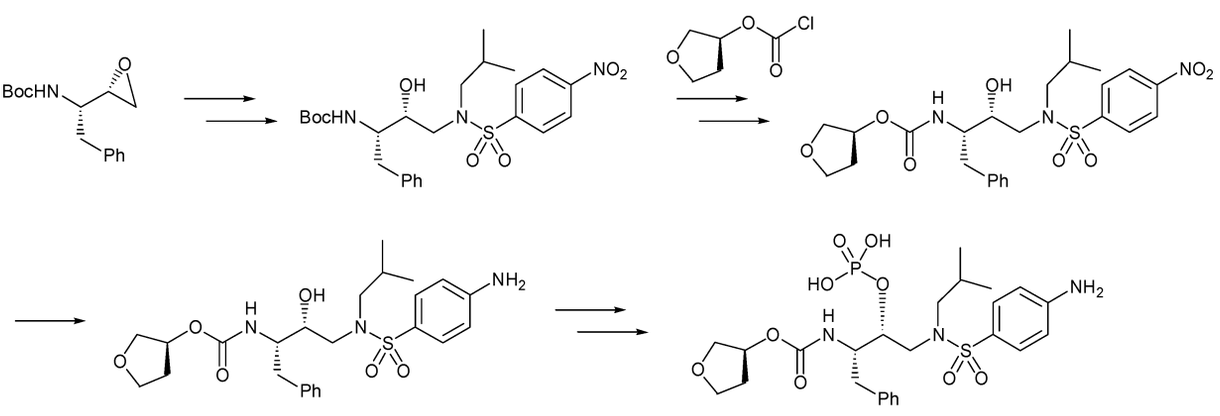
Introduction

Due to the the remarkable progress in HAART (highly active anti-retroviral therapy) in the treatment of HIV, the significance of AIDS drugs has been widely recognized and it is anticipated that the demand for them will increase in the future.[1] This demand is matched by a need for technologies to produce these compounds economically on an industrial scale. Amprenavir,[2] developed by Vertex and GlaxoSmithKline, is an HIV protease inhibitor that was approved by the FDA in 1999. Fosamprenavir,[3] launched in 2003, is a prodrug with increased therapeutic efficacy.

The synthetic method for Amprenavir originally developed by Glaxo Group and described in the patent literature uses a Boc-protected amino epoxide derived from L-phenylalanine as a key intermediate (Scheme 1).[4] This method involves aminolysis of the epoxide with isobutylamine, followed by sulfonylation and coupling with the optically active tetrahydrofuranyloxy unit at the amino terminus, and finally hydrogenation of the aromatic nitro group. Many other synthetic approaches have also been reported over the past decade.[5,6]

We previously focused our attention on the synthesis of *N*-protected amino epoxides as important intermediates for HIV protease inhibitors[7,8] and studied the synthesis of halomethyl ketones as their likely definitive precursors.[9,10] We also examined an efficient application of cross-Claisen condensation using amino acid derivatives in the synthesis of β-ketoesters, which were regarded as versatile building blocks.[11,12] We duly reported a new synthetic approach to halomethyl ketones involving the halogenation of β-ketoesters.[13]

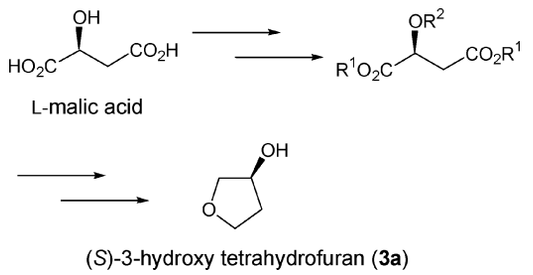
Another key material that is expensive to use on an industrial scale is (3*S*)-3-hydroxytetrahydrofuran – a building block of the *N*-substituent of the chiral amino alcohol unit. The efficient preparation of this optically active alcohol is similarly crucial to the economic synthesis of Amprenavir and Fosamprenavir. To prepare chiral 3-hydroxytetrahydrofuran, various asymmetric synthetic approaches such as hydroboration or hydrosilylation of dihydrofuran have been reported, but the optical purity achieved in these systems has been limited in most cases.[14,15] Although the asymmetric hydrogenation of 4-chloro-3-oxobutanoate followed by reduction of the ester gave its optically active chloro-diol precursor, intramolecular etherification requires precise control to avoid side reactions, *e.g.* epoxidation and elimination.[16] The enzymatic resolution of a racemic compound could provide an effective method.[17] As an efficient transformation from an readily available natural compound, Tandon *et al.* reported the cyclization of an optically active triol derived from malic acid.[18] However, it has been pointed out that the secondary hydroxyl group of L-malic acid or its esters should be protected against substantial racemization during reduction with lithium aluminum hydride.[18,19] This observation



Scheme 1 Outline for the synthesis of Amprenavir described in the patent literature by Glaxo Group and the transformation to Fosamprenavir reported by Vertex.

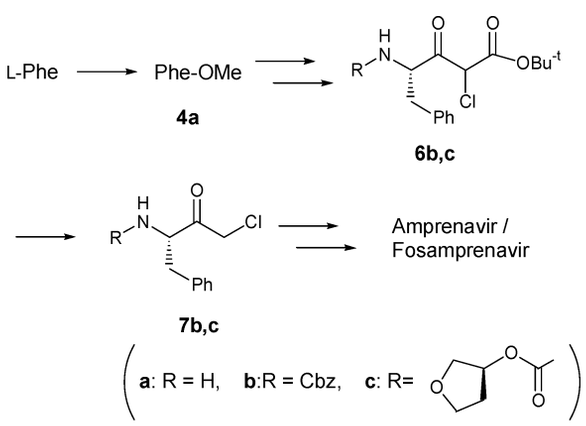
DOI: 10.1039/b404071f

prompted us to attempt to develop an industrial-scale process for preparing (3*S*)-3-hydroxytetrahydrofuran that required minimal purification; for example, by means of extraction of the lipophilic intermediate (Scheme 2).



Scheme 2 Synthesis of (*S*)-3-hydroxytetrahydrofuran from L-malic acid.

In this report, we describe our synthetic approaches toward precursors of Amprenavir and Fosamprenavir, which should facilitate economic industrial-scale manufacture providing two key building blocks to reduce the number of steps (Scheme 3).



Scheme 3 Preparation of halomethyl ketone using cross-Claisen condensation.

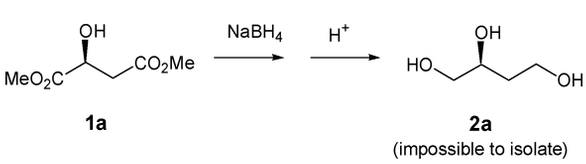
Results and discussion

(1) Synthesis of (3*S*)-3-hydroxytetrahydrofuran

3-Hydroxytetrahydrofuran can be synthesized by the cyclization of 1,2,4-butanetriol under acidic conditions.[18] While the (*S*)-triol might be obtained by reducing readily available L-malic acid, it has been reported that racemization can occur when this reduction is carried out with lithium aluminum hydride.[18,19] Also, reducing agents other than lithium aluminum hydride are preferable from an industrial perspective.

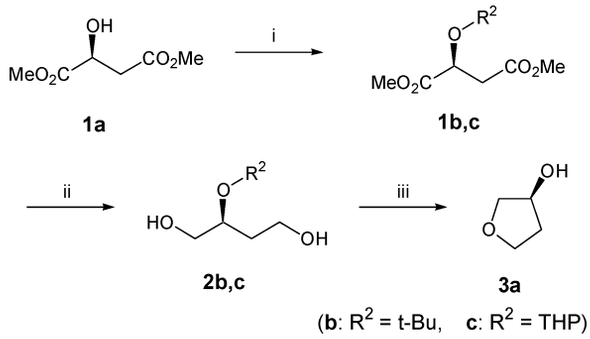
Our first attempt involved the reduction of dimethyl malate **1a** by sodium borohydride in ethanol, followed by quenching, filtering out the resulting salts and then distillation, since the triol **2a** cannot be extracted with organic solvents. However, none of the fractions furnished by the distillation process contained the triol **2a** (bp 97–99 °C/0.05 mm Hg), and instead distillation gave only a decomposed residue, despite the detection of **2a** in the reaction mixture by GC. The most likely explanation for this was that the triol could not easily be released from the boron complex (Scheme 4).

We then examined hydrophobic protection of the 2-hydroxyl group to facilitate isolation by extraction with organic solvents.



Scheme 4 Reduction of dimethyl L-malate by sodium borohydride

Dimethyl malate was converted to the *tert*-butoxy derivative **1b** by a reaction with isobutene in the presence of phosphoric acid and boron trifluoride as catalysts,[20] and **1b** was reduced to crude diol **2b** with sodium borohydride, which was easily isolated by extraction with ethyl acetate. Under distillation conditions (heating under reduced pressure) in the presence of a catalytic amount of *p*-toluenesulfonic acid, cyclization and cleavage of the *tert*-butyl group of **2b** took place concurrently, and hydroxytetrahydrofuran **3a** was successfully produced as a distillate (Scheme 5). Tetrahydropyranyl ether **1c**, a less stable intermediate, did not give a good result. The optical purity of the resulting **3a** was examined by GC after derivatization to Mosher's ester with MTPA-Cl; no stereoisomer was detected.[21] The optical rotation ($[\alpha]_D^{20}$ +17.653 in CH_3OH) was also equivalent to that of the commercially available product.[22]

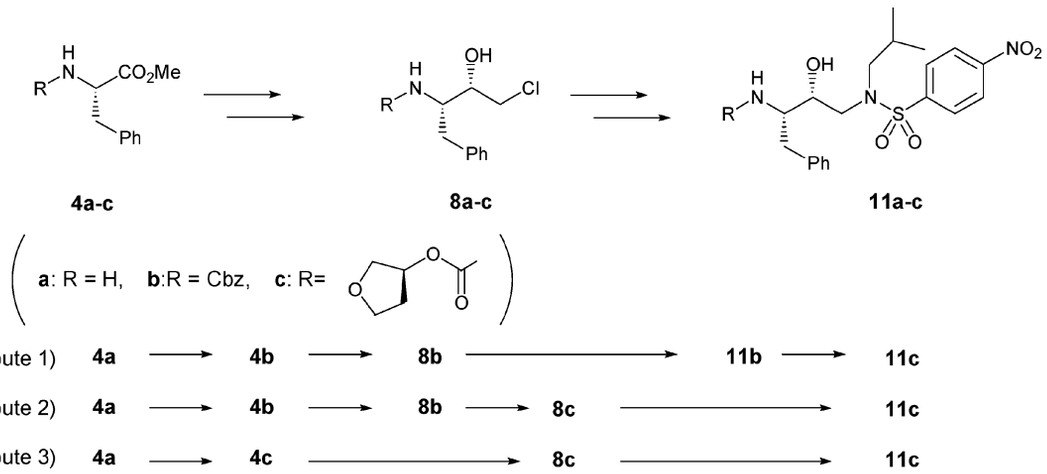


Scheme 5 Preparation of (*S*)-3-hydroxytetrahydrofuran **3a**. *Reagents and conditions via* **1b** *and* **2b**: (i) isobutene, *cat.* $P_2O_5/H_3PO_4/BF_3OEt_2$, CH_2Cl_2, ambient temp., 82.8%, (ii) (a) $NaBH_4$, EtOH, ambient temp., (b) HCl *aq*., 80.5%, (iii) cat. *p*-Tos–OH, 77 °C, 65.0%.

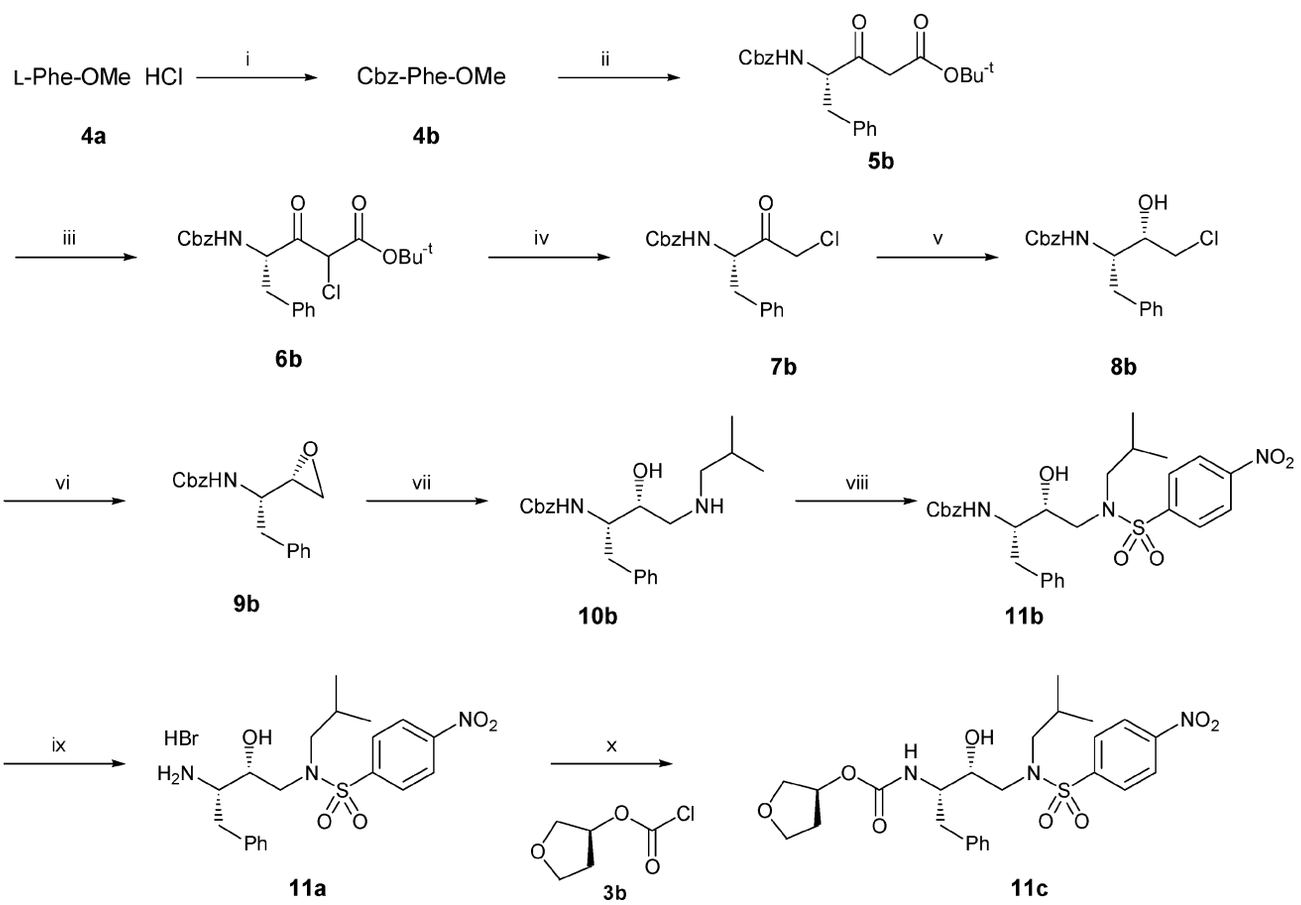
(2) Synthetic approaches to the common intermediate for amprenavir/fosamprenavir

With methods for obtaining the two key intermediates (the halomethyl ketone **8** and hydroxytetrahydrofuran **3a**) in hand, we then turned our attention to studying economical synthetic routes to Amprenavir and Fosamprenavir. There are three possible approaches derived from our halomethyl ketone synthetic method (Scheme 6).[13] Routes 1 and 2 adopt a Cbz-protected halomethyl ketone as an intermediate. Route 3 uses an *N*-tetrahydrofuranyloxy carbonyl group instead of general protecting groups. These routes give the sulfonamide **11c**, which can be easily converted to Amprenavir by known processes.[4]

(2.1) Route 1. A cross-Claisen condensation between the methyl ester **4b** and *tert*-butyl acetate quantitatively gave the β-ketoester **5b** (Scheme 7).[11] Chloromethyl ketone **7b** was obtained as a key intermediate in two steps from crude **5b** in 68% yield after purification by recrystallization.[13] There have been several reports in which **7b** could be diastereoselectively reduced by sodium borohydride to provide the (*S*,*S*(*syn*)) amino alcohol derivative.[23] In our study, **7b** was reduced to **8b** and its isomer in a ratio of (*S*,*S*)/(*R*,*S*) = 84 : 16 in methanol–methylene chloride at 0 °C, and the mixture was then converted into the amino epoxide **9b** in potassium carbonate/ethanol in a yield of 82% from **7b**.[8] The crude Cbz-sulfonamide **11b** was obtained by a two-step reaction.[4] Crystallization of crude **11b** in ethanol was an effective method for removing the diastereomer into the mother liquor give pure material. The yield of **11b** after a simple crystallization was 85%(**11b** ((*R*,*S*(*syn*))/(*S*,*S*) = 98.2 : 1.8) from the (*S*,*S*(*syn*)) isomer in **9b**). Deprotection of the Cbz group with HBr/acetic acid, followed by a Schotten–Baumann reaction with the chloroformate **3b** (prepared by treatment of (3*S*)-3-hydroxytetrahydrofuran **3a** with triphosgene) resulted in the formation of **11c**.[24] A single isomer of **11c** was obtained in 62% yield from **11b** after crystallization in ethanol. Thus, the overall yield of **11c** (diastereomers



Scheme 6 Three possible approaches to the common intermediate **11c** for Amprenavir.

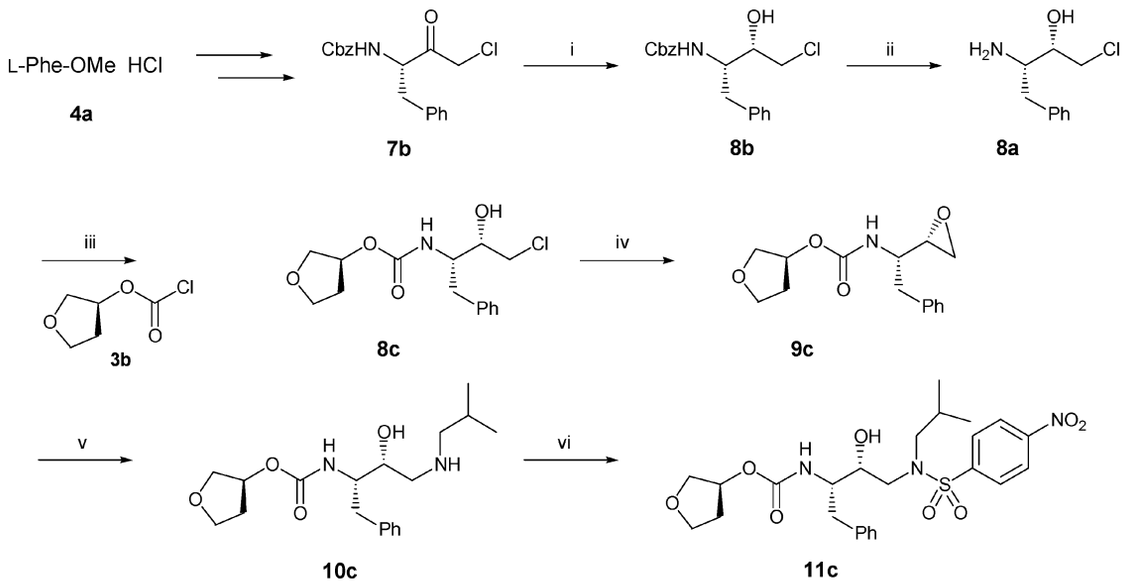


Scheme 7 Synthetic scheme for Route 1. *Reagents and conditions*: (i) Cbz-Cl, 1 M Na_2CO_3, toluene, 10 °C, (ii) (a) *t*-BuOAc, LDA, THF, −45 °C, (b) 2 M HCl, *quant.*, (iii) SO_2Cl_2, CH_2Cl_2, 10 °C, 90%, (iv) HCO_2H, 80 °C, 68% from **5b**, (v) (a) $NaBH_4$, CH_2Cl_2, MeOH, 0 °C, (b) AcOH, (vi) K_2CO_3, MeOH, ambient temp., 82% from **7b**, (vii) *iso*-$BuNH_2$, EtOH, 70 °C, (viii) *p*-NBSCl, Na_2CO_3*aq*, ambient temp., 85% from **9b**, (ix) 30% HBr in AcOH, CH_2Cl_2, 17 °C, (x) **3b**, 15% K_2CO_3, CH_2Cl_2, 15 °C, 62% from **11b**.

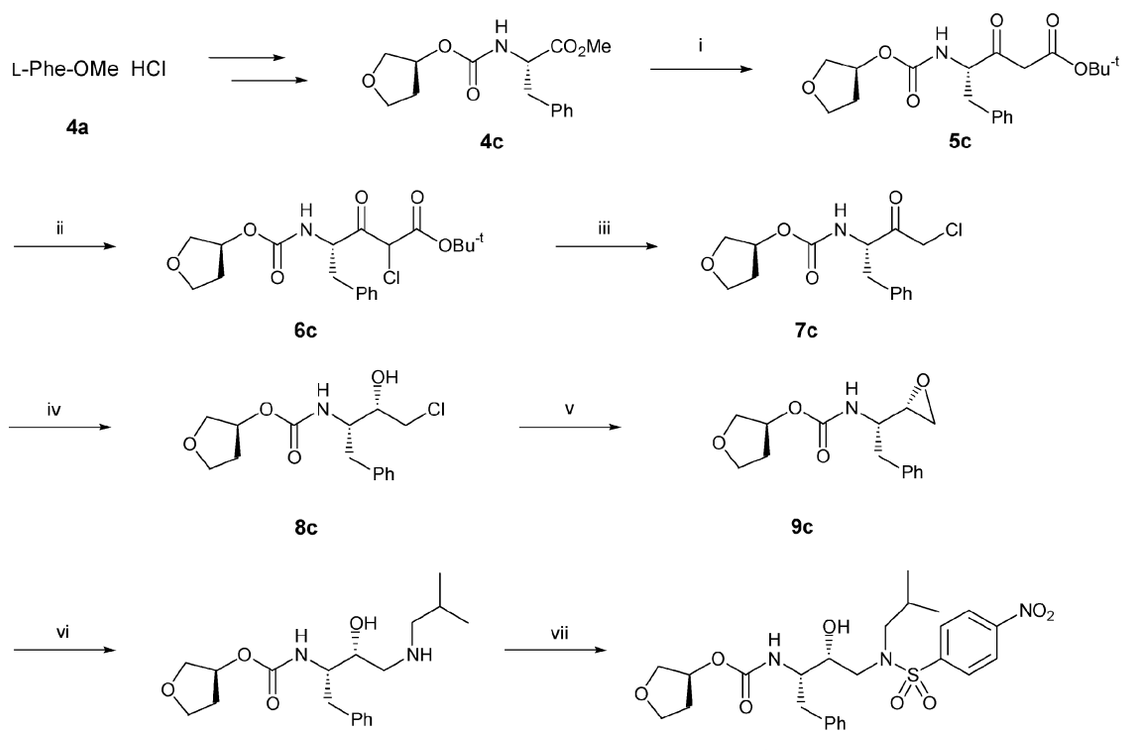
not detectable) in 10 steps from **4a** was 28%. Hydrogenation of the aromatic nitro group of **11c** can convert this compound into Amprenavir.[4]

(2.2) Route 2. Another interesting approach is to exchange the Cbz group with a tetrahydrofuranyloxy group prior to amination (Scheme 8). Using the same procedures as in Route 1 to **8b** followed by crystallization in ethanol, purified **8b** ((*R*,*S*)/(*S*,*S*) = 98.1 : 1.9) was obtained in 77% yield from **7b**. Hydrogenolysis of **8b** with Pd–C selectively induced cleavage of the Cbz group to give crude **8a** as a solid without harming the chloromethyl unit. Treatment of **8a** with 3-((3*S*)-tetrahydrofuranyloxy) chloroformate **3b** by the same method as in Route 1 provided **8c**. Compound **8c** was not isolated, and the above sequence of epoxidation and amide formation gave the sulfonamide **11c**. The sulfonamide could be purified as a single stereoisomer ((*S*,*R*,*S*)/(*S*,*S*,*S*) = 99.8 : 0.2) in two recrystallizations from ethanol. The overall yield of **11c** ((*S*,*R*,*S*)/(*S*,*S*,*S*) = 99.8 : 0.2) in 10 steps from **4a** was 34%. This suggests that Route 2 may be superior to Route 1 in terms of yield. However, the poor solubility of the tetrahydrofuranyloxy carbonyl intermediates (**8b**–**11b**) in Route 2 has an adverse effect on productivity.

(2.3) Route 3. Both Routes 1 and 2 involve protection and deprotection of the nitrogen atom with a Cbz group, and subsequent attachment of the tetrahydrofuranyloxy carbonyl (Scheme 9). Therefore, we undertook further studies that did



Scheme 8 Synthetic scheme for Route 2. *Reagents and conditions*: (i) (a) $NaBH_4$, CH_2Cl_2, MeOH, −4 °C, (b) 1 M HCl, 77%, (ii) H_2, 5% Pd–C, MeOH, 5 °C, (iii) **3b**, 10% Na_2CO_3, CH_2Cl_2, (iv) K_2CO_3, MeOH, ambient temp., (v) *iso*-$BuNH_2$, EtOH, refl., (vi) *p*-NBSCl, 10% K_2CO_3, ambient temp., 49% from **8b**.



Scheme 9 Synthetic scheme for Route 3. *Reagents and conditions*: (i) (a) *t*-BuOAc, LDA, THF, −45 °C, (b) AcOH, 98%, (ii) SO_2Cl_2, CH_2Cl_2, ambient temp., (iii) HCO_2H, 80 °C, 70% from **5c**, (iv) (a) $NaBH_4$, CH_2Cl_2, MeOH, −3 °C, (b) AcOH, (v) K_2CO_3, MeOH, ambient temp., 93% from **7c**, (vi) *iso*-$BuNH_2$, EtOH, 70 °C, (vii) *p*-NBSCl, 6% $NaHCO_3$, ambient temp., 90% from **9c**.

not use common protecting groups such as Cbz and Boc with a view to installing the tetrahydrofuranyloxy carbonyl group at an earlier stage. We hoped that this would reduce the number of steps. Processes that avoid protection-cleavage of Cbz groups may also help to improve quality profiles. Kamijo *et al.* reported this concept in the patent literature, and applied it to another synthetic route involving the epoxidation of a 2-amino-3-butene derivative.[6]

Tetrahydrofuranyloxy carbonization of L-phenylalanine methyl ester afforded crude **4c** in an oily form in 80% yield. Compound **4c** was quantitatively transformed to the β-ketoester **5c**, and subsequent chlorination and decarboxylation to give the crystalline chloromethyl ketone **7c** in 70% yield. The ketone **7c** was then reduced with sodium borohydride as described above to give chlorohydrin **8c** in a diastereomeric ratio of (*S*,*S*,*S*)/(*S*,*R*,*S*) = 83 : 17. Treatment of **8c** with potassium carbonate converted the diastereomeric mixture to the epoxide **9c**, where the yield of the (*S*,*S*,*S*)-isomer was 77% from **7c**. The sulfonamide **11c** was obtained as a mixture of (*S*,*R*,*S*) and (*S*,*S*,*S*) isomers by using the same method as described in the previous routes. (*S*,*R*,*S*)-**11c** was crystallized from ethanol in 90% yield with 94.4%de from (*S*,*S*,*S*)-**9c**. Further recrystallization from ethanol gave the pure compound **11c** as a single isomer. The overall yield of **11c** ((*S*,*R*,*S*)/(*S*,*S*,*S*) = 98.2 : 1.8) in eight steps from **4a** was 45%, and that of **11c** ((*S*,*S*,*S*) not detectable) after recrystallization from **4a** was 32%.

Conclusion

We have described here new processes that may be suitable for the industrial-scale synthesis of the intermediates of the HIV protease inhibitors Amprenavir/Fosamprenavir (developed by Vertex-GlaxoSmithKline). To prepare the optically active side chain, a new approach to 3-hydroxytetrahydrofuran from commonly available malic acid has been established.

By combining this with our method for halomethyl ketone synthesis, several routes to the precursor of Amprenavir were investigated. Synthetic processes that involve safe and practical reactions with readily available raw materials were realized. The process in which the tetrahydrofuranyloxy carbonyl group is installed at an early stage, without using common protecting groups, was quite efficient and may have real industrial potential.

Experimental

General

All reagents were purchased and used without further purification. Thin-layer chromatography (TLC) was conducted on precoated TLC plates (Merck 60F250). High-performance liquid chromatography (HPLC) was performed with a Hitachi L-6000 pump and L-4000 UV detector system using an Inertsil ODS-2 column. Chiral HPLC was measured with the above system using a Daicel Chiralcel OD–H or a Daicel Chiralpak AS column. Gas chromatography (GC) was performed with a Hewlett Packard 5890 series II system equipped with an FID detector using a J&W DB1701 capillary column.

Melting points were measured with a Büchi B-545 or a Yanaco melting point apparatus MP model, and are uncorrected. Optical rotations were measured on a Japan-Spectroscopic DIP-370 digital polarimeter with a path length of 1 dm. Concentrations are quoted in g 100 mL^{-1}. NMR spectra were obtained on a Varian XL-300 spectrometer. All proton NMR spectra were measured in $CDCl_3$ or DMSO-d6 solvent, and chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.00) or $CDCl_3$ (δ 7.26) as an internal standard. Data are reported as follows: chemical shift (integrated intensity or assignment, multiplicity, coupling constants in hertz, assignment). All carbon NMR spectra were measured in $CDCl_3$ or DMSO-d6 solvent, and chemical shifts are reported as δ values in parts per million relative $CDCl_3$ (δ 77.0) or DMSO-d6 (δ 39.5) as an internal standard. Mass spectra (MS) were obtained with a ThermoQuest TSQ700 or a JEOL JMS-HX110 instrument with ESI (electrospray) or FAB (fast atom bombardment) ionization. High-resolution mass spectra (HRMS) were obtained with a JEOL MS700V (JEOL datum Ltd.).

Synthesis of (*S*)-hydroxytetrahydrofuran

***O*-*tert*-Butyl dimethyl L-malate (1b).** Phosphoric acid (85%, 3.5 ml, 51 mmol) and phosphorous pentoxide (1.4 g, 9.9 mmol) were added sequentially to a solution of dimethyl L-malate (**1a**) (25.02 g, 154 mmol) in methylene chloride (250 ml). To the cooled solution (−70 °C) was added boron trifluoride diethyl etherate (6.5 ml, 53 mmol) and isobutene (130 ml at −49 °C, 1.56 mol), and the reaction flask was then sealed. After the reaction mixture was stirred for 17 h at ambient temperature, it was added dropwise to a solution prepared from 25% ammonia water (50 ml) and water (50 ml) cooled in an ice bath. The solution was stirred for 1 h at ambient temperature to evacuate excess isobutene. The organic layer was separated, washed with saturated NaCl aqueous solution (200 ml × 2), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give crude L-(*S*)-**1b** (43.9 g, purity 63.6 wt.%, 128 mmol, 82.8% yield) as a colorless syrup.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.20 (s, 9H), 2.66 (dd, 1H, J = 7.4, 15.3 Hz), 2.71 (dd, 1H, J = 5.7, 15.3 Hz), 3.60 (s, 3H), 3.64 (s, 3H), 4.48 (dd, 1H, J = 5.7, 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 27.5, 39.2, 51.6, 52.0, 68.2, 75.5; $[a]_D^{25}$ −39.5 (c 2.10, CH_3OH); MS (+EI) m/z 203 (M–CH_3); HRMS (+EI) calcd for $C_9H_{15}O_5$ (M–CH_3), 203.0920, found 203.0911.

(2*S*)-2-*tert*-Butoxy-1,4-butanediol (2b). An ethanol (70 ml) solution of sodium borohydride (26.6 g, 704 mmol) was added dropwise to a solution of crude L-(*S*)-**1b** (net 40.3 g, 185 mmol) in ethanol (704 ml) with cooling in an ice bath. After the mixture was stirred for 4.2 h at ambient temperature, 6 M hydrochloric acid (40 ml) and 2 M hydrochloric acid (170 ml) were added to adjust the pH to 6.3 (17 °C). The suspended mixture was filtered to remove inorganic salts, and the filtrate was concentrated under reduced pressure and then filtered again to remove precipitated salts. The aqueous filtrate was washed with *n*-hexane (200 ml), and then extracted three times with ethyl acetate (250 ml, 200 ml, 200 ml). The combined organic layers were concentrated under reduced pressure to give crude (*S*)-**2b** (38.5 g, purity 62.6%, net 24.1 g, 149 mmol, 80.5% yield) as a colorless oil.

^{1}H NMR (300 MHz, DMSO-d6) δ = 1.12 (s, 9H), 1.38–1.49 (m, 1H), 1.62–1.73 (m, 1H), 3.29–3.56 (m, 4H), 4.30 (t, 1H, J = 5.0 Hz), 4.43 (t, 1H, J = 5.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 28.4, 35.8, 59.5, 65.4, 70.0, 74.4; $[a]_D^{25}$ −23.8 (c 1.93, CH_3OH); MS (+FAB) m/z 163.20 (MH^+); HRMS (+FAB) calcd for $C_8H_{19}O_3$ (MH^+), 163.1334, found 163.1324.

(3*S*)-3-Hydroxytetrahydrofuran (3a). A mixture of *p*-toluenesulfonic acid monohydrate (720 mg, 3.8 mmol) and crude (*S*)-**2b** (38.5 g, net 24.1 g, 149 mmol) was distilled under reduced pressure (18–77 °C/12.5–15 mm Hg) to afford crude (3*S*)-hydroxytetrahydrofuran (12.3 g). The distillate was then re-distilled under reduced pressure (75–99 °C/15 mm Hg) to provide (*S*)-**3a** (8.77 g, purity 97.1%, 96.7 mmol, 65% yield) as a colorless syrup.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.86–1.95 (m, 1H), 2.02–2.14 (m, 1H), 2.98 (b, 1H), 3.75–3.87 (m, 3H), 3.93–4.01 (m, 1H), 4.46–4.50 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 35.1, 66.4, 71.2, 75.1; $[a]_D^{20}$ +17.7 (c 2.40, CH_3OH, 100 mm cell); MS (+FAB) m/z 89.0 (MH^+); HRMS (+FAB) calcd for $C_4H_9O_2$ (MH^+), 89.0603, found 89.0611.

Route 1

***tert*-Butyl(4*S*)-4-*N*-benzyloxycarbonylamino-3-oxo-5-phenylpentanoate (5b).** Benzyl chloroformate (22.56 g, 132.2 mmol) was added to a suspended solution of L-phenylalanine methyl ester hydrochloride (30.0 g, 139 mmol) in toluene (140 ml) with cooling in an ice bath, and 1 M Na_2CO_3 aqueous solution (68 ml) was added dropwise with vigorous stirring over 40 min at 5–12 °C. After this addition was complete, the mixture was stirred for 60 min at 5–10 °C. The organic layer was separated, washed with 0.2 M HCl (50 ml) and 5% $NaHCO_3$ aqueous solution (50 ml), and then dried over anhydrous $MgSO_4$. Concentration of the solution at 40–45 °C under reduced pressure provided Cbz–L–Phe–OMe (**4b**) (39.5 g, 126 mmol, 91% from L-phenylalanine methyl ester) as a colorless oil.

A solution of *tert*-butyl acetate (58.1 g, 500 mmol) in THF (40 ml) was added dropwise to a mixture of dry THF (400 ml) and LDA (2 M solution in THF–heptane–ethylbenzene, 231 ml, 462 mmol) with stirring under an argon atmosphere over 40 min at −45 °C. After the mixture was stirred for 60 min at −45 °C, a solution of Cbz–L–Phe–OMe (**4b**) (39.4 g, 125 mmol) in THF (40 ml) was added dropwise over 30 min at −45 °C. The resulting mixture was stirred at −45 °C for 60 min and then poured into a mixture of 2 M HCl (500 ml) and ice (150 g) to quench the reaction. The organic layer was separated and the aqueous layer was extracted with toluene (350 ml). The

combined organic layers were washed with 5% $NaHCO_3$ aqueous solution (50 ml) and 25% NaCl aqueous solution, and then dried over anhydrous $MgSO_4$, and concentrated under reduced pressure at 40–45 °C to give crude (*S*)-**5b** (58.1 g, purity: 86.4% by HPLC, net 126 mmol, quantitative from **4b**) as a yellowish oil. This material was used in the subsequent transformation without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.44 (s, 9H), 2.99 (dd, 1H, *J* = 7.1, 14.1 Hz), 3.17 (dd, 1H, *J* = 6.1, 14.1 Hz), 3.38 (m, 2H), 4.68 (bq, 1H, *J* = approx. 7 Hz), 5.07 (s, 2H), 5.38 (bd, 1H, *J* = 7.9 Hz), 7.12–7.35 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 28.0, 37.1, 48.2, 60.7, 67.0, 82.4, 127.1, 128.1, 128.2, 128.5, 128.7, 129.2, 135.8, 137.9, 165.8, 182.0, 201.7; MS (+FAB) *m*/*z* 398 (MH^+); HRMS (+FAB) calcd for $C_{23}H_{28}NO_5$ (MH^+), 398.1967, found 398.1949.

***tert*-Butyl(4*S*)-4-*N*-benzyloxycarbonylamino-2-chloro-3-oxo-5-phenylpentanoate (6b).** Sulfuryl chloride (7.23 ml, 90 mmol) was added dropwise to a solution of (*S*)-**5b** (40.5 g, purity: 86.4%, net 88 mmol) in dichloromethane (88 ml) in an ice bath with stirring over 30 min at a rate sufficient to maintain the temperature at 10 °C. When the addition was complete, the ice bath was removed and the reaction was continued with stirring for 30 min at 20 °C. The resulting mixture was concentrated under reduced pressure at 25–30 °C to give crude (*S*)-**6b** (48.6 g) as pale yellowish crystals. A portion (2.0 g) of the crude material was recrystallized from toluene (10 ml) to give pure crystals. The remaining material was used in the subsequent transformation without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.44 (s, 9H), 2.99 (dd, 1H, *J* = 7.5, 14.1 Hz), 3.20 (dd, 1H, *J* = 6.1, 14.1 Hz), 4.85 (s, 1H), 4.97 (bq, 1H, *J* = 8.4 Hz), 5.06 (s, 2H), 5.25 (bd, 1H, *J* = 8.4 Hz), 7.14–7.35 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 27.5, 37.7, 59.5, 60.0, 67.2, 85.0, 127.3, 128.1, 128.3, 128.5, 128.9, 129.2, 135.3, 136.0, 155.6, 163.1, 197.4; mp = 79–80 °C; $[a]_D^{25}$ −47.2 (*c* 1.05, CH_3OH); MS (+FAB) *m*/*z* 431.8 (MH^+); HRMS (+FAB) calcd for $C_{23}H_{27}ClNO_5$ (MH^+), 432.1578, found 432.1568.

(3*S*)-1-Chloro-2-oxo-3-*N*-benzyloxycarbonylamino-4-phenylbutane (7b). Crude crystals of (*S*)-**6b** (46.6 g, prepared as above) were added to 90% formic acid (80 ml) at ambient temperature and the suspended mixture was heated in an oil bath with stirring for 20 min at 80 °C. The resulting mixture was cooled to ambient temperature, concentrated under reduced pressure at 30–35 °C, and then concentrated again in the same manner after the addition of isopropanol (100 ml) to completely remove formic acid. To the residual solid was added isopropanol (200 ml) which had been warmed to 60 °C. The mixture was recrystallized at 5 °C, filtered, washed with cold isopropanol (50 ml), and dried at 40 °C *in vacuo* to give (*S*)-**7b** (20.1 g, 60 mmol, 68.2% from (*S*)-**5b** (2 steps)) as slightly yellowish crystals.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.00 (dd, 1H, *J* = 7.0, 13.9 Hz), 3.09 (dd, 1H, *J* = 6.9, 13.9 Hz), 3.97 (d, 1H, *J* = 16.2 Hz), 4.14 (d, 1H, *J* = 16.2 Hz), 4.75 (bq, 1H, *J* = approx. 7 Hz), 5.06 (s, 2H), 5.38 (bd, 1H, *J* = 7.6 Hz), 7.11–7.38 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 37.6, 47.3, 58.7, 67.2, 127.4, 128.1, 128.3, 128.5, 128.9, 129.0, 135.2, 135.9, 155.7, 200.8; mp = 109–111 °C; $[a]_D^{25}$ −51.1 (*c* 1.06, CH_3OH); MS (+FAB) *m*/*z* 331.8 (MH^+); HRMS (+FAB) calcd for $C_{18}H_{19}ClNO_3$ (MH^+), 332.1053, found 332.1041.

(2*S*,3*S*)-1-Chloro-2-hydroxy-3-*N*-benzyloxycarbonylamino-4-phenylbutane (8b). Sodium borohydride (2.03 g, 53.8 mmol) was added portionwise over 10 min with stirring to a solution of (*S*)-**7b** (17 g, 51.2 mmol) in a mixture of dichloromethane (180 ml) and methanol (180 ml) that had been cooled to −3 °C. After the mixture was stirred for 30 min at 0 °C, acetic acid (12.9 ml, 226 mmol) was added to quench the reaction, and the mixture was concentrated to about 50 ml under reduced pressure at 35–40 °C. Water (50 ml) and dichloromethane (150 ml) were added to the concentrate and extracted, and the aqueous layer was then extracted again with dichloromethane (50 ml). The combined organic layers were concentrated under reduced pressure to give crude (2*S*,3*S*)-**8b** (17.5 g) as a colorless solid. The peak area of the diastereomer ((2*R*,3*S*)-form) was about 16% in an HPLC analysis. A portion (1.0 g) of the crude material was recrystallized from *n*-hexane–ethyl acetate (1/1) (15 ml) to give pure crystals (0.6 g, (2*R*,3*S*)/(2*S*,3*S*) = 98.5/1.5). The remaining material was used in the subsequent transformation without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) (2*S*,3*S*) form δ = 2.87 (dd, 1H, *J* = 9.0, 14.1 Hz), 3.00 (dd, 1H, *J* = 4.6, 14.1 Hz), 3.55 (dd, 1H, *J* = 7.3, 11.3 Hz), 3.60 (bs, 1H), 3.62 (dd, 1H, *J* = 4.3, 11.3 Hz), 3.86 (bq, 1H, *J* = approx. 5 Hz), 3.96–4.06 (m, 1H), 5.01 (s, 2H), 5.31 (bd, 1H, *J* = approx. 8.5 Hz), 7.18–7.33 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) (2*S*,3*S*) form δ = 35.3, 47.1, 54.6, 66.5, 73.2, 126.4, 127.8, 127.9, 128.3, 128.3, 129.3, 136.3, 137.5, 156.0; mp = 153–154 °C; $[a]_D^{25}$ −24.5 (*c* 0.56, CH_3OH); MS (+FAB) *m*/*z* 333.8 (MH^+); HRMS (+FAB) calcd for $C_{18}H_{21}ClNO_3$ (MH^+), 334.1210, found 334.1184.

(1*S*,1′*S*)-1-(1′-*N*-Benzyloxycarbonylamino-2′-phenyl)ethyloxirane (9b). To a solution of crude **8b** (16.5 g, prepared as above) in methanol (600 ml) was added portionwise anhydrous K_2CO_3 (14.1 g, 102 mmol). After the mixture was stirred at ambient temperature for 3 h, the suspended salts were removed by filtration and were washed with methanol (20 ml). The combined filtrate and washing liquor were concentrated to about 100 ml under reduced pressure at 35 °C. Dichloromethane (150 ml) and 0.5 M HCl (100 ml) were added to the concentrate and extracted, and the aqueous layer was then extracted again with dichloromethane (150 ml). The combined organic layers were concentrated under reduced pressure below 40 °C to give **9b** (14.0 g, 47.1 mmol, containing about 16% of the diastereoisomer, 97.6% yield from (*S*)-**7b** (2 steps), 82% yield as the (1*S*,1′*S*) form), as a colorless solid. A portion (1.0 g) of the crude material was recrystallized from *n*-hexane–ethyl acetate (1/1) (6 ml) to give pure crystals (0.58 g, (1*S*,1′*S*)/(1*R*,1′*S*) = 98.5/1.5). Another portion of remaining material was used in the subsequent transformation without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) (1*S*,1′*S*) form δ = 2.71–2.80 (m, 2H), 2.85 (dd, 1H, *J* = 8.1, 14.1 Hz), 2.91 (dd, 1H, *J* = 2.7, 6.4 Hz), 2.97 (dd, 1H, *J* = 5.1, 14.1 Hz), 3.68–3.82 (m, 1H), 4.77 (bd, 1H, *J* = 5.9 Hz), 5.03 (s, 2H), 7.17–7.33 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) (1*S*,1′*S*) form δ = 37.5, 46.7, 53.0, 53.2, 66.8, 126.8, 128.0, 128.1, 128.5, 128.6, 129.3, 136.2, 136.4, 155.7; mp = 77–80 °C; MS (+FAB) *m*/*z* 297.9 (MH^+); HRMS (+FAB) calcd for $C_{18}H_{20}NO_3$ (MH^+), 298.1443, found 298.1456.

(2*R*,3*S*)-3-*N*-Benzyloxycarbonylamino-2-hydroxy-1-*N*-isobutylamino-4-phenylbutane (10b). A solution of crude **9b** (4.47 g, 15.0 mmol, (1*S*,1′*S*)/(1*R*,1′*S*) = 84/16) in ethanol (29 ml) was added in one portion to isobutylamine (22.4 ml, 225 mmol). The resulting mixture was heated in an oil bath with stirring for 60 min at 70 °C, and then concentrated under reduced pressure to remove the solvent and excess isobutylamine. Volatile matter was completely removed *in vacuo* to give crude **10b** (6.08 g, (2*R*,3*S*)/(2*S*,3*S*) theoretically 84/16, quantitative) as a colorless solid. This material was used in the subsequent transformation without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) (2*S*,3*S*) form δ = 0.90 (d, 6H, *J* = 6.6, Hz), 1.60–1.80 (m, 1H), 2.38 (d, 2H, *J* = 6.8 Hz), 2.65 (dd, 1H, *J* = 6.8, 12.4 Hz), 2.70 (dd, 1H, *J* = 4.0, 12.4 Hz), 2.7 (bs, 1H), 2.86 (dd, 1H, *J* = 8.1, 14.1 Hz), 2.99 (dd, 1H, *J* = 4.8, 14.1 Hz), 3.49 (bq, 1H, *J* = approx. 4.5 Hz), 3.80–3.95 (m, 1H), 5.02 (s, 2H), 5.11 (bd, 1H, *J* = 9.0 H), 7.19–7.32 (m, 10H); ^{13}C

NMR (75 MHz, $CDCl_3$) (2*S*,3*S*) form δ = 20.5, 28.3, 36.6, 51.4, 55.0, 57.9, 66.5, 70.4, 126.4, 127.8, 128.0, 128.4, 128.4, 129.5, 136.6, 137.7, 156.3; MS (+EI) 371.2 (MH^+).

4-Nitro-*N*-((2*R*(*syn*),3*S*)-3-(*N*-benzyloxycarbonylamino)-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-benzenesulfonamide (11b). An aqueous solution (20 ml) of Na_2CO_3 (2.55 g, 24.1 mmol) was added to a solution of crude **10b** (6.08 g, 15.0 mmol, (2*R*,3*S*)/(2*S*,3*S*) = 84/16) in dichloromethane (40 ml). To the cooled mixture (below 10 °C) was added dropwise with stirring a solution of 4-nitrobenzenesulfonyl chloride (4.00 g, 18.0 mmol) in dichloromethane (5 ml). After the resulting mixture was warmed to ambient temperature and stirred for 3 h, water (20 ml) and dichloromethane (20 ml) were added and extracted. The organic layer was separated and concentrated under reduced pressure to give crude product as slightly yellowish crystals. The crude crystals were dissolved in ethanol (100 ml) at 70 °C, and the temperature was then dropped to 55 °C with stirring to give nucleation. The slurry was aged at 55 °C for 1 h after nucleation, and then cooled at 20 °C for 3 h, filtered, washed with ethanol (30 ml), and dried under reduced pressure to give **11b** (6.07 g, 10.9 mmol, (2*R*,3*S*)/(2*S*,3*S*) = 98.2/1.8, 72.7% from a diastereomixture of **9b** (2steps), in 85% yield from (1*S*,1′*S*) form) as colorless crystals. For further purification, some of the crystals (2.73 g, 4.91 mmol) were recrystallized from ethanol (50 ml) in the same manner as described above and filtered, washed with ethanol (15 ml), and dried to give (*R*,*S*)-**11b** (2.34 g, 4.21 mmol, (2*R*,3*S*)/(2*S*,3*S*) = 99.7/0.3 by HPLC peak area, 86% from the crystals obtained above) as colorless crystals.

^{1}H NMR (300 MHz, $CDCl_3$) (2*S*,3*S*) form δ = 0.84 (d, 3H, *J* = 6.1, Hz), 0.86 (d, 3H, *J* = 6.3, Hz), 1.75–1.95 (m, 1H), 2.88 (dd, 2H, *J* = 7.5, 14.1 Hz), 2.90 (bs, 1H), 2.96 (d, 2H, *J* = 6.8 Hz), 3.00 (dd, 1H, *J* = 4.7, 14.1 Hz), 3.12–3.26 (m, 2H), 3.80–3.91 (m, 2H), 4.99 (bd, 1H, *J* = 8.7 Hz), 5.01 (s, 2H), 7.21–7.32 (m, 10H), 7.92 (d, 2H, *J* = 8.7 Hz), 8.29 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (2*S*,3*S*) form δ = 19.3, 19.9, 35.5, 52.4, 57.7, 66.9, 72.1, 124.3, 126.7, 127.8, 128.2, 128.5, 128.5, 128.6, 129.3, 136.1, 137.2, 144.6, 150.0, 156.5; mp = 79–80 °C; $[a]_D^{25}$ −6.7 (*c* 1.10, CH_3OH); MS (+FAB) *m*/*z* 555.6 (MH^+); HRMS (+FAB) calcd for $C_{28}H_{34}N_3O_7S$ (MH^+), 556.2117, found 556.2086.

4-Nitro-*N*-((2*R*(*syn*),3*S*)-2-hydroxy-4-phenyl-3-((*S*)-tetrahydrofuran-3-yloxycarbonylamino)-butyl)-*N*-isobutylbenzenesulfonamide (11c). A solution of 30% HBr in acetic acid (970 mg, 3.60 mmol) was added dropwise with stirring to a solution of (*R*,*S*)-**11b** (500 mg, 0.90 mmol) in dichloromethane (4 ml) that has been cooled in an ice bath, and the mixture was then stirred for 14 h at 17 °C. After the resulting mixture was neutralized (with cooling in an ice bath) by a 10% Na_2CO_3 aqueous solution, the organic layer was separated and washed with brine to give crude **11a** as a solution. Triphosgene (312 mg, 1.05 mmol) was dissolved with a solution of (*S*)-**3a** (206 mg, 2.34 mmol) in dichloromethane (1.5 ml). To the cooled (−40 °C) solution was added dropwise with stirring over 15 min a solution of pyridine (0.244 ml, 3.16 mmol) in dichloromethane (1.0 ml), and the mixture was then stirred for 3.5 h at ambient temperature to form (*S*)-**3b**. The resulting solution was added dropwise to the solution of **11a** obtained above with cooling in an ice bath. A 15% K_2CO_3 aqueous solution (10 ml) was then added dropwise to the two-layer mixture (pH = 9–10), and the mixture was stirred at 15 °C for 3 days. The organic layer was separated and washed with 10% citric acid aqueous solution, water, and brine, and then concentrated under reduced pressure to give crude (*R*,*S*)-**11c** (480 mg) as a slightly yellowish solid. The crude solid was dissolved in ethanol (45 ml) at 60 °C and recrystallized, filtered, and dried *in vacuo* to give (*R*,*S*)-**11c** (300 mg, 0.56 mmol, (*R*,*S*)/(*S*,*S*) = 100/0, 62.2% yield) as colorless crystals.

^{1}H NMR (300 MHz, $CDCl_3$) (2*R*,3*S*) form δ = 0.87 (d, 3H, *J* = 7.0 Hz), 0.89 (d, 3H, *J* = 7.0 Hz), 1.89 (hep, 1H, *J* = 6.8 Hz), 1.90–1.94 (m, 1H), 2.08–2.15 (m, 1H), 2.86–3.04 (m, 4H), 3.11–3.24 (m, 2H), 3.58 (bs, 6H), 3.65–3.87 (m, 6H), 4.85 (bd, 1H, *J* = 5.2 Hz), 5.10–5.18 (m, 1H), 7.20–7.37 (m, 5H), 7.95 (d, 2H, *J* = 8.9 Hz), 8.34 (d, 2H, *J* = 8.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (2*R*,3*S*) form δ = 19.8, 19.9, 27.0, 32.7, 35.4, 52.7, 55.3, 57.8, 66.8, 72.1, 73.1, 75.6, 124.3, 126.7, 128.5, 128.6, 129.3, 137.2, 144.7, 150.0, 156.2; mp = 161–162 °C; MS (+FAB) *m*/*z* 535.6 (MH^+); HRMS (+FAB) calcd for $C_{25}H_{34}N_3O_8S$ (MH^+), 536.2067, found 536.2078.

Route 2

(2*S*,3*S*)-1-Chloro-2-hydroxy-3-*N*-(benzyloxycarbonylamino)-4-phenylbutane (8b). (*S*)-**7b** (10.0 g, 30.3 mmol) was dissolved with dichloromethane (100 ml) and diluted in methanol (40 ml). To the solution was added sodium borohydride (597 mg, 15.8 mmol), portionwise with stirring at −4 °C. After this addition was complete, the mixture was stirred at 0 °C for an additional 40 min. To the resulting mixture was added 1 M HCl (16.0 ml, 16.0 mmol) in one portion to quench the reaction, and the solution was stirred for 30 min and concentrated under reduced pressure to give a colorless solid. Water (200 ml) and ethyl acetate (200 ml) were added to the residual solid and extracted. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residual solid was dissolved in ethanol (77 ml) at 55 °C and recrystallized, filtered, and dried *in vacuo* to give (*S*,*S*)-**8b** (5.51 g, 16.5 mmol) as colorless crystals. The diastereomer ratio (*S*,*S*)/(*R*,*S*) = 98.1/1.9 was determined by HPLC analysis. The filtrate was concentrated under reduced pressure and dissolved with toluene at 75 °C, recrystallized and dried to give a second crop of crystals (2.31 g, 6.9 mmol, (*S*,*S*)/(*R*,*S*) = 98.6/1.4). The combined yield of crystals from (*S*)-**7b** was 77.2%.

(2*S*,3*S*)-1-Chloro-2-hydroxy-3-*N*-((*S*)-tetrahydrofuran-3-yloxycarbonylamino)-4-phenylbutane (8c). A mixture of (*S*)-**8b** (7.80 g, 23.4 mmol) and 5% palladium on activated carbon (50% wet, 470 mg) in methanol (650 ml) was stirred under a hydrogen atmosphere for 4.5 h at 5 °C. The catalyst was filtered off and the filtrate was concentrated under reduced pressure to give crude **8a** (4.91 g, quantitative) as a colorless solid. The solid (**8a**) was dissolved in dichloromethane (150 ml) and this was mixed with 10% Na_2CO_3 aqueous solution (140 ml). To the mixture cooled at 2 °C with stirring was added dropwise a solution of (3*S*)-chlorocarboxytetrahydrofuran **3b** prepared from (*S*)-**3a** (4.54 g, 51.5 mmol), triphosgene (6.88 g, 23.2 mmol), and pyridine (5.57 ml, 69.5 mmol) in dichloromethane (100 ml) as previously described. The mixture was stirred at ambient temperature for 1 h. Water (100 ml) and dichloromethane (130 ml) were added to the resulting mixture and extracted, and the aqueous layer was then extracted again with dichloromethane (100 ml). The combined organic layers were washed with 10% citric acid aqueous solution (30 ml), water (30 ml), and brine (30 ml), and then dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give crude (*S*,*S*)-**8c** (7.12g, 22.6 mmol) as a colorless solid. All of this material was used in the subsequent transformation without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) (2*S*,3*S*) form δ = 1.90–2.00 (m, 1H), 2.05–2.18 (m, 1H), 2.80 (dd, 1H, *J* = 9.3, 14.0 Hz), 3.01 (dd, 1H, *J* = 4.3, 14.0 Hz), 3.54 (bs, 1H), 3.52–3.66 (m, 2H), 3.67–3.90 (m, 5H), 3.94–4.03 (m, 1H), 5.08–5.16 (m, 1H), 5.64 (bd, 1H, *J* = 9.4 Hz), 7.20–7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) (2*S*,3*S*) δ = 32.4, 35.1, 46.8, 54.2, 66.5, 72.9, 73.0, 74.7, 126.0, 128.0, 129.1, 137.6, 155.5; $[a]_D^{25}$ −17.1 (*c* 1.02, CH_3OH); MS (+FAB) *m*/*z* 314.2 (MH^+); HRMS (+FAB) calcd for $C_{15}H_{21}ClNO_4$ (MH^+), 314.1159, found 314.1169.

(1*S*,1′*S*)-1-(1′-*N*-((*S*)-Tetrahydrofuran-3-yloxycarbonyl-amino)-2′-phenyl)ethyloxirane (9c). (*S*,*S*)-**8c** (7.12g, 22.6 mmol) and anhydrous potassium carbonate (5.02 g, 36.3 mmol) were mixed in methanol (280 ml). The mixture was stirred at ambient temperature for 6 h, and then filtered to remove suspended salts. The filtrate was concentrated under reduced pressure, and then water (100 ml) was added to the concentrate. The mixture was extracted twice with ethyl acetate (120 ml × 2), washed with brine (30 ml), and concentrated under reduced pressure to give crude (*S*,*S*)-**9c** (6.61 g) as a yellowish solid. All of this material was used in the subsequent transformation without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) (1*S*,1′*S*) form δ = 2.72–2.78 (m, 2H), 2.86–2.83 (m, 1H), 2.86–3.02 (m, 2H), 3.70–3.90 (m, 5H), 4.65–4.68 (b, 1H), 5.15–5.21 (m, 1H), 7.20–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) (1*S*,1′*S*) form δ = 32.7, 37.5, 46.7, 53.0, 53.0, 66.9, 73.2, 75.4, 126.9, 128.7, 129.4, 136.3, 155.5; $[a]_D^{25}$ −23.5 (*c* 0.64, CH_3OH); MS (+FAB) *m*/*z* 278.2 (MH^+); HRMS (+FAB) calcd for $C_{15}H_{20}NO_4$ (MH^+), 278.1392, found 278.1365.

(2*R*,3*S*)-3-*N*-((*S*)-Tetrahydrofuran-3-yloxycarbonylamino)-2-hydroxy-1-*N*-(isobutyl)amino-4-phenylbutane (10c). Crude (*S*,*S*)-**9c** (prepared above) and isobutylamine (5.53 ml, 55.6 mmol) were mixed in ethanol (40 ml) and the mixture was refluxed with stirring for 3 h. The resulting mixture was concentrated under reduced pressure to give (*R*,*S*)-**10c** (7.55 g) as an off-white solid. All of this material was used in the subsequent transformation without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) (2*R*,3*S*) form δ = 0.91 (d, 6H, *J* = 6.6 Hz), 1.72 (hep, 1H, *J* = 6.6 Hz), 1.80–1.95 (m, 1H), 2.02–2.14 (m, 1H), 2.37–2.44 (m, 2H), 2.64–2.99 (m, 5H), 3.55–3.86 (m, 5H), 5.11 (b, 1H), 5.43 (bd, 1H, *J* = 8.7 Hz), 7.19–7.28 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) (2*R*,3*S*) form δ = 20.2, 28.2, 32.7, 36.6, 51.4, 55.2, 57.7, 66.8, 70.3, 73.2, 75.0, 126.3, 128.3, 129.3, 137.7, 155.9; MS (+EI) 351.3 (MH^+).

4-Nitro-*N*-((2*R*(*syn*),3*S*)-2-hydroxy-4-phenyl-3-((*S*)-tetrahydrofuran-3-yloxycarbonylamino)-butyl)-*N*-isobutylbenzene-sulfonamide (11c). A solution of (*R*,*S*)-**10c** (prepared above) in dichloromethane (100 ml) and 10% K_2CO_3 (22 ml) were mixed. To the mixture with cooling in an ice bath and stirring was added a solution of 4-nitrobenzenesulfonyl chloride (3.46 g, 18.2 mmol) in dichloromethane (15 ml). After this addition was complete, the mixture was stirred at ambient temperature for an additional 8 h. After water (50 ml) was added to the resulting mixture, the organic layer was separated, washed with 10% citric acid (20 ml), water (20 ml), and brine (20 ml), and then concentrated under reduced pressure. The residue was dissolved in ethanol (400 ml) at 73 °C and recrystallized, filtered, and dried at 45 °C *in vacuo* to give (*R*,*S*)-**11c** (6.72 g, 12.5 mmol, 53.4% from (*S*)-**7b**) as a colorless crystals, which had a diastereomer ratio of (2*R*,3*S*)/(2*S*,3*S*) = 98.4/1.6 as determined by HPLC analysis. It was again recrystallized from ethanol (400 ml, 65 °C) and dried in the same manner to give pure crystals (6.22 g, 11.6 mmol, (2*R*,3*S*)/(2*S*,3*S*) = 99.8/0.2, 49.6% from (*S*)-**7b**).

Route 3

***N*-(*S*)-Tetrahydrofuran-3-yloxycarbonyl-L-phenylalanine methyl ester (4c).** A solution of L-phenylalanine methyl ester hydrochloride (5.82 g, 27.0 mmol) in dichloromethane (15 ml) was added dropwise to a solution of (3*S*)-chlorocarboxy-tetrahydrofuran **3b** prepared from (*S*)-**3a** (2.64 g, 30 mmol), triphosgene (4.02 g, 13.5 mmol), and pyridine (3.12 ml, 40.5 mmol) in dichloromethane (45 ml) as described previously. A Na_2CO_3 aqueous solution (6.36 g, 60 mmol in 60 ml H_2O) was then added dropwise over 15 min to the mixture with cooling in an ice bath and stirring. The mixture was stirred at ambient temperature for 2.5 h. The organic layer was separated, washed with 1 M HCl (20 ml × 2), and H_2O (20 ml), and then concentrated under reduced pressure to give crude (*S*)-**4c** (6.3 g, 21.6 mmol, 80% yield) as a pale yellowish oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.96–2.15 (m, 2H), 3.05 (dd, 1H, *J* = 5.6, 13.9 Hz), 3.13 (dd, 1H, *J* = 6.4, 13.9 Hz), 3.72 (s, 3H), 3.75–3.91 (m, 4H), 4.62 (bq, 1H, *J* = approx. 6Hz), 5.19–5.23 (m, 1H), 5.26 (bq, 1H, *J* = 8.7 Hz), 7.10–7.29 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 32.7, 38.2, 52.3, 54.7, 66.9, 73.2, 75.5, 127.1, 128.6, 129.2, 135.7, 155.3, 172.0; MS (+FAB) 294 (MH^+).

***tert*-Butyl(4*S*)-4-*N*-((*S*)-tetrahydrofuran-3-yloxycarbonyl-amino)-5-phenyl-3-oxo-pentanoate) (5c).** A solution of tert-butyl acetate (9.2 g, 80 mmol) in THF (12 ml) was added dropwise to a solution prepared from LDA (2 M solution in THF/heptane/ethylbenzene, 36.0 ml, 72.0 mmol) and dry THF (80 ml) under an argon atmosphere with cooling to −45 to −50 °C with stirring over 40 min. The mixture was stirred at −45 °C for an additional 30 min then a solution of (*S*)-**4c** (6.24 g, 21.2 mmol) in THF (12 ml) was added dropwise at −40 to −45 °C with stirring for 30 min. After this addition had was complete, the reaction mixture was stirred at −45 °C for an additional 60 min. To the resulting mixture was added in one portion acetic acid (9.2 ml, 160 mmol) to terminate the reaction. Water (80 ml) and toluene (200 ml) were added to the solution and extracted. The organic layer was separated, washed with 5% $NaHCO_3$ aqueous solution (30 ml) and water (30 ml), and then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give crude (*S*)-**5c** (8.72 g, about 90% purity determined by HPLC area%, 20.8 mmol, 98.1% from (*S*)-**4c**) as a yellowish oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.46 (s, 9H), 1.96–2.17 (m, 2H), 2.97 (dd, 1H, *J* = 7.3, 14.2 Hz), 3.17 (dd, 1H, *J* = 6.2, 14.2 Hz), 3.39 (bs, 2H), 3.70–3.90 (m, 4H), 4.66 (bq, 1H, *J* = approx. 6.5 Hz), 5.15–5.23 (m, 1H), 5.34 (bd, 1H, *J* = 7.8 Hz), 7.15–7.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 27.9, 32.7, 37.1, 48.2, 60.6, 66.9, 73.2, 75.6, 82.3, 127.1, 128.7, 129.2, 135.7, 155.4, 165.8, 201.6; MS (+FAB) *m*/*z* 378.2 (MH^+); HRMS (+FAB) calcd for $C_{20}H_{28}NO_6$ (MH^+), 378.1917, found 378.1913.

***tert*-Butyl(4*S*)-4-*N*-((*S*)-tetrahydrofuran-3-yloxycarbonyl-amino)-2-chloro-5-phenyl-3-oxo-pentanoate) (6c).** Sulfuryl chloride (1.87 ml, 23.0 mmol) was added dropwise to a solution of (*S*)-**5c** (7.0 g, purity: 90%, net 16.7 mmol) in dichloromethane (40 ml) with cooling in an ice bath with stirring. The reaction was carried out at ambient temperature for 30 min. The resulting mixture was concentrated at 30 °C under reduced pressure to give crude (*S*)-**6c** as pale yellow crystals. All of this material was used in the subsequent transformation without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.40 (s, 9H), 1.95–2.17 (m, 2H), 2.92–3.02 (m, 1H), 3.17–3.25 (m, 1H), 3.67–3.90 (m, 4H), 4.90 (d, 1H, *J* = 13.5 Hz), 4.98 (bq, 1H, *J* = approx. 6.0 Hz), 5.15–5.19 (m, 1H), 5.27 (bd, 1H, *J* = 8.3 Hz), 7.18–7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 27.7, 32.7, 37.6, 59.1, 60.9, 66.9, 73.0, 75.9, 84.8, 127.3, 128.8, 129.3, 135.3, 155.3, 163.3, 197.4.

(3*S*)-1-Chloro-2-oxo-3-*N*-((*S*)-tetrahydrofuran-3-yloxycarbonylamino)-4-phenylbutane (7c). To the crude crystal obtained above was added formic acid (15 ml), and the suspended mixture was heated at 80 °C for 20 min with stirring. The mixture was then cooled and concentrated under reduced pressure. The residual solid was dissolved in isopropanol (35 ml) with warming at 60 °C, and recrystallized with stirring at ambient temperature for 14 h. Crystals were separated, washed with isopropanol (5 ml), and dried *in vacuo* to give (*S*)-**7c** (3.64 g, 11.7 mmol, 70.0% from (*S*)-**5c**) as colorless crystals.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.93–2.03 (m, 1H), 2.08–2.20 (m, 1H), 3.00 (dd, 1H, *J* = 7.1, 13.8 Hz), 3.10 (dd, 1H,

J = 6.8, 13.8 Hz), 3.75–3.92 (m, 4H), 3.98 (d, 1H, J = 16.2), 4.16 (d, 1H, J = 16.2 Hz), 4.75 (bq, 1H, J = approx. 7.5 Hz), 5.17–5.22 (m, 1H), 5.36 (bq, 1H, J = 7.1 Hz), 7.20–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 32.7, 37.7, 47.3, 58.5, 66.9, 73.1, 75.9, 127.5, 129.0, 129.0, 135.2, 155.4, 201.0; mp = 121–122 °C; $[a]_D^{25}$ −43.5 (c 0.41, CH_3OH); MS (+FAB) m/z 312.2 (MH^+); HRMS (+FAB) calcd for $C_{15}H_{19}ClNO_4$ (MH^+), 312.1003, found 312.1003.

(2*S*,3*S*)-1-Chloro-2-hydroxy-3-*N*-((*S*)-tetrahydrofuran-3-yloxycarbonylamino)-4-phenylbutane (8c). (*S*)-**7c** (0.706 g, 2.26 mmol) was dissolved in dichloromethane (8 ml) and diluted with methanol (8 ml). To this solution with stirring at −2–3 °C was added portionwise over 5 min sodium borohydride (60 mg, 1.6 mmol). After this addition was complete, the mixture was stirred at −3 °C for an additional 60 min. To the resulting mixture was added acetic acid (0.385 ml, 6.72 mmol) in one portion to quench the reaction, and the solution was concentrated under reduced pressure. Water (5 ml) was added to the concentrate and the mixture was extracted twice with dichloromethane (20 ml, 10 ml), and concentrated under reduced pressure to give **8c** as a colorless solid. The diastereomer ((2*R*,3*S*)-form) comprised about 17% of the total yield by HPLC analysis. All of this material was used in the subsequent transformation without further purification.

(1*S*,1′*S*)-1-(1′-*N*-((*S*)-Tetrahydrofuran-3-yloxycarbonylamino)-2′-phenyl)ethyloxirane (9c). To a suspended mixture of the residual solid prepared above in methanol (20 ml) was added anhydrous potassium carbonate (624 mg, 4.52 mmol). The mixture was stirred at ambient temperature for 2 h and then filtered to remove inorganic salts. The filtrate was concentrated at 35 °C under reduced pressure and acidified by addition of 0.5 M HCl (10 ml). The mixture was extracted twice with dichloromethane (10 ml × 2), concentrated at 40 °C under reduced pressure to give **9c** (0.58 g, 2.1 mmol, 92.9% from (*S*)-**7c**, 77.1% as (1*S*,1′*S*) form) as colorless crystals. The (1*R*,1′*S*)-isomer acconted for was about 17% of the total yield. All of this material was used in the subsequent transformation without further purification.

(2*R*,3*S*)-3-*N*-((*S*)-Tetrahydrofuran-3-yloxycarbonylamino)-2-hydroxy-1-*N*-(isobutyl)amino-4-phenylbutane (10c). A suspended solution of **9c** ((1*S*,1′*S*)/(1*R*,1′*S*) = 83/17, 0.58 g, 2.10 mmol, 1.74 mmol as (1*S*,1′*S*) form) in ethanol (4 ml) was added to isobutylamine (3.4 ml, 33.9 mmol) and the mixture was heated at 70 °C with stirring for 60 min. The resulting mixture was concentrated under reduced pressure to give **10c** [(2*R*,3*S*) form/(2*S*,3*S*) form = 83/17] as a colorless solid. All of this material was used in the subsequent transformation without further purification.

4-Nitro-*N*-((2*R*(*syn*),3*S*)-2-hydroxy-4-phenyl-3-((*S*)-tetrahydrofuran-3-yloxycarbonylamino)-butyl)-*N*-isobutylbenzenesulfonamide (11c). A solution of the residual solid prepared above in dichloromethane (8 ml) was added to a solution of $NaHCO_3$ (233 mg, 2.2 mmol) dissolved in water (4 ml). To the mixture with cooling in an ice bath with stirring was added over 2 min a solution of 4-nitrobenzenesulfonyl chloride (488 mg, 2.2 mmol) in dichloromethane (2 ml). After this addition was complete, the mixture was stirred at ambient temperature for an addtional 3 h. The organic layer was separated and concentrated under reduced pressure to give crude **11c** (1107 mg) [(2*R*,3*S*) form/(2*S*,3*S*) form = 83/17] as a colorless solid. It was purified by recrystallization from ethanol (60 ml), dissolved at 70 °C, nuclearized at 55 °C, aged at 5 °C, and separated. The crystal was washed with ethanol (5 ml) and dried *in vacuo* to give (*R*,*S*)-**11c** (771 mg, 1.44 mmol, (2*R*,3*S*)/(2*S*,3*S*) = 98.2/1.8, 89.8% from (*S*,*S*)-**9c** as a desired isomer). It was again recrystallized from ethanol (50 ml) and dried by the same manner to afford (*R*,*S*)-**11c**. (583 mg, 1.09 mmol, (*R*,*S*)/(*S*,*S*) = 100/0, 62.6% from (*S*,*S*)-**9c**).

Acknowledgements

The authors thank Mr Masahiko Kurauchi, Mr Takashi Ineyama, Dr Hiroshi Shiragami, Mr Takahiro Sato, Mr Masakazu Nakazawa, and Dr Tomoyuki Onishi for their assistance during this work. We are also grateful to Ms Naoko Hirose and Ms Izumi Tani for their technical assistance, and to the staff members of the Analytical Department of Ajinomoto Co., Inc. for measuring spectral data.

References

1 For progress in the treatment of HIV with HAART, for example, see: (*a*) T. W. Chun, D. Engel, S. B. Mizell, C. W. Hallahan, M. Fischette, S. Park, R. T. Davey, M. Dybul, J. A. Kovacs, J. A. Metcalf, J. M. Mican, M. Berrey, L. Corey, H. C. Lane and A. S. Fauci, *Nat. Med.*, 1999, **5**, 651–655; (*b*) S. Glushakova, L. Dubrovsky, J.-C. Grivel, O. Haffar and M. Bukrinsky, *Antiviral Res.*, 2000, **47**, 89–95.

2 (*a*) R. D. Tung, M. A. Murcko and G. R. Bhisetti, Vertex Pharmaceuticals Inc., PCT Int. Appl., WO9405639, 1994; (*b*) E. E. Kim, C. T. Baker, M. D. Dwyer, M. A. Murcko, B. G. Rao, R. D. Tung and M. A. Navia, *J. Am. Chem. Soc.*, 1995, **117**, 1181–1182.

3 (*a*) R. D. Tung, M. R. Hale, C. T. Baker, E. S. Furfine, I. Kaldor, W. W. Kazmierski and A. R. Spaltenstein, Vertex Pharmaceuticals, PCT Int. Appl., WO9933815, 1999; (*b*) R. D. Tung, M. R. Hale, C. T. Baker, E. S. Furfine, I. Kaldor, W. W. Kazmierski and A. R. Spaltenstein, Vertex Pharmaceuticals, U.S. Patent 6 559 137, 2003.

4 E. Al-Farhan, D. D. Deininger, S. S. McGhie, J. O'Callaghan, M. S. Robertson, K. Rodgers, S. J. Rout, H. Singh and R. D. Tung, Glaxo Group Ltd., PCT Int. Appl., WO9948885, 1999.

5 (*a*) N. Shibata, T. Katoh and S. Terashima, *Tetrahedron Lett.*, 1997, **38**, 619–620; (*b*) E. J. Corey and F.-Y. Zhang, *Angew. Chem., Int. Ed. Engl.*, 1999, **38**, 1931–1934; (*c*) B. M. Kim, S. J. Bae, S. M. So, H. Y. Yoo, S. K. Chang, J. H. Lee and J. Kang, *Org. Lett.*, 2001, **3**, 2349–2351; (*d*) A. K. Ghosh, J. F. Kincaid, W. Cho, D. E. Walters, K. Krishnan, K. A. Hussain, Y. Koo, H. Cho, C. Rudall, L. Holland and J. Buthod, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 687–690.

6 (*a*) T. Kamijo, T. Yamaguchi, T. Yanagi, I. Tsuchiya and H. Takeuchi, Kissei Pharmaceutical Co., Ltd., Japan Kokai Tokkyo Koho, JP09071584, 1997; (*b*) T. Kamijo, T. Yamaguchi, T. Yanagi, I. Tsuchiya and H. Takeuchi, Kissei Pharmaceutical Co., Ltd., Japan Kokai Tokkyo Koho, JP09124630, 1997.

7 For the preparation of *N*-protected amino epoxide and conversion to HIV protease inhibitors, see: (*a*) P. L. Beaulieu, D. Wernic, J.-S. Duceppe and Y. Guindon, *Tetrahedron Lett.*, 1995, **36**, 3317–3320; (*b*) J. S. Ng, C. A. Przybyla, C. Liu, C. Yen, F. W. Muellner and C. L. Weyker, *Tetrahedron*, 1995, **51**, 6397–6410; (*c*) C. Liu, J . S. Ng, J. R. Behling, C. H. Yen, A. L. Campbell, K. S. Fuzail, F. E. Yonan and D. V. Mehrota, *Org. Proc. Res. Dev.*, 1997, **1**, 45–54.

8 For the preparation of amino epoxide **9b** from chlorohydrin **7b**, see: P. L. Beaulieu and D. Wernic, *J. Org. Chem.*, 1996, **61**, 3635–3645.

9 For synthetic approaches to halomethyl ketones, see: (*a*) D. P. Getman, G. A. DeCrescenzo, R. M. Heintz, K. L. Reed, J. J. Talley, M. L. Bryant, M. Clare, K. A. Houseman, J. Marr, R. A. Mueller, M. L. Vazques, H.-S. Shieh, W. C. Stallings and R. A. Stegeman, *J. Med. Chem.*, 1993, **36**, 288–291; (*b*) P. Raddatz, A. Jonczyk, K.-O. Minck, C. J. Schmitges and J. Sombroek, *J. Med. Chem.*, 1991, **34**, 3267–3280; (*c*) L. E. Fisher and J. M. Muchowski, *Org. Prep. Proc. Int.*, 1990, **22**, 399–484; (*d*) A. Heinsoo, G. Raidaru, K. Linask, J. Jarv, M. Zetterstrom and U. Langel, *Tetrahedron: Asymmetry*, 1995, **6**, 2245–2247; (*e*) B. K. Handa, P. J. Machin, J. A. Martin, S. Redshaw and G. J. Thomas, F. Hoffmann La Roche AG, Eur. Pat. Appl., EP346847, 1989; (*f*) A. Albeck and R. Persky, *Tetrahedron*, 1994, **50**, 6333–6346; (*g*) A. Nishiyama, T. Sugawa, H. Manabe, K. Inoue and N. Yoshida, Kaneka Corp., U.S. Patent 5 929 284, 1999; (*h*) P. Chen, P. T. W. Cheng, S. H. Spergel, R. Zahler, X. Wang, J. Thottathil, J. C. Barrish and R. P. Polniaszek, *Tetrahedron Lett.*, 1997, **38**, 3175–3187; (*i*) J. Barluenga, B. Baragana, A. Alonso and J. M. Concellon, *J. Chem. Soc., Chem. Commun.*, 1994, 969–970.

10 For the chloromethylation of amino acid derivatives recently

reported by our group, see: (*a*) T. Onishi, N. Hirose, T. Nakano, M. Nakazawa and K. Izawa, *Tetrahedron Lett.*, 2001, **42**, 5883–5885; (*b*) T. Onishi, T. Nakano, N. Hirose, M. Nakazawa and K. Izawa, *Tetrahedron Lett.*, 2001, **42**, 6337–6340.

11 Y. Honda, S. Katayama, M. Kojima, T. Suzuki and K. Izawa, *Tetrahedron Lett.*, 2003, **44**, 3163–3166.

12 For the general synthesis of β-ketoesters *via* activation of carbonyl, see: (*a*) R. V. Hoffman and J. Tao, *J. Org. Chem.*, 1997, **62**, 2292–2297; (*b*) R. V. Hoffman and H. Kim, *Tetrahedron Lett.*, 1992, **25**, 3579–3582; (*c*) R. V. Hoffman, W. S. Weiner and N. Maslouh, *J. Org. Chem.*, 2001, **66**, 5790–5795.

13 (*a*) Y. Honda, S. Katayama, M. Kojima, T. Suzuki and K. Izawa, *Org. Lett.*, 2002, **4**, 447–449; (*b*) Y. Honda, S. Katayama, K. Izawa, M. Nakazawa, T. Suzuki and K. Kanno, Ajinomoto Co., Inc., Eur. Pat. Appl., EP0774453, May 21, 1997; (*c*) Y. Honda, S. Katayama, K. Izawa, M. Nakazawa, T. Suzuki and N. Kanno, Ajinomoto Co., Inc., U.S. Patent 5 902 887, May 11, 1999.

14 (*a*) H. C. Brown, J. V. N. Vara Prasad and M. Zaidlewicz, *J. Org. Chem.*, 1988, **53**, 2911–2916; (*b*) A. Schnyder, A. Togni and O. Werbitzky, Lonza A. G., Ger. Offen., DE19807330, 1998.

15 Y. Uozumi and T. Hayashi, *Tetrahedron Lett.*, 1993, **34**, 2335–2338.

16 (*a*) Y. Yuasa and H. Tsuruta, *Liebigs Ann. Chem.*, 1997, 1877–1879; (*b*) K. Kinoshita, T. Moroshima, Y. Yanagida, N. Nagashima, Y. Saka, T. Honda, Y. Fuse and Y. Ueda, Kaneka Corp., PCT Int. Appl., WO0063199, 2000.

17 (*a*) F. Nomoto, N. Shirasaka and K. Otsuka, Nagase and Co., Ltd., Japan Kokai Tokkyo Koho, JP10337197, 1998; (*b*) M. Baumann, B. H. Hauer and U. T. Bornscheuer, *Tetrahedron: Asymmetry*, 2000, **11**, 4781–4790.

18 V. K. Tandon, A. M. van Leusen and H. Wynberg, *J. Org. Chem.*, 1983, **48**, 2767–2769.

19 (*a*) H. Hayashi, K. Nakanishi, C. Brandon and J. Marmur, *J. Am. Chem. Soc.*, 1973, **95**, 8749–8757; (*b*) S. Cicchi, A. Goti and A. Brandi, *J. Org. Chem.*, 1995, **60**, 4743–4748.

20 For a reaction modified from the original method reported in the literature, see: K. Bischofberger and J. R. Bull, *Tetrahedron*, 1985, **41**, 365–374.

21 For derivatization to MTPA ester, see: (*a*) J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543–2549; (*b*) S. Yamaguchi, in *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press, New York, 1983, vol. 1, p. 128.

22 Optical rotation of **3a**: $[\alpha]_D^{20}$ +17.653 (*c* 2.40, CH_3OH, 100 mm), and product by Aldrich (29,668–6): $[\alpha]_D^{20}$ +17.5 (2.4, MeOH)-(specification described in the catalog); $[\alpha]_D^{20}$ +17.638 (2.40, MeOH) (measured).

23 (*a*) A. Albeck and Persky, *Tetrahedron*, 1994, **50**, 6333–6346; (*b*) M.-N. Dufour, P. Jouin, J. Poncet, A. Pantaloni and B. Castro, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1895–1899; (*c*) P. Chen, P. T. W. Cheng, S. H. Spergel, J. C. Barrish, J. K. Thottathil, P. P. Zahler, P. Richard and X. Wang, Bristol-Myers Squibb Co., U.S. Patent 5 481 011, 1996; (*d*) D. P. Rotella, *Tetrahedron Lett.*, 1995, **36**, 5453–5456.

24 For the preparation of chloroformate from alcohol with triphosgene, see: H. Eckert and B. Forster, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 894–895.