Development of a Scalable Chiral Synthesis of MK-3281, an Inhibitor of the Hepatitis C Virus NS5B Polymerase

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Abstract: The development of a scalable chiral synthesis for the HCV NS5B inhibitor MK-3281 is being reported. Several alternative routes were explored and are being described.

Key words: chiral pool, MK-3281, HCV NS5B polymerase inhibitor, medicinal chemistry, heterocycles

About 3% of the world population is chronically infected with hepatitis C virus (HCV). The virus infects the liver and as such is a major cause of acute hepatitis and chronic liver disease, including cirrhosis and liver cancer.[2] The virally encoded nonstructural proteins of the hepatitis C virus are attractive targets for direct antiviral drug therapy.[3] As such, the hepatitis C virus NS5B polymerase is a key enzyme necessary for the replication of the viral genome and has recently been the focus of intense research.[4] During our research in the field we have identified the indole derivative MK-3281 (**1**, Figure 1) as a candidate for preclinical development.[5]

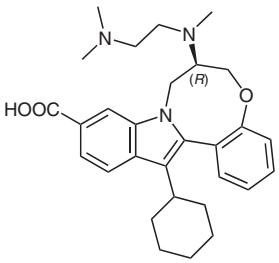

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Figure 1 HCV NS5B polymerase inhibitor MK-3281

To allow for efficacy studies in different animal models of HCV infection, and in particular in HCV-infected chimpanzees, we needed a robust and scalable synthesis of MK-3281 (**1**) which could afford multigram amounts of material. In this letter we describe the evolution of different strategies which led to the successful multigram synthesis of MK-3281.

Our initial route started from phenol **2**[5] and used readily available glycidyl nosylates or tosylates to establish the stereocenter on the benzoxazocine ring. Compound **1** was obtained in nine steps and 7% overall yield (Scheme 1). Three steps in the synthetic sequence proved especially problematic for scale-up. The formation of the benzoxazocine **4** from epoxide **3** was accomplished only in 55% isolated yield even after some optimization (unpublished results). To obtain amine **6**, the alcohol was converted into a tosylate and then reacted with trimethylsilyl azide in the presence of tetrabutylammonium triphenyldifluorosilicate (TBAT) to give azide **5**.[6] Although slow, the azide formation proceeded with good yield and high enantiomeric excess, but a severe loss in yield (<50%) was observed when the reaction was run on a gramscale. Alternative reactions conditions had failed to give good yields and high enantioselectivity.[5] The introduction of the *N*,*N*-dimethylaminoethyl side chain necessitated preformation of the imine, and **7** was isolated in only 46% yield. Furthermore, purification by flash chromatography was required after almost every reaction step, and the final product had to be purified by RP-HPLC and was obtained with an enantiomeric excess in the range of 92–96%.

A clear improvement in the synthetic efficacy was required to rapidly produce multigram amounts of material in high optical purity. In this letter we describe the evolution of different strategies which led to the successful multigram synthesis of MK-3281.

Initially, we explored an 'achiral' route from the ketone **8** (Scheme 2), with final resolution of the enantiomers of **1**, to produce a few grams of material in a relatively short time frame. Alcohol **4** was oxidized to **8** with Dess–Martin periodinane, and the crude material was used directly. Two consecutive reductive aminations were necessary to obtain bisamine **10**, since **7** did not react efficiently with secondary amines. Reduction to the racemic alcohol **4** was always the major product. Both amines **9** and **10** were formed cleanly, and this allowed their purification by simple trituration of their respective hydrochloride salts with diethyl ether. Final hydrolysis of **10** afforded a material which was pure enough to be directly subjected to enantiomeric separation by SFC on a chiral phase. Compound **1** was obtained in 4% overall yield, 99.5% purity and >99% ee starting from phenol **2**. This route allowed for the preparation of 1–2 grams of final compound in a single cycle.

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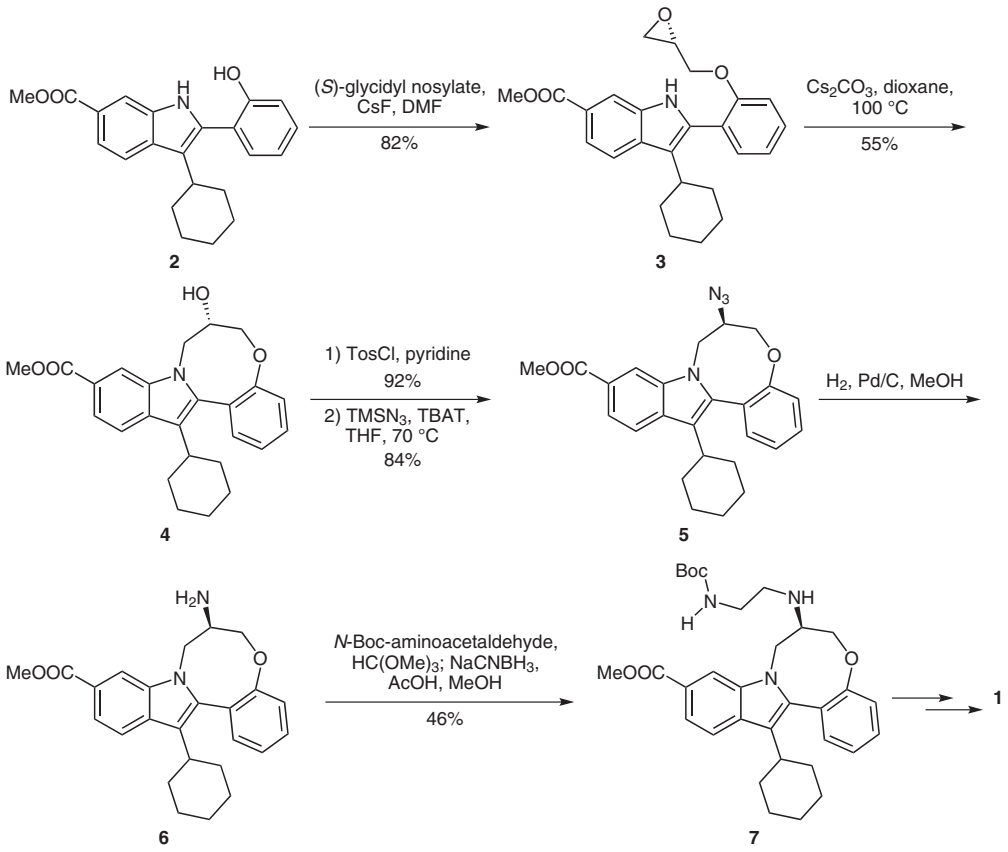
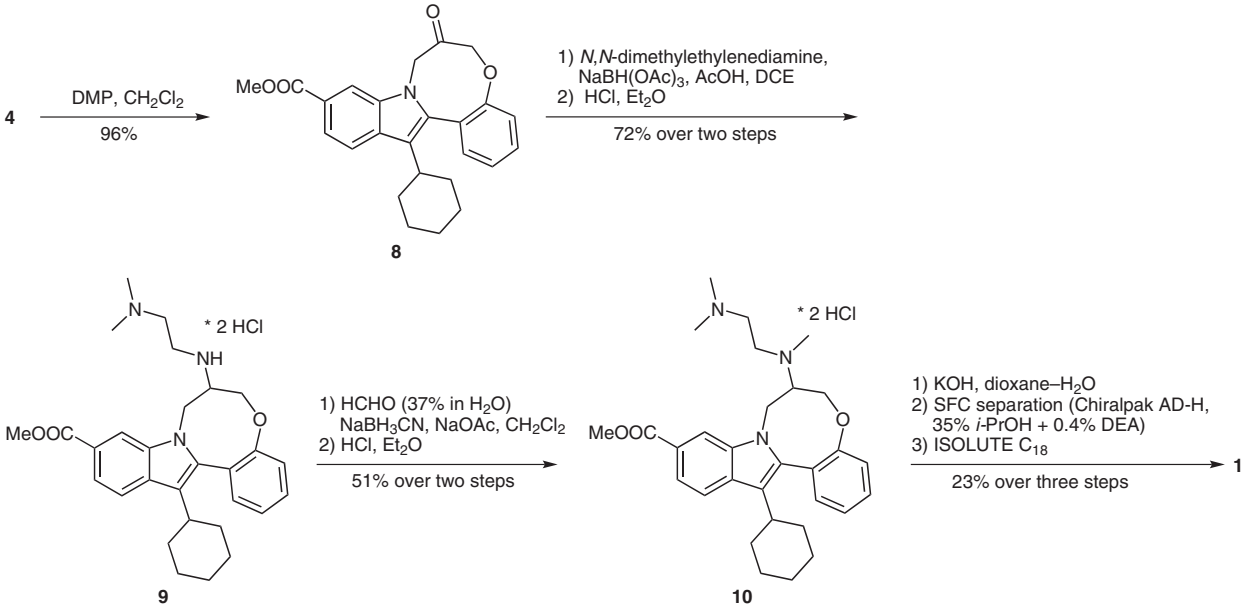


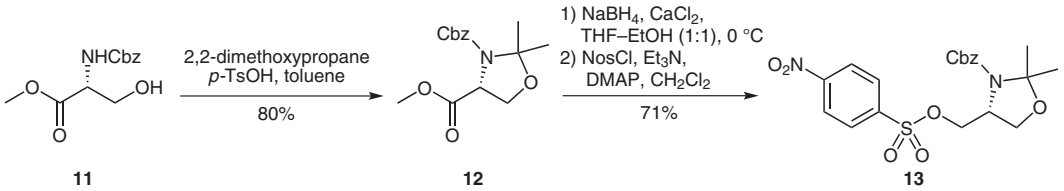
Scheme 1 The oxirane route to MK-3281

This route, although overall not higher yielding, was faster than our initial synthesis, but still not applicable for the preparation of **1** in a scale >10 g. This was partially due to low throughput of the SFC apparatus available. Furthermore, the introduction of the amine side chain looked still cumbersome and proceeded with loss of material. We also had not resolved the low yield in the formation of the medium-sized ring in **4**. Clearly, we also wanted to avoid final separation of the enantiomers and the loss of half of the material.

For our second-generation approach we thought of replacing the epoxide with two chiral nitrogen-containing building blocks, which would already contain the amine in the desired configuration and lead to key intermediate **6** in a more convergent fashion.



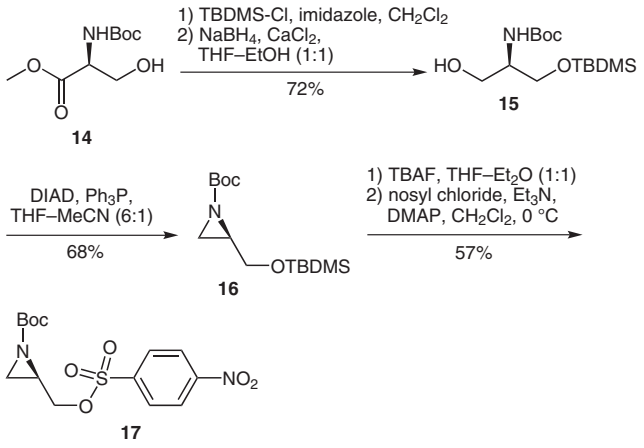
Scheme 2 Achiral synthesis of MK-3281



Scheme 3 Ex-chiral-pool intermediate **13** from D-serine

Oxazolidine nosylate **13** was obtained in three steps starting from commercially available Cbz-protected D-serine methyl ester **11**.[7] The intermediate oxazolidine **12** was reduced to the alcohol with in situ formed calcium borohydride, which was converted into nosylate **13** (Scheme 3).[8,9] The reaction sequence proved to be fairly robust and high yielding (57% over three steps).

The synthesis of aziridine nosylate **17** required five steps starting from Boc-protected L-serine (Scheme 4), which after treatment with TBDMS chloride and ester reduction led to alcohol **15**. The alcohol was then treated under Mitsonobu conditions with diisopropyl azodicarboxylate and triphenylphosphine, which allowed the ring closure to the protected aziridine **16**.[10] Cleavage of the silicon protective group and activation of the alcohol as nosylate gave intermediate **17**. The deprotection–activation sequence needed to be carried out with strict temperature control to avoid opening of the aziridine. Both products **13** and **17** exhibited reasonable storage stability, when kept in a freezer.



Scheme 4 Ex-chiral-pool intermediate **17** from L-serine

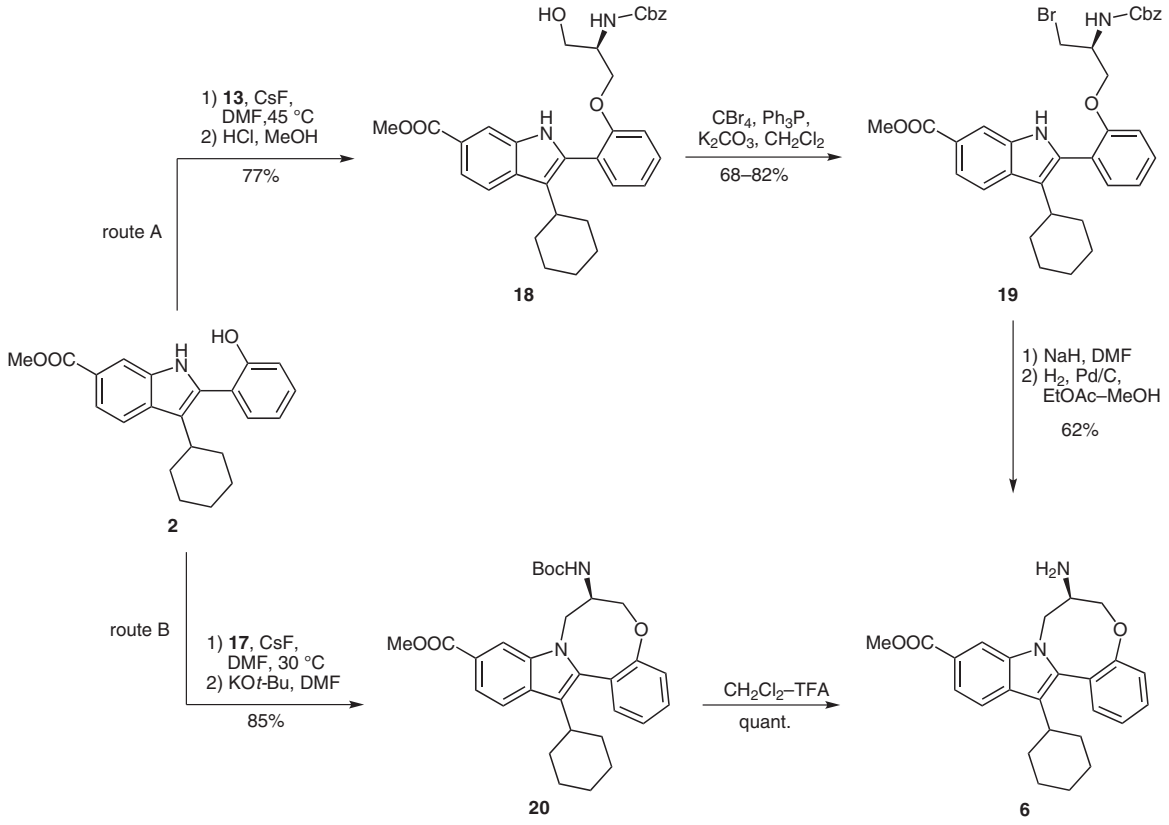
Both chiral building blocks were then employed in the second-generation chiral routes to key intermediate **6**. Phenol **2** was thus reacted with oxazolidine **13** (Scheme 5, route A) in the presence of cesium fluoride as base, and the oxazolidine subsequently opened under acidic conditions to afford alcohol **18**. Activation of **18** for the ring closure using nosyl chloride gave unsatisfactory results due to the extremely sluggish nosylate formation. The transformation into the corresponding iodide (with iodine, imidazole, and triphenylphosphine in toluene–acetonitrile, 74%) or the bromide **19** (under Appel conditions with carbon tetrabromide and triphenylphosphine in dichloromethane) resulted in clean product formation. Since the iodide showed poor shelf stability, we preferred the bromide. Treatment of **19** with sodium hydride in DMF resulted cleanly in formation of the eight-membered ring. After cleavage of the Cbz group amine **6** was obtained in 62% isolated yield. When the aziridine intermediate **17** was employed (Scheme 5, route B), the tetracyclic intermediate **20** was formed smoothly in a one-pot process in high yield from phenol **2**, using CsF in DMF for the alkylation, followed by addition of potassium *tert*-butoxide to the reaction mixture to induce cyclization. Acidic cleavage of the Boc group gave amine **6** in 85% isolated yield. The optical purity of amine **6** was satisfactory for both routes, as evidentiated by the high ee (>99%) obtained for compound **1**.

The use of aziridine **17** was clearly more efficient both in terms of yield (85% vs. 36%), number of steps, and the number of chromatographic purifications required (1 vs. 3) and was therefore judged more amenable to produce large quantities of key intermediate **6**.

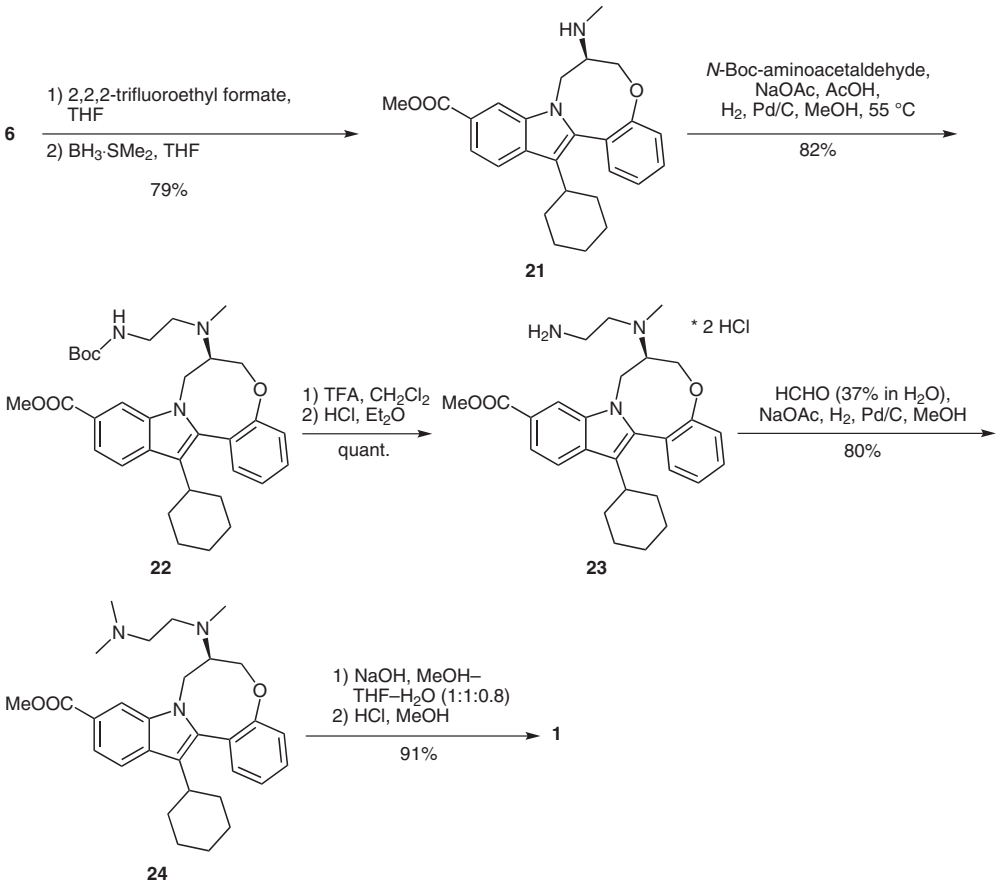
Relying on this methodology, the remaining steps for the synthesis of **1** were accomplished as described in Scheme 6. Amine **6** was formylated with 2,2,2-trifluoroethyl formate[11] and selectively reduced in situ with borane dimethylsulfide complex giving the monomethylated amine **21** in 80% yield as its hydrochloride salt. The use of this methodology avoided impurities such as dimethylation of the amine, which had been observed using aqueous formaldehyde. Reductive amination with *N*-Boc-aminoacetaldehyde was carried out under hydrogenation conditions at elevated temperature, which was superior when compared with classical reductive amination conditions using complex hydrides. Acidic cleavage of the Boc group from **22** delivered **23**, which was purified by crystallization of the hydrochloride salt from diethyl ether. Reductive amination with formaldehyde gave **24**, which was then subjected to basic hydrolysis of the ester. After workup, compound **1**[12] was purified by trituration of the hydrochloride salt with boiling acetonitrile.

The synthesis was concluded in about 40% overall yield starting from phenol **2**. Only four chromatographic steps were required to afford the final product which was obtained in excellent purity (>99.5%) and enantiopurity (ee >99%). A single synthetic run produced 10 g of intermediate **20** whilst final hydrolysis was feasible also on a 20 g scale with normal lab equipment.

In summary, we have accomplished the development of a robust, scalable, and high-yielding route to the hepatitis C virus NS5B-polymerase inhibitor MK-3281. We have been able to improve synthetic efficiency using readily



Scheme 5



Scheme 6

available chiral starting materials. In the course of our studies we have been able to greatly improve the overall yield and to minimize notably the purification effort. The final product was obtained with chemical and optical purity. Our studies were a useful starting point for the development of a process route to the compound, which has been object of a recent publication.[13]

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References and Notes

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(2) (a) Cohen, J. *Science* **1999**, *285*, 26. (b) Lauer, G. M.; Walker, B. D. *N. Engl. J. Med.* **2001**, *345*, 41. (c) WHO Factsheet No. 164: Hepatitis C, accessed 09 May 2007, http://www.who.int/mediacentre/factsheets/fs164/en/print.html. (d) Brown, R. S. *Nature (London)* **2005**, *436*, 97.
(3) (a) Gordon, C. P.; Keller, P. A. *J. Med. Chem.* **2005**, *48*, 1. (b) De Francesco, R.; Migliaccio, G. *Nature (London)* **2005**, *463*, 953. (c) Kwong, A. D.; McNair, L.; Jacobsen, I.; George, S. *Curr. Opin. Pharmacol.* **2008**, *8*, 522.
(4) (a) Beaulieu, P. L. *Expert Opin. Ther. Pat.* **2009**, *19*, 145. (b) Koch, U.; Narjes, F. *Curr. Top. Med. Chem.* **2007**, *7*, 1302.
(5) Narjes, F.; Crescenzi, B.; Ferrara, M.; Habermann, J.; Colarusso, S.; Rico Ferreira, Md. R.; StansfieldI, ; Mackay, A.; Conte, I.; Ercolani, C.; Zaramella, S.; Palumbi, M.-C.; Meuleman, P.; Leroux-Roels, G.; Giuliano, C.; Fiore, F.; Di Marco, S.; Baiocco, P.; Koch, U.; Migliaccio, G.; Altamura, S.; Laufer, R.; De Francesco, R.; Rowley, M. *J. Med. Chem.* **2011**, *54*, 289.
(6) Soli, E. D.; Manoso, A. S.; Patterson, M. C.; DeShong, P.; Favor, D. A.; Hirschmann, R.; Smith, A. B. III. *J. Org. Chem.* **1999**, *64*, 3171.
(7) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.
(8) Narasimhan, S.; Prasad, K. G.; Madhavan, S. *Synth. Commun.* **1995**, *25*, 1689.
(9) Mahler, G.; Serra, G.; Manta, E. *Synth. Commun.* **2005**, *35*, 1481.
(10) (a) Ho, M.; Chung, J. K. K.; Tang, N. *Tetrahedron Lett.* **1993**, *34*, 6513. (b) Travins, J. M.; Etzkorn, F. A. *Tetrahedron Lett.* **1998**, *39*, 9389.
(11) Hill, D. R.; Hsiao, C.-N.; Kurukulasuriya, R.; Wittenberger, S. J. *Org. Lett.* **2002**, *4*, 111.
(12) **Experimental Procedure for the Synthesis of 1**
Preparation of 15
A suspension of $CaCl_2$ (49.9 g, 450 mmol) in dry THF (400 mL) was cooled to 0 °C, and $NaBH_4$ (34.0 g, 900 mmol) was added under stirring. To the resulting suspension, a solution of Boc-Ser(TBDMS)OMe (100 g, 300 mmol) in dry EtOH (400 mL) was added dropwise over the course of 2 h. Stirring was then continued over night. The mixture was poured onto crushed ice (600 g) and a sat. aq NH_4Cl solution (600 mL) was added. This mixture was left stirring until evolution of gas had ceased, then EtOAc was added. The phases were separated, the aqueous phase was treated with 1 N HCl to dissolve all material, then extracted twice with EtOAc. The combined organic phases were extracted with sat. aq $NaHCO_3$ solution and with brine, then dried over Na_2SO_4. After filtration, the volatiles were evaporated in vacuo to leave a colorless oil. The material was supported on silica gel and loaded on top of 1 kg of silica gel on a sintered frit. of CH_2Cl_2 (5 L) was allowed to flow through, then the product was eluted with of EtOAc (5 L). The solvent was evaporated in vacuo leaving **15** as clear oil (66 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.15 (br s, 1 H), 3.89–3.78 (m, 3 H), 3.75–3.63 (m, 2 H), 2.71 (br s, 1 H), 1.47 (s, 9 H), 0.92 (s, 9 H), 0.1 (s, 6 H).
Preparation of 16
A solution of Ph_3P (30.9 g, 118 mmol) in THF–MeCN (9:1, 1160 mL) was treated dropwise over 15 min with DIAD (22.91 mL, 118 mmol) at 0 °C. After 15 min, a solution of **15** (24 g, 79 mmol) in THF (120 mL) was added dropwise over 30 min. A white solid formed upon addition. The ice–water bath was removed and stirring continued overnight at r.t. ^{1}H NMR control showed formation of product and consumption of the starting material after 24 h and represented the most unambiguous way to assess completeness of the reaction. All volatiles were evaporated in vacuo, and the residual material was treated with PE–CH_2Cl_2 (95:5) to precipitate most of the triphenylphosphine oxide. The precipitate was filtered off and washed with small portions of the same solvent mixture until no more desired product was detectable by TLC in the filtrate. The filtrate was evaporated in vacuo leaving ca. 40 g of crude product. Column chromatography on 600 g silica gel (PE–EtOAc = 95:5, 6 L) afforded after evaporation of the eluent 16.05 g (68%) of **16**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.81 (dd, 1 H, *J* = 4.73, 11.39 Hz), 3.63 (dd, 1 H, *J* = 4.87, 11.39 Hz), 2.61–2.54 (m, 1 H), 2.26 (d, 1 H, *J* = 6.08 Hz), 2.07 (d, 1 H, *J* = 3.59 Hz), 1.46 (s, 9 H), 0.92 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H).
Preparation of 17
A solution of **16** (25 g, 87 mmol) in THF (250 mL) and Et_2O (250 mL) was cooled to 0 °C and treated dropwise over 20 min with 1 M TBAF in THF (91 mL, 91 mmol). The resulting solution was stirred at 0 °C for 30 min. The reaction mixture was quenched by the addition of sat. aq $NaHCO_3$ solution (500 ml) and extracted into Et_2O–PE (4:1, 300 mL + 200 mL). The organic layers were collected, washed with brine, dried over Na_2SO_4, and after filtration evaporated in vacuo, keeping the water bath at r.t. The residual oil (ca. 42 g) was dissolved in dry CH_2Cl_2 (500 mL) and Et_3N (15.8 mL, 113 mmol) and cooled to 0 °C. DMAP (1.06 g, 8.7 mmol) was added, followed by 4-nitrobenzenesulfonyl chloride (21.2 g, 96 mmol). The resulting orange heterogeneous mixture was stirred at r.t. overnight. After dilution with CH_2Cl_2 the mixture was washed with sat. aq $NaHCO_3$ solution, H_2O, and brine. After drying over Na_2SO_4, filtration, and evaporation in vacuo a residue was obtained which was purified by chromatography (PE–EtOAc, 8:2, 750 g silica gel) to afford 19.89 g (57%) of **17** as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48–8.44 (m, 2 H), 8.22–8.18 (m, 2 H), 4.37 (dd, 1 H, *J* = 4.20, 11.30 Hz), 3.99 (dd, 1 H, *J* = 7.36, 11.30 Hz), 2.78–2.71 (m, 1 H), 2.30 (d, 1 H, *J* = 6.42 Hz), 2.05 (d, 1 H, *J* = 3.58 Hz), 1.35 (s, 9 H).
Preparation of 20
A solution of **2**[5] (19 g, 54.4 mmol) in DMF (360 mL) was treated with CsF (33.0 g, 218 mmol) in one portion. The resulting fluorescent yellow mixture was stirred 20 min at r.t. then a solution of **17** (24.9 g, 69.6 mmol in 130 mL of DMF) was added dropwise over 30 min. The resulting orange clear solution was stirred at 30 °C overnight. The reaction mixture was cooled to 0 °C, and powdered KO*t*-Bu (8.54 g, 76 mmol) was added slowly to the reaction mixture. After 1.5 h

the reaction was quenched by the addition of sat. aq NH_4Cl solution and the product extracted into EtOAc. The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residual material was purified by chromatography (PE–EtOAc, 80:20, 600–700 g silica gel) affording 23.2 g (85%) of **20**. $C_{30}H_{36}N_2O_5$; MS (ES^+): *m/z* = 527 $[M + Na]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.36 (s, 1 H), 7.93–7.86 (m, 1 H), 7.73–7.62 (m, 1 H), 7.58–7.46 (m, 1 H), 7.35–7.11 (m, 3 H), 4.40–4.25 (m, 2 H), 3.90–3.65 (m, 6 H), 2.75–2.64 (m, 1 H), 2.03–1.28 (m, 20 H).

Preparation of 6

Compound **20** (14 g, 27.7 mmol) was treated with CH_2Cl_2–TFA (220 mL, 9:1) at r.t. for 1 h. The reaction was diluted with CH_2Cl_2, and sat. aq $NaHCO_3$ was slowly added. The mixture was extracted exhaustively with CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4, and filtered. After evaporation in vacuo 11.21 g (quant.) of off-white **6** were obtained which were used without further purification. $C_{25}H_{28}N_2O_3$; MS (ES^+): *m/z* = 405 $[M + H]^+$.

Preparation of 21

A solution of **6** (18.4 g, 45 mmol) in THF (131 mL) was treated dropwise with 2,2,2-trifluoroethyl formate (7 mL, 55 mmol) and stirred overnight at r.t. All volatiles were evaporated in vacuo, and the residual material was dissolved in THF (400 mL). Borane dimethylsulfide complex in THF (114 mL, 228 mmol) was added dropwise. The resulting yellow solution was stirred at r.t. for 20 h. The reaction was quenched by the careful addition of HCl–MeOH (1.25 M, 100 mL), and the resulting solution was heated in an open flask for 2 h to destroy all the boron adducts and remove $B(OMe)_3$. All remaining volatiles were then evaporated in vacuo. The residual material was partitioned between sat. aq $NaHCO_3$ and EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to afford a residue which was purified by chromatography (EtOAc–PE, 8:2 + 1% Et_3N). After evaporation of the eluents in vacuo **21** was obtained as a colorless solid (14.9 g, 79%). $C_{26}H_{30}N_2O_3$; MS (ES^+): *m/z* = 419 $[M + H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.15 (s, 1 H), 7.89 (d, 1 H, *J* = 8.49 Hz), 7.68 (dd, 1 H, *J* = 1.35, 8.49 Hz), 7.55–7.49 (m, 1 H), 7.34–7.24 (m, 3 H), 4.51 (d, 1 H, *J* = 15.23 Hz), 4.27 (dd, 1 H, *J* = 4.33, 12.13 Hz), 3.88 (s, 3 H), 3.73 (dd, 1 H, *J* = 8.42, 12.13 Hz), 3.50 (dd, 1 H, *J* = 10.28, 15.23 Hz), 2.87–2.77 (m, 1 H), 2.74–2.63 (m, 1 H), 2.48 (s, 3 H), 2.14–1.50 (m, 8 H), 1.44–1.10 (m, 3 H).

Preparation of 22

To a solution of Boc-amino acetaldehyde (5.7 g, 35.5 mmol) in dry MeOH (93 mL) was added a mixture of **21** (14.9 g, 35.5 mmol), AcOH (4.1 mL, 71.0 mmol), and NaOAc (2.9 g, 35.5 mmol) in dry MeOH (260 mL), and the mixture was stirred at r.t. for 15 min. Then Pd/C (10 mol%, 5.67 g, 5.34 mmol) was added, the mixture was degassed thoroughly, and H_2 atmosphere was applied. The resulting mixture was stirred under H_2 atmosphere at 63 °C for 5 h, then at 55 °C overnight. The mixture was cooled to r.t., degassed, and flushed with argon. Filtration through Celite with MeOH and EtOAc as solvent afforded after evaporation in vacuo a residue (26.9 g) that was purified by chromatography (PE–EtOAc = 2.5:1 to 1.5:1) to give **22** (16.4 g, 82%). $C_{33}H_{43}N_3O_5$; MS (ES^+): *m/z* = 562 $[M + H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.11 (s, 1 H), 7.90 (d, 1 H, *J* = 8.36 Hz), 7.68 (d, 1 H, *J* = 8.36 Hz), 7.57–7.51 (m, 1 H), 7.34–7.26 (m, 3 H), 6.70–6.63 (m, 1 H), 4.56 (d, 1 H, *J* = 14.78 Hz), 4.26 (dd, 1 H, *J* = 4.86, 12.26 Hz), 3.97 (dd, 1 H, *J* = 9.92, 12.26 Hz), 3.88 (s, 3 H), 3.74–3.62 (m, 1 H), 3.06–2.94 (m, 3 H), 2.75–2.56 (m, 3 H), 2.41 (s, 3 H), 2.01–1.63 (m, 7 H), 1.44–1.32 (m, 3 H), 1.37 (s, 9 H).

Preparation of 23

TFA (120 mL) was added at r.t. to a solution of **22** (16.4 g, 15.3 mmol) in dry CH_2Cl_2 (370 mL), and the mixture was stirred for 1.5 h. Evaporation to dryness gave a residue that was dissolved in CH_2Cl_2 (450 mL), treated with 2 M HCl–Et_2O (65 mL) and evaporated again. This treatment was repeated twice. The residue obtained was dried under high vacuum for 2 h. The light brown powder (**23**, 13.3 g, 87%) was used as such. $C_{28}H_{35}N_3O_2{\cdot}2HCl$; MS ($ES^+$): *m/z* = 462 $[M + H]^+$.

Preparation of 24

NaOAc (6.15 g, 75 mmol) and 37% aq HCHO (4.3 mL, 57.5 mmol) were added to a stirred solution of **29** (13.36 g, 25 mmol) in dry MeOH (200 mL), and the mixture was stirred at r.t. for 10 min. Pd/C (10 mol%, 2.66 g, 2.5 mmol) was added portionwise. The mixture was thoroughly degassed and H_2 atmosphere (balloon) was applied. The reaction was stirred for 20 h at r.t. The catalyst was filtered off over Celite, and the filtrate was concentrated in vacuo. The residual material was dissolved in EtOAc, washed with sat. aq $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo to give 29 g of crude product. Chromatography (silica gel, EtOAc–MeOH–Et_3N = 100:6:2) afforded a main fraction that was triturated with Et_2O–pentane. After filtration a pale yellow solid was obtained which was dried in vacuo to yield pure methyl ester **24** (9.8 g, 80%). $C_{30}H_{39}N_3O_3$; MS (ES^+): *m/z* = 490 $[M + H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.12 (s, 1 H), 7.90 (d, 1 H, *J* = 8.48 Hz), 7.68 (d, 1 H, *J* = 8.48 Hz), 7.58–7.51 (m, 1 H), 7.36–7.26 (m, 3 H), 4.56 (d, 1 H, *J* = 14.96 Hz), 4.29 (dd, 1 H, *J* = 4.91, 12.06 Hz), 4.05–3.96 (m, 1 H), 3.87 (s, 3 H), 3.76–3.67 (m, 1 H), 3.07–2.98 (m, 1 H), 2.81–2.63 (m, 3 H), 2.36 (s, 3 H), 2.38–2.32 (m, 2 H), 2.17 (s, 6 H), 2.04–1.64 (m, 6 H), 1.60–1.12 (m, 4 H).

Preparation of 1

Freshly prepared 1 M aq NaOH (85 mL, 85 mmol) was added dropwise under N_2 atmosphere to a solution of **24** (20.38 g, 41.6 mmol) in THF (100 mL) and MeOH (100 mL), and the mixture was stirred at 60 °C for 4 h. The mixture was concentrated in vacuo to ca. 10% of its volume, then H_2O (200 mL) was added, followed by dropwise addition of 1 N aq HCl (85 mL). The aqueous layer was extracted with *n*-BuOH (1 × 500 mL, then 2 × 250 mL), and the organic layer was washed twice with small amounts of ice-cold water, dried over Na_2SO_4, and concentrated to give a residue which was dissolved in CH_2Cl_2 and filtered. Evaporation to dryness afforded a residue that was taken into MeCN, and 1 N aq HCl (100 mL) was added. The resulting solution was evaporated to dryness, and this operation was repeated twice, using 40 mL of 1 N HCl each time. The material was dried under high vacuum overnight to remove H_2O, then was triturated with hot MeCN, and filtered to give 20.8 g (91%) of **1** (bishydrochloride salt, 20.8 g, >99% ee, 99.2% purity). $C_{29}H_{37}N_3O_3{\cdot}2HCl$. MS ($ES^+$): *m/z* = 476 $[M + H]^+$; $[\alpha]_D^{20}$ +55.5 (*c* 1.0, MeCN:H_2O, 1:1). ^1H NMR (free base, 400 MHz, DMSO-d_6): δ = 8.11 (s, 1 H), 7.86 (d, 1 H, *J* = 8.45 Hz), 7.66 (d, 1 H, *J* = 8.45 Hz), 7.56–7.49 (m, 1 H), 7.34–7.25 (m, 3 H), 4.54 (d, 1 H, *J* = 14.69 Hz), 4.28 (dd, 1 H, *J* = 4.62, 12.27 Hz), 4.00 (dd, 1 H, *J* = 9.65, 12.27 Hz), 3.71 (dd, 1 H, *J* = 10.06, 15.09 Hz), 3.08–2.97 (m, 1 H), 2.81–2.63 (m, 3 H), 2.43–2.37 (m, 2 H), 2.37 (s, 3 H), 2.20 (s, 6 H), 2.04–1.64 (m, 6 H), 1.58–1.09 (m, 5 H). Anal. Calcd for $C_{29}H_{39}Cl_2N_3O_3$: C, 63.50; H, 7.17; N, 7.66. Found: C, 63.04; H, 6.89; N, 7.24.

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