Synthetic Studies toward Ecteinascidin 743 (Trabectedin)

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Abstract: An alternative synthetic route to an intermediate in the synthesis of ecteinascidin 743 has been established by using a Pictet–Spengler reaction and a Friedel–Crafts type reaction.

Key words: alkaloids, anticancer drugs, Pictet–Spengler reaction, Friedel–Crafts reaction, total synthesis

Tetrahydroisoquinoline alkaloids show a broad range of biological properties, including antitumor and antimicrobial activities.[2] Ecteinascidin 743 (Et 743, **1**; Figure 1, also known as trabectedin or Yondelis®), isolated from the Caribbean tunicate *Ecteinascidia turbinate*,[3] has been shown to display highly potent cytotoxicity against a variety of tumor cell lines at very low concentrations. Because of the unique mechanism of action against the tumor cell lines,[4] Et 743 was considered as a potential anticancer drug. Extensive clinical trials resulted in the approval of Et 743 in 2007 for the treatment of advanced soft tissue sarcoma and, in 2009, for relapsed platinum-sensitive ovarian cancer in combination with liposomal doxorubicin. Et 743 is currently in clinical trials for the treatment of breast, lung, pancreas, and prostate cancers.[5]

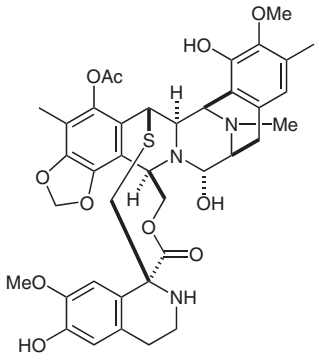

Figure 1 Structure of ecteinascidin 743 (**1**; trabectedin)

The structural complexity and the limited availability of Et 743 from nature have made it a very attractive synthetic target. The first total synthesis of Et 743 was accomplished in 1996 by Corey and co-workers.[6] Since then, total syntheses have been reported from our own laboratories[7] and also by Zhu and co-workers.[8] Three formal total syntheses were reported by Williams,[9] Danishefsky,[10] and Takemoto[11] along with synthetic approaches by several other research groups.[12] Despite considerable effort toward the total synthesis of Et 743, its clinical supply relies solely on a long semisynthetic route from cyanosafracin B, produced by bacterial fermentation.[13] A practical and scalable synthesis of Et 743 is therefore eagerly sought.

Our previous synthesis of Et 743, featuring the Ugi four-component condensation reaction, allowed easy access to the diketopiperazine through an intramolecular Heck reaction for the construction of the bicyclo [3.3.1] skeleton. Phenol-aldehyde cyclization was employed to construct the B ring, followed by the acid-induced ten-membered sulfide formation (Scheme 1).[7b] Herein, we disclose another synthetic approach to the key intermediate **7** via a Pictet–Spengler reaction and a Friedel–Crafts type reaction of an iminolactone.

In our previous total synthesis, amine **2** was prepared by the addition of phenol **10** to iminolactone **11** (Scheme 2). Transformation of the resulting adduct **12** into amine **2**, however, required a rather tedious cleavage of the chiral auxiliary, which was clearly problematic from a synthetic perspective. As illustrated in Scheme 3, we envisioned that the intermediate **7** could be constructed by incorporating the chiral auxiliary moiety in a synthetic intermediate itself. In a retrosynthetic sense, cleavage of the oxazolidine ring in **7** and manipulation of the diols at C4 and C22 would lead to lactone **14**. The addition of an aryl group to iminolactone **15** would occur from the less hindered face, giving the desired *trans* product. The iminolactone **15** could be derived from aminoalcohol **16**, which, in turn, could be prepared via a Pictet–Spengler reaction between aldehyde **17** and amine **18**.

Our synthesis commenced with the preparation of the amine unit **18** (Scheme 4). After benzylation of the known aldehyde **19**,[14] a Horner–Wadsworth–Emmons reaction of **20** was conducted with phosphonate **21**[15] using *N*,*N*,*N*′,*N*′-tetramethylguanidine as a base to give dehydrophenylalanine **22** stereoselectively. Asymmetric hydrogenation of **22** through the use of {Rh[(cod)-(*S*,*S*)-Et-DuPHOS]OTf}[16] under a hydrogen atmosphere (500 psi) at 50 °C proceeded uneventfully to give aminoester **23** in 85% yield with 95% enantiomeric excess. After switching the Boc group to a Cbz group,[17] the methyl ester was converted into Weinreb amide **24** via a two-step sequence involving basic hydrolysis followed by condensation of the resulting carboxylic acid with *N*,*O*-dimethylhydroxyl-

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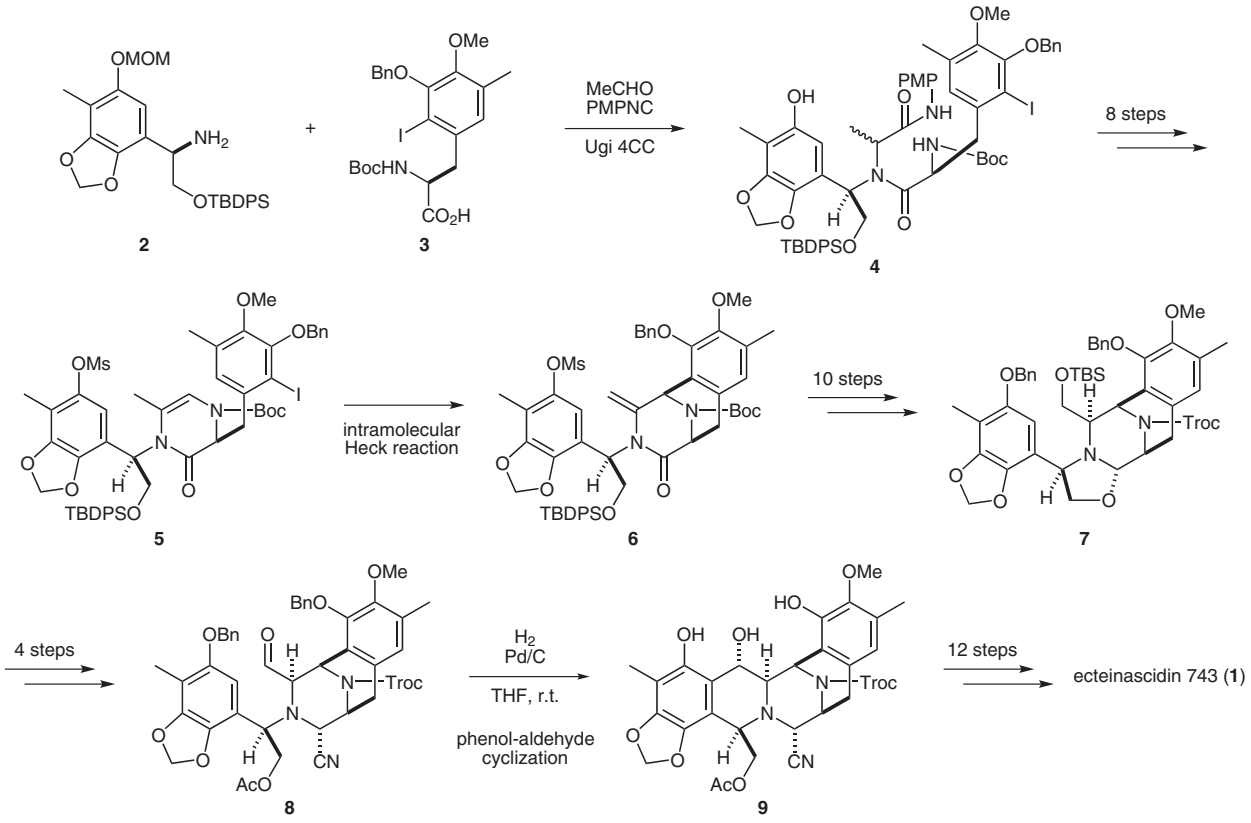
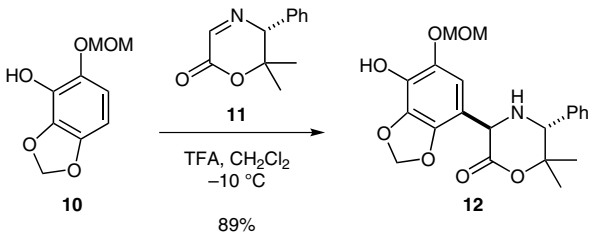


Scheme 1



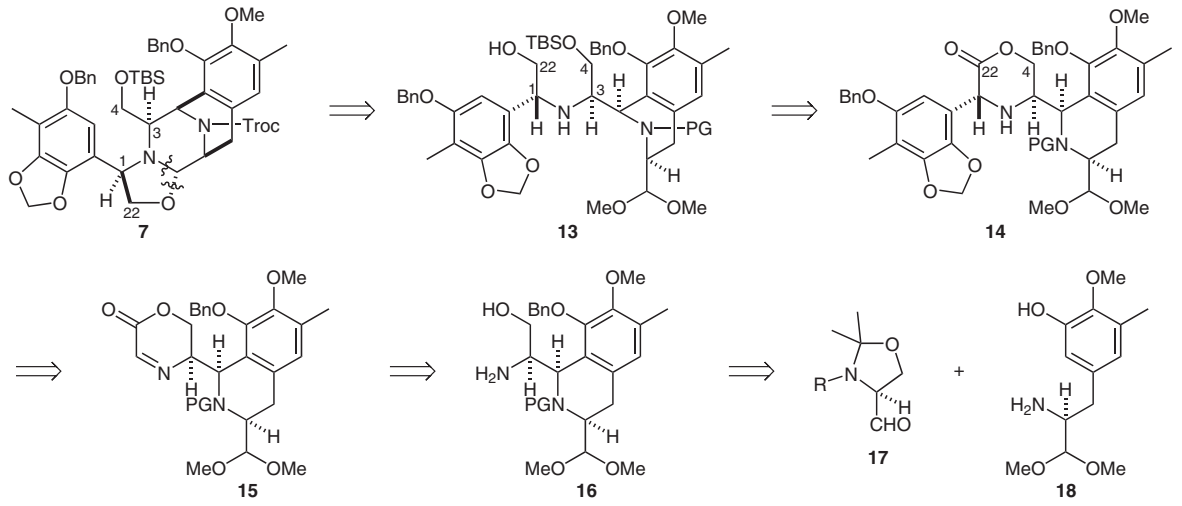
Scheme 2

amine. Reduction of **24** with diisobutylaluminum hydride (DIBAL-H) gave an aldehyde, which was protected as its dimethyl acetal. Subsequent hydrogenolysis of the Cbz and benzyl groups afforded **18**.

The aldehyde unit was prepared in the following manner (Scheme 5). A *p*-nosyl group was introduced to the amino group of L-serine methyl ester (**25**). After formation of the acetonide, the methyl ester moiety was reduced with DIBAL-H to afford **27** in good yield.[18]

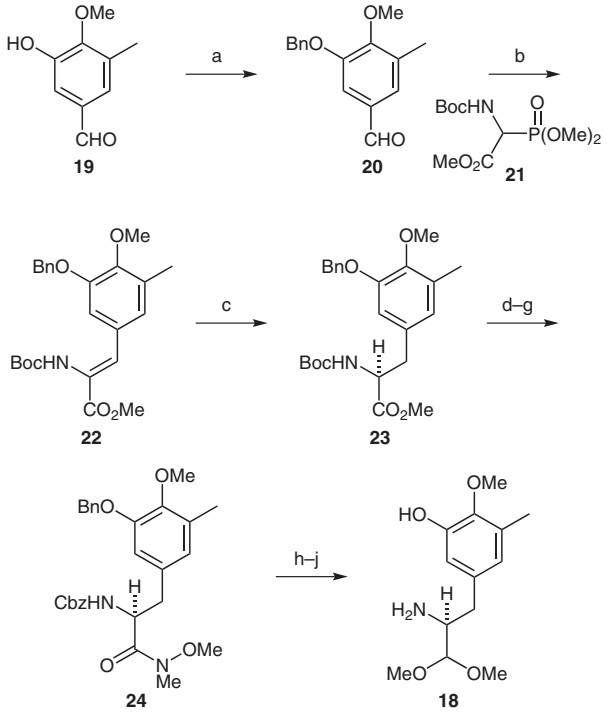
With the amine unit **18** and the aldehyde unit **27** in hand, we next attempted the crucial Pictet–Spengler reaction (Scheme 6). After extensive optimization, we found that the reaction proceeded in dichloromethane by mixing **18** and **27** in the presence of formic acid and sodium sulfate at ambient temperature, thereby providing the desired tetrahydroisoquinoline **28** as a single diastereomer. The regio- and stereoselectivity of the reaction was secured by a NOESY experiment as shown in Scheme 6, which showed that the reaction proceeded with complete *cis*-selectivity. Selective benzylation of the phenol in **28** and protection of the secondary amine moiety as its 2-chloroethyl carbamate furnished **29**. Treatment of **29** with 2-mercaptoethanol and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) caused concomitant cleavage of the *p*-nosyl group and the acetonide to give 1,2-aminoalcohol **30** in 84% yield.

We next focused on introducing the A ring unit via a Friedel–Crafts type arylation of an iminolactone (Scheme 7).[19] Aminoalcohol **30** was treated with phenyl bromoacetate (**31**) according to Harwood's procedure[20] to furnish morpholinone **32**, which was oxidized with *N*-bromosuccinimide (NBS) to give iminolactone **33** in good yield. Addition of phenol **34** to **33** proceeded smoothly in the presence of a large excess of trifluoroacetic acid (TFA) at 0 °C, yielding **35** as a single product. The reaction occurred from the less hindered face of the iminolactone to produce the desired isomer. The product **35** was then converted into the intermediate of our previous synthetic route. Thus, conversion of the phenol into the corresponding triflate, followed by methanolysis, afforded a hydroxyester, which was protected with a TBS group to give **36** in good yield. The ester moiety in **36** was reduced to give alcohol **37**.[21] Upon treatment with $BF_3 \cdot OEt_2$, **37** underwent cleavage of the dimethyl acetal moiety, which induced formation of a bicyclo [3.3.1] skeleton and an oxazolidine ring to furnish **38** in 73% yield. This result confirmed that the crucial Pictet–Spengler reaction pro-

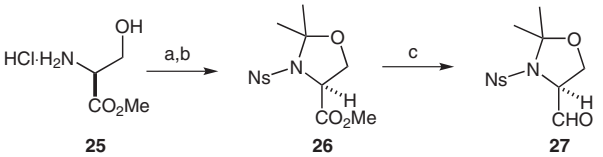


Scheme 3

ceeded with *cis*-selectivity. At this stage,[22] a Pd-catalyzed cross coupling between **38** and MeZnCl[23] was performed to give **39** in 76% yield. Finally, the protective group on the secondary amine was converted into a 2,2,2-trichloroethoxycarbonyl (Troc) group in three steps to afford the desired synthetic intermediate **7**, the spectral data of which were consistent with those reported previously.



Scheme 4 *Reagents and conditions*: (a) BnBr, K_2CO_3, acetone, r.t., 90%; (b) phosphonate **21**, *N*,*N*,*N*′,*N*′-tetramethylguanidine, r.t., 89%; (c) H_2 (500 psi), {Rh[(cod)-(*S*,*S*)-Et-DuPHOS]OTf} (1.5 mol%), EtOAc, 50 °C, 85%; (d) AcCl, MeOH, 0 °C to r.t.; (e) CbzCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 75% (2 steps); (f) LiOH, H_2O, 0 °C to r.t.; (g) MeNHOMe·HCl, EDCI·HCl, HOBt, Et_3N, 0 °C to r.t., 80% (2 steps); (h) DIBAL-H, –78 °C; (i) $HC(OMe)_3$, TsOH, MeOH, r.t.; (j) 10% Pd/C, MeOH, 62% (3 steps).



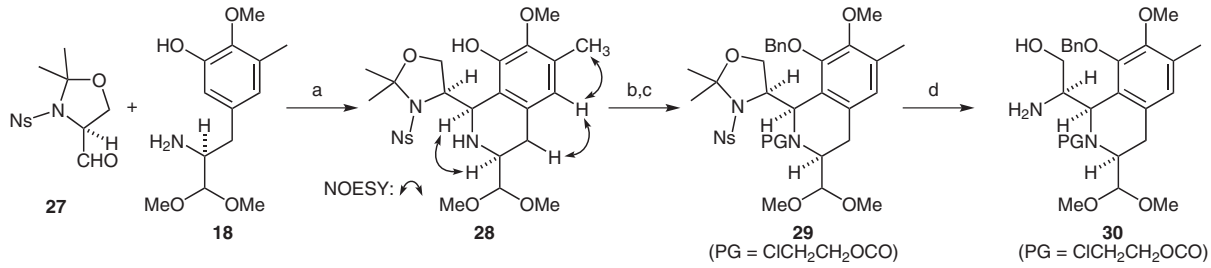
Scheme 5 *Reagents and conditions*: (a) *p*-NsCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 92%; (b) 2,2-dimethoxypropane, TsOH, benzene, reflux, 98%; (c) DIBAL-H, –78 °C, toluene, quant.

In summary, an alternative synthetic route to the late-stage intermediate in our previous synthesis of ecteinascidin 743 has been developed. The approach features a Pictet–Spengler reaction and a Friedel–Crafts type reaction as key steps. Further investigations to establish a truly practical synthesis of ecteinascidin 743 are underway in our laboratories.

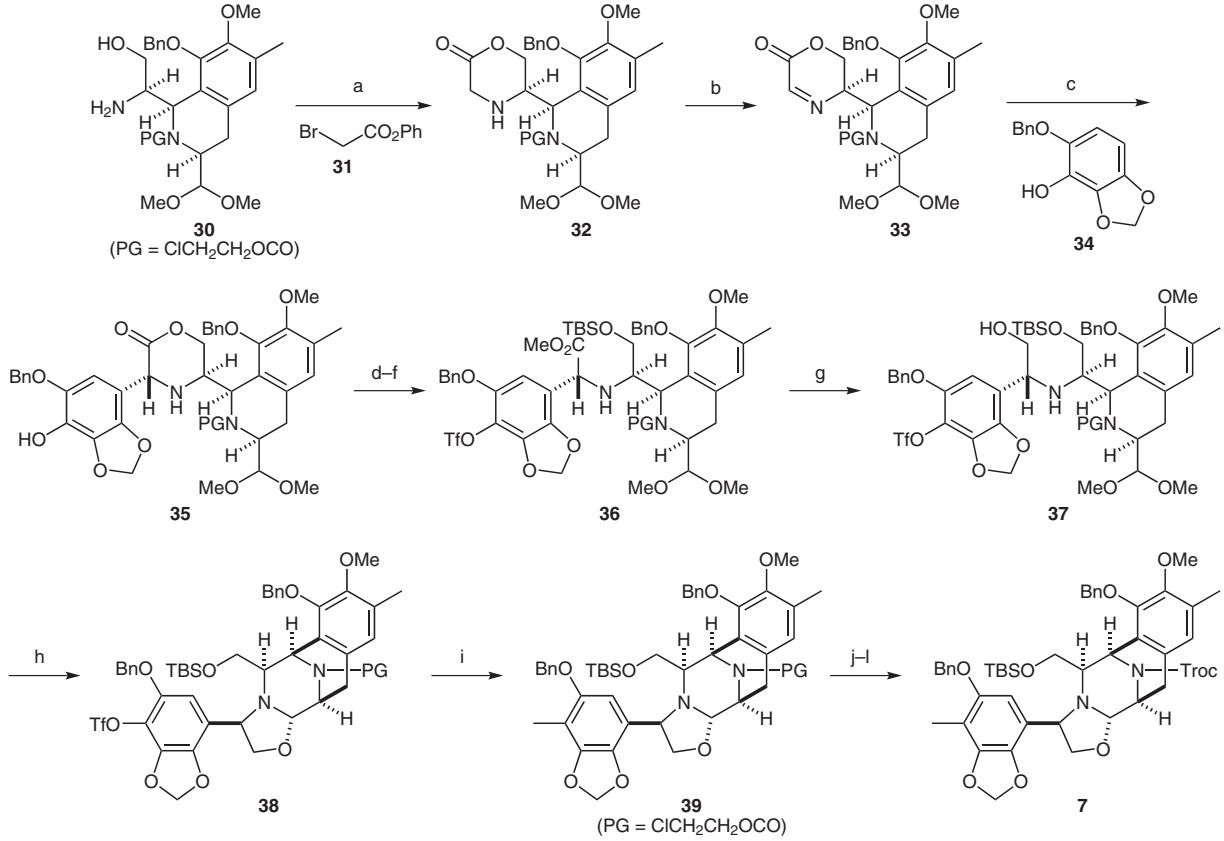
All non-aqueous reactions were carried out in oven-dried glass tubes under a slightly positive pressure of argon unless otherwise noted. Dehydrated CH_2Cl_2, toluene, THF, Et_2O, MeCN, DMF, MeOH, and EtOH were purchased from Kanto Chemical Co., Inc. and stored over 3 Å or 4 Å molecular sieves. Pyridine, Et_3N and *N*,*N*-diisopropylethylamine (DIPEA) were dried over KOH. All other reagents were commercially available and used without further purification. Preparative flash chromatography was performed using Silica Gel 60 (spherical, 40–100 μm) purchased from Kanto Chemical Co., Inc. ^1H and ^{13}C NMR spectra were recorded with JEOL LA-MHz and ECS-400 spectrometers. IR spectra were recorded with a JASCO FT/IR-5300 Fourier Transform Infrared Spectrophotometer. Mass spectra (MS) were obtained with an Agilent 6530 Q-TOF/MS (HRMS), Shimazu QP2010 (GC-MS) instrument. Optical rotations were measured with a JASCO DIP-370 instrument. Melting points were measured with an Ishii melting points apparatus.

(*S*)-Methyl 2,2-Dimethyl-3-[(4-nitrophenyl)sulfonyl]oxazolidine-4-carboxylate (26)

To a mixture of L-serine methyl ester (**25**; 15.3 g, 98.3 mmol) and Et_3N (34.3 mL, 246 mmol, 2.50 equiv) in CH_2Cl_2 (300 mL) was added *p*-nitrobenzenesulfonyl chloride (24.0 g, 108 mmol, 1.10 equiv) portionwise at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred for 16.5 h. The mixture was diluted with EtOAc (300 mL) and poured into ice-cooled sat. aq $NaHCO_3$



Scheme 6 *Reagents and conditions*: (a) HCO_2H, Na_2SO_4, CH_2Cl_2, 83%; (b) BnBr, K_2CO_3, acetone, 99%; (c) 2-chloroethyl chloroformate, pyridine, CH_2Cl_2, 0 °C to r.t., 90%; (d) 2-mercaptoethanol, DBU, MeCN, 0 °C to r.t., 84%.



Scheme 7 *Reagents and conditions*: (a) phenyl bromoacetate (**31**), *i*-Pr_2NEt, MeCN, 0 °C to r.t., 90%; (b) NBS, Et_3N, CH_2Cl_2, 0 °C to r.t., 89%; (c) phenol **34**, TFA, CH_2Cl_2, 0 °C, 81%; (d) Tf_2O, pyridine, CH_2Cl_2, 0 °C, 80%; (e) Et_3N, MeOH; (f) TBSCl, imidazole, DMF, 0 °C to r.t., 90% (2 steps); (g) $NaBH_4$, LiCl, THF–EtOH, 89%; (h) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 73%; (i) MeZnCl, [$PdCl_2$(dppf)], THF, reflux, 76%; (j) NaI, DMF, 110 °C, 96%; (k) Zn, AcOH, THF, r.t.; (l) TrocCl, pyridine, CH_2Cl_2, 44% (2 steps).

(100 mL). The resulting mixture was extracted with EtOAc (3 × 20 mL), and the combined organic phase was sequentially washed with brine (50 mL), 1 M aq HCl (50 mL), brine (50 mL), sat. aq $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting solid was washed with ice-cooled EtOAc (5 mL) to afford a *p*-nitrobenzenesulfonamide.

Yield: 27.4 g (90.0 mmol, 92%); white solid; mp 160–162 °C (dec.); $[\alpha]_D^{25}$ –2.5 (*c* 0.59, MeOH).

IR (neat film): 2361, 2341, 1743, 1606, 1529, 1440, 1350, 1311, 1222, 1167, 1126, 1093, 854, 769, 738 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 8.36 (d, *J* = 8.7 Hz, 2 H), 8.07 (d, *J* = 8.7 Hz, 2 H), 4.08 (dd, *J* = 5.0 Hz, 1 H), 3.77 (dd, *J* = 11.0, 5.0 Hz, 1 H), 3.68 (dd, *J* = 11.0, 5.0 Hz, 1 H), 3.48 (s, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 171.2, 151.1, 147.9, 129.3, 124.9, 63.9, 59.5, 52.6.

HRMS (ESI): *m*/*z* $[M - H]^+$ calcd for $C_{10}H_{11}N_2O_7S$: 303.0287; found: 303.0295.

To a solution of the above *p*-nitrobenzenesulfonamide (1.11 g, 3.65 mmol) in benzene (15 mL) were added 2,2-dimethoxypropane (2.3 mL, 19 mmol, 5.0 equiv) and *p*-TsOH·H_2O (36 mg, 0.19 mmol, 5.0 mol%). The reaction mixture was heated to reflux for 2.5 h. After cooling, the mixture was diluted with EtOAc (15 mL), and quenched with sat. aq $NaHCO_3$ (15 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc–*n*-hexane, 33%) to afford **26**.

Yield: 1.23 g (3.57 mmol, 98%); orange solid; mp 75–77 °C; $[\alpha]_D^{25}$ –51 (*c* 0.56, $CHCl_3$).

IR (neat film): 2361, 2341, 1755, 1531, 1352, 1309, 1259, 1205, 1165, 1101, 1035, 856, 771, 738 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.35 (d, *J* = 9.0 Hz, 2 H), 8.09 (d, *J* = 9.0 Hz, 2 H), 4.52 (dd, *J* = 6.8, 2.7 Hz, 1 H), 4.21 (dd, *J* = 9.6, 6.8 Hz, 1 H), 4.12 (dd, *J* = 9.6, 2.7 Hz, 1 H), 3.64 (s, 3 H), 1.70 (s, 3 H), 1.62 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 149.8, 146.1, 128.7, 123.9, 99.3, 67.2, 60.2, 52.8, 27.3, 26.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{17}N_2O_7S$: 345.0756; found: 345.0760.

(*S*)-2,2-Dimethyl-3-[(4-nitrophenyl)sulfonyl]oxazolidine-4-carbaldehyde (27)

To a stirred solution of **26** (1.23 g, 3.57 mmol) in toluene (40 mL) was added DIBAL-H (0.99 M in toluene, 5.5 mL, 5.5 mmol, 1.5 equiv) dropwise over 55 min at –78 °C under argon. After stirring at –78 °C for 35 min, MeOH (4 mL) and 30% aq Rochelle's salt (10 mL) were added to the mixture. The mixture was then diluted with EtOAc (10 mL), and stirred at r.t. for 1 h. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc–*n*-hexane, 33%) to afford **27**.

Yield: 1.16 g (3.69 mmol, quant); orange solid; mp 77–78 °C; $[\alpha]_D^{22}$ –85 (*c* 0.21, $CHCl_3$).

IR (neat film): 3107, 2989, 2939, 2866, 2363, 1736, 1606, 1531, 1479, 1402, 1352, 1311, 1228, 1209, 1165, 1099, 1035, 1010, 920, 856, 831, 738, 686 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.59 (d, *J* = 2.7 Hz, 1 H), 8.39 (ddd, *J* = 8.5, 2.4, 2.4 Hz, 2 H), 8.06 (ddd, *J* = 8.5, 2.4, 2.4 Hz, 2 H), 4.13–4.18 (m, 2 H), 4.05–4.09 (m, 1 H), 1.74 (s, 3 H), 1.55 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.2, 150.0, 145.5, 128.6, 124.3, 99.3, 65.6, 64.4, 28.5, 25.1.

GC-MS (SCI): *m*/*z* = 315 $[M + H]^+$.

3-(Benzyloxy)-4-methoxy-5-methylbenzaldehyde (20)

To a solution of **19** (3.24 g, 19.5 mmol) in acetone (50 mL) were added benzyl bromide (12 mL, 100 mmol, 5.0 equiv) and K_2CO_3 (13.5 g, 97.7 mmol, 5.00 equiv) at r.t., and the mixture was stirred at r.t. for 2 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc–*n*-hexane, 10→30%) to afford **20**.

Yield: 4.51 g (17.6 mmol, 90%); colorless oil.

IR (neat film): 2935, 2829, 2735, 2361, 2341, 1689, 1583, 1489, 1437, 1381, 1329, 1294, 1234, 1138, 1086, 1003, 854, 736, 696, 669 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.83 (s, 1 H), 7.32–7.47 (m, 7 H), 5.15 (s, 2 H), 3.92 (s, 3 H), 2.33 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.0, 153.0, 151.9, 136.2, 132.4, 131.7, 128.4, 127.9, 127.2, 127.1, 110.4, 70.7, 60.4, 16.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{17}O_3$: 257.1178; found: 257.1176.

(*Z*)-Methyl 3-[3-(Benzyloxy)-4-methoxy-5-methylphenyl]-2-[(*tert*-butoxycarbonyl)amino]acrylate (22)

To a mixture of **20** (4.51 g, 17.6 mmol) and phosphonate **21** (8.0 g, 27 mmol, 1.5 equiv) in CH_2Cl_2 (100 mL) was added *N*,*N*,*N*′,*N*′-tetramethylguanidine (3.3 mL, 26 mmol, 1.5 equiv) at r.t., and the mixture was stirred at r.t. for 2 d. The reaction mixture was quenched with 15% aq citric acid (30 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phase was washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc–*n*-hexane, 10→30%) to afford **22**.

Yield: 6.69 g (15.6 mmol, 89%); yellow solid; mp 95–97 °C.

IR (neat film): 3315, 3065, 2978, 2949, 2361, 2339, 1718, 1639, 1579, 1494, 1454, 1435, 1367, 1334, 1292, 1251, 1159, 1132, 1089, 1051, 1028, 1006, 912, 844, 773, 736, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.46 (m, 4 H), 7.18 (br, 1 H), 7.09 and 7.10 (s, 1 H), 6.99 and 7.00 (s, 1 H), 6.11 (br, 1 H), 5.08 (s, 2 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 2.25 (s, 3 H), 1.42 (br, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 152.7, 151.2, 148.6, 136.6, 131.8, 130.7, 129.1, 128.4, 127.8, 127.1, 125.5, 123.2, 113.1, 80.8, 70.6, 60.2, 52.5, 28.2, 16.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{29}NO_6Na$: 450.1893; found: 450.1890.

(*S*)-Methyl 3-[3-(Benzyloxy)-4-methoxy-5-methylphenyl]-2-[(*tert*-butoxycarbonyl)amino]propanoate (23)

A degassed solution of **22** (13.7 g, 31.9 mmol) and {Rh[(cod)-(*S*,*S*)-Et-DuPHOS]OTf} (346 mg, 0.479 mmol, 1.50 mol%) in EtOAc (130 mL) was placed in a high-pressure Parr reactor, which was sealed under hydrogen (500 psi). After stirring at 50 °C for 3 d, the solution was concentrated under reduced pressure, and the residue was purified by flash column chromatography (EtOAc–CH_2Cl_2, 5%) to afford **23**. The enantiomeric excess of the product was determined after conversion of the Boc group into a Cbz group.

Yield: 12.5 g (29.1 mmol, 91%); pale-yellow foam; $[\alpha]_D^{25}$ 27 (*c* 0.31, $CHCl_3$).

IR (neat film): 3362, 2976, 2930, 2361, 2341, 1745, 1714, 1589, 1498, 1437, 1390, 1365, 1284, 1230, 1167, 1076, 1012, 844, 738, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.45 (m, 5 H), 6.57 and 6.57 (s, 1 H), 6.54 (s, 1 H), 5.06 (s, 2 H), 4.95 and 5.04 (d, *J* = 7.3 Hz, 1 H), 4.51–4.56 (m, 1 H), 3.81 and 3.82 (s, 3 H), 3.67 (s, 3 H), 2.91–3.02 (m, 2 H), 2.23 and 2.24 (s, 3 H), 1.43 (br, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 154.8, 151.4, 146.6, 136.9, 131.8, 131.1, 128.4, 127.7, 127.1, 124.0, 112.8, 79.9, 70.7, 60.2, 54.4, 52.2, 38.0, 28.4, 16.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{31}NO_6Na$: 452.2049; found: 452.2058.

(*S*)-Benzyl {3-[3-(Benzyloxy)-4-methoxy-5-methylphenyl]-1-[methoxy(methyl)amino]-1-oxopropan-2-yl}carbamate (24)

To a solution of **23** (12.5 g, 29.1 mmol) in a mixture of MeOH (25 mL) and CH_2Cl_2 (12 mL) at 0 °C, was added a solution of ice-cooled HCl in MeOH [prepared by mixing AcCl (21.0 mL, 295 mmol, 10.0 equiv) with MeOH (29 mL) at 0 °C], and the mixture was allowed to warm to r.t. After stirring for 1.5 h, the reaction mixture was concentrated under reduced pressure. To a solution of the crude product in CH_2Cl_2 (25 mL) were added CbzCl (8.3 mL, 58 mmol, 2.0 equiv) and a solution of Et_3N (12.2 mL, 87.9 mmol, 3.00 equiv) in CH_2Cl_2 (10 mL) at 0 °C, and the mixture was allowed to warm to r.t. and stirred for 1 h. To the mixture was added Et_3N (5.0 mL, 36 mmol, 1.2 equiv) and the mixture was stirred for an additional 2 h. The reaction mixture was diluted with EtOAc (35 mL), and quenched with sat. aq $NaHCO_3$ (30 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc–*n*-hexane, 30%) to afford a Cbz-protected amino ester.

Yield: 10.1 g (21.8 mmol, 75% over 2 steps); colorless oil; $[\alpha]_D^{25}$ 34.2 (*c* 1.82, $CHCl_3$); 95% ee {determined by HPLC (DAICEL-

CHIRALCEL-OD-H; hexane–*i*-PrOH, 90:10; flow rate 1.0 mL/min) t_R = 23.3 (*S*), 28.5 (*R*) min}.

IR (neat film): 3342, 3032, 2951, 2361, 2339, 1722, 1589, 1498, 1439, 1377, 1346, 1282, 1215, 1149, 1060, 1010, 910, 842, 738, 696, 667 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.41 (m, 10 H), 6.54 (s, 1 H), 6.51 (s, 1 H), 5.05–5.20 (m, 3 H), 5.01 (s, 2 H), 4.60 (dd, *J* = 13.9, 5.9 Hz, 1 H), 3.80 (s, 3 H), 3.66 (s, 3 H), 2.97–3.00 (m, 2 H), 2.21 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 155.4, 151.4, 146.7, 136.8, 136.0, 131.9, 130.7, 128.3, 128.0, 127.9, 127.6, 127.0, 126.7, 123.9, 112.7, 70.6, 66.9, 60.1, 54.8, 52.2, 37.9, 16.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{30}NO_6$: 464.2073; found: 464.2076.

To a solution of the above Cbz-protected amino ester (10.1 g, 21.8 mmol) in a mixture of MeOH (50 mL), H_2O (12.5 mL), and THF (12.5 mL) was added LiOH (1.90 g, 45.3 mmol, 2.00 equiv) at 0 °C. The mixture was allowed to warm to r.t. and stirred for 55 min. The reaction mixture was diluted with toluene (100 mL) and concentrated under reduced pressure. To the residue was added 10% aq citric acid (30 mL), and the resulting suspension was extracted with EtOAc (3 × 20 mL). The organic layer was washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give a carboxylic acid. To a mixture of the crude carboxylic acid and *N*,*O*-dimethylhydroxylamine hydrochloride (3.20 g, 32.8 mmol, 1.50 equiv) in CH_2Cl_2 (100 mL) were added WSCD·HCl (5.80 g, 32.6 mmol, 1.50 equiv), HOBt (5.00 g, 32.7 mmol, 1.50 equiv) and Et_3N (9.2 mL, 66 mmol, 3.0 equiv) at 0 °C. The mixture was allowed to warm to r.t. and stirred for 24 h. The reaction mixture was diluted with EtOAc (100 mL), and washed with brine. The aqueous phase was extracted three times with EtOAc (3 × 20 mL). The combined organic phase was washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc–*n*-hexane, 40%) to afford **24**.

Yield: 8.60 g (17.5 mmol, 80% over 2 steps); colorless oil; $[\alpha]_D^{25}$ 9.9 (*c* 1.5, $CHCl_3$).

IR (neat film): 3304, 3063, 3034, 2937, 2827, 2363, 2249, 1720, 1658, 1589, 1529, 1496, 1454, 1388, 1323, 1282, 1253, 1232, 1180, 1149, 1089, 1053, 1028, 1010, 910, 846, 773, 736, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.42 (m, 10 H), 6.59 (s, 1 H), 6.56 (s, 1 H), 5.40 (br, 1 H), 5.02–5.11 (m, 4 H), 4.94 (br, 1 H), 3.79 (s, 3 H), 3.62 (s, 3 H), 3.13 and 3.39 (s, 3 H), 2.94 (br, 1 H), 2.80 (br, 1 H), 2.21 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9, 155.9, 151.6, 146.8, 137.2, 136.3, 132.0, 131.6, 128.6, 128.2, 128.0, 127.9, 127.3, 124.2, 113.1, 70.7, 66.9, 61.6, 60.3, 52.0, 38.3, 32.1, 16.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{33}N_2O_6$: 493.2339; found: 493.2328.

(*S*)-5-(2-Amino-3,3-dimethoxypropyl)-2-methoxy-3-methylphenol (18)

To a stirred solution of **24** (8.60 g, 17.5 mmol) in toluene (120 mL) was added DIBAL-H (0.99 M in toluene, 27.0 mL, 26.7 mmol, 1.50 equiv) dropwise over 1 h at –78 °C under argon. To the mixture was added additional DIBAL-H (0.99 M in toluene, 6.0 mL, 5.9 mmol, 0.3 equiv) dropwise over 15 min at –78 °C. After stirring at –78 °C for an additional 15 min, MeOH (25 mL) and 30% aq Rochelle's salt (60 mL) were added to the mixture. The mixture was then diluted with EtOAc (30 mL), and stirred at r.t. for 1 h. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with sat. aq NaCl (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was filtered through a pad of silica gel and concentrated under reduced pressure, then used without further purification.

To a mixture of the crude product and trimethyl orthoformate (75.0 mL, 685 mmol, 39.1 equiv) in MeOH (220 mL) was added $TsOH·H_2O$ (332 mg, 1.75 mmol, 10.0 mol%), and the resulting mixture was stirred at r.t. for 1.5 h. To the reaction mixture was added NaH (100 mg, 2.50 mmol, 0.14 equiv) and the mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography (MeOH–$CHCl_3$, 1%) to afford a dimethyl acetal.

Yield: 9.60 g; white solid; mp 100–101 °C; $[\alpha]_D^{25}$ –25 (*c* 0.81, $CHCl_3$).

IR (neat film): 3317, 3065, 3036, 2932, 2829, 2361, 1689, 1589, 1548, 1498, 1442, 1385, 1340, 1286, 1265, 1230, 1186, 1149, 1130, 1072, 1008, 964, 912, 852, 773, 734, 696 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.44 (m, 10 H), 6.65 (s, 1 H), 6.61 (s, 1 H), 4.93–5.11 (m, 5 H), 4.13 (d, *J* = 3.2 Hz, 1 H), 3.99–4.06 (m, 1 H), 3.81 (s, 3 H), 3.38 (s, 3 H), 3.35 (s, 3 H), 2.79 (dd, *J* = 13.9, 6.3 Hz, 1 H), 2.70 (dd, *J* = 13.9, 7.6 Hz, 1 H), 2.23 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 151.3, 146.1, 137.0, 136.3, 132.9, 131.7, 128.3, 127.8, 127.7, 127.6, 127.0, 123.9, 112.7, 104.4, 70.5, 66.6, 60.2, 55.7, 55.7, 53.4, 35.9, 16.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{28}H_{33}NO_6Na$: 502.2206; found: 502.2208.

A mixture of the above dimethyl acetal (9.60 g, 37.5 mmol) and 10% Pd/C [10.0 g, AD-type (wet), 50% water; purchased from Kawaken Fine Chemicals Co.] in MeOH (120 mL) was stirred under 1 atm of hydrogen at r.t. for 2 d. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (MeOH–$CHCl_3$, 10%) to afford **18**.

Yield: 3.37 g (13.2 mmol, 62% over 3 steps); yellow oil; $[\alpha]_D^{21}$ –23 (*c* 0.99, $CHCl_3$).

IR (neat film): 3360, 3292, 2935, 2833, 1589, 1494, 1446, 1315, 1278, 1232, 1190, 1140, 1066, 1008, 970, 842 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.64 (d, *J* = 1.9 Hz, 1 H), 6.53 (d, *J* = 1.9 Hz, 1 H), 4.14 (d, *J* = 5.8 Hz, 1 H), 3.77 (s, 3 H), 3.45 (s, 3 H), 3.44 (s, 3 H), 3.10 (ddd, *J* = 9.5, 3.9, 1.7 Hz, 1 H), 2.85 (dd, *J* = 13.4, 3.9 Hz, 1 H), 2.39 (dd, *J* = 13.4, 9.5 Hz, 1 H), 2.25 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.9, 144.0, 134.5, 130.8, 122.8, 114.2, 107.2, 60.3, 55.2, 55.0, 54.0, 37.7, 16.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{22}NO_4$: 256.1549; found: 256.1547.

(1*R*,3*S*)-3-(Dimethoxymethyl)-1-{(*R*)-2,2-dimethyl-3-[(4-nitrophenyl)sulfonyl]oxazolidin-4-yl}-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinolin-8-ol (28)

To a mixture of dried Na_2SO_4 (10.1 g), amine **18** (1.02 g, 4.00 mmol) and aldehyde **27** (1.39 g, 4.42 mmol, 1.10 equiv) in CH_2Cl_2 (30 mL) at 0 °C, was added HCO_2H (0.76 mL, 20.1 mmol, 5.00 equiv), and the reaction mixture was allowed to warm to r.t. and stirred for 24 h. The reaction mixture was diluted with EtOAc (30 mL), and quenched with sat. aq $NaHCO_3$ (30 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was dissolved in a minimum amount of EtOAc, and hexane was added to induce precipitation. The precipitates were collected by filtration to afford **28**.

Yield: 1.83 g (3.32 mmol, 83%); yellow solid; mp 96–98 °C; $[\alpha]_D^{23}$ –105 (*c* 0.63, $CHCl_3$).

IR (neat film): 3458, 3107, 2988, 2941, 2893, 2835, 1668, 1606, 1581, 1531, 1500, 1458, 1417, 1350, 1309, 1290, 1232, 1203, 1165, 1147, 1084, 1064, 1032, 999, 958, 910, 856, 831, 736, 688 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.39 (ddd, *J* = 9.0, 2.2, 2.2 Hz, 2 H), 8.23 (ddd, *J* = 9.0, 2.2, 2.2 Hz, 2 H), 6.48 (s, 1 H), 6.02 (s, 1 H), 4.93 (br, 1 H), 4.72 (ddd, *J* = 7.3, 6.1, 2.9 Hz, 1 H), 4.26 (d, *J* = 7.3 Hz, 1 H), 3.85 (dd, *J* = 8.5, 6.1 Hz, 1 H), 3.77 (s, 3 H), 3.53 (dd, *J* = 8.5, 7.3 Hz, 1 H), 3.44 (s, 3 H), 3.41 (s, 3 H), 2.95–3.00 (m, 1 H), 2.66 (dd, *J* = 15.1, 2.2 Hz, 1 H), 2.51 (dd, *J* = 15.1, 10.9 Hz, 1 H), 2.40 (br, 1 H), 2.25 (s, 3 H), 1.75 (s, 3 H), 1.53 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.6, 145.6, 145.1, 143.1, 132.5, 128.9, 128.5, 123.9, 122.7, 118.6, 107.0, 99.3, 65.4, 60.9, 60.4, 54.0, 53.7, 52.7, 52.6, 32.4, 28.4, 25.4, 15.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{34}N_3O_9S$: 552.2016; found: 552.2015.

(1*R*,3*S*)-2-Chloroethyl 8-(Benzyloxy)-3-(dimethoxymethyl)-1-{(*R*)-2,2-dimethyl-3-[(4-nitrophenyl)sulfonyl]oxazolidin-4-yl}-7-methoxy-6-methyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (29)

To a solution of **28** (2.01 g, 3.65 mmol) in acetone (40 mL) at 0 °C, were added benzyl bromide (0.53 mL, 4.46 mmol, 1.20 equiv) and K_2CO_3 (606 mg, 4.38 mmol, 1.20 equiv), and the reaction mixture was allowed to warm to r.t. and stirred for 24 h. To the mixture were added benzyl bromide (3.80 mL, 31.9 mmol, 8.60 equiv) and K_2CO_3 (4.50 g, 32.6 mmol, 8.90 equiv) at 0 °C, and the reaction mixture was allowed to warm to r.t. and stirred for an additional 17.5 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc–*n*-hexane, 0→20%) to afford a benzyl ether.

Yield: 2.32 g (3.62 mmol, 99%); pale-yellow foam; $[\alpha]_D^{23}$ –115 (*c* 0.57, $CHCl_3$).

IR (neat film): 3364, 3105, 2988, 2937, 2891, 2835, 2363, 1606, 1531, 1483, 1452, 1413, 1350, 1313, 1232, 1201, 1167, 1149, 1084, 1064, 1030, 1001, 964, 910, 856, 833, 738, 688 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.83 (ddd, *J* = 9.0, 2.2, 2.2 Hz, 2 H), 7.76 (ddd, *J* = 9.0, 2.2, 2.2 Hz, 2 H), 7.59–7.61 (m, 2 H), 7.36–7.44 (m, 3 H), 5.18 (d, *J* = 10.4 Hz, 1 H), 5.08 (br, 1 H), 4.92 (d, *J* = 10.4 Hz, 1 H), 4.61 (ddd, *J* = 6.8, 6.8, 3.1,Hz, 1 H), 4.26 (d, *J* = 7.1 Hz, 1 H), 3.87 (s, 3 H), 3.72 (dd, *J* = 8.7, 6.8 Hz, 1 H), 3.47 (s, 3 H), 3.43 (s, 3 H), 3.40 (dd, *J* = 8.7, 6.8 Hz, 1 H), 3.00–3.05 (m, 1 H), 2.71 (dd, *J* = 15.3, 2.6 Hz, 1 H), 2.53 (dd, *J* = 15.3, 10.9 Hz, 1 H), 2.39 (br, 1 H), 2.26 (s, 3 H), 1.69 (s, 3 H), 1.37 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.6, 149.2, 148.9, 146.0, 137.0, 132.1, 131.0, 128.8, 128.6, 128.5, 128.4, 126.8, 126.2, 123.7, 107.2, 98.7, 75.7, 65.2, 62.4, 60.8, 54.0, 54.0, 53.2, 52.6, 32.6, 28.2, 25.4, 15.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{32}H_{40}N_3O_9S$: 642.2485; found: 642.2485.

To a solution of the above benzyl ether (49.3 mg, 0.0768 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C were added pyridine (0.07 mL, 0.9 mmol, 10 equiv), and 2-chloroethyl chloroformate (0.08 mL, 0.8 mmol, 10 equiv), and the mixture was allowed to warm to r.t. and stirred for 1 h. The reaction mixture was diluted with EtOAc (5 mL), and quenched with sat. aq $NaHCO_3$ (5 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with sat. aq NaCl (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (MeOH–CH_2Cl_2, 1%) to afford **29**.

Yield: 51.7 mg (0.0691 mmol, 90%); pale-yellow foam; $[\alpha]_D^{23}$ –32.7 (*c* 1.03, $CHCl_3$).

IR (neat film): 3624, 2935, 2361, 2341, 1697, 1604, 1531, 1462, 1404, 1354, 1307, 1238, 1167, 1066, 912, 854, 733 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.3 Hz, 2 H), 7.86 (d, *J* = 8.3 Hz, 2 H), 7.56–7.62 (m, 2 H), 7.32–7.41 (m, 3 H), 6.76 (s, 1 H), 5.86–5.97 (m, 1 H), 5.14–5.22 (m, 1 H), 4.80–4.82 (m, 2 H), 4.56–4.59 (m, 2 H), 4.24 (br, 1 H), 4.08 (br, 2 H), 3.89–3.92 (m, 3 H), 3.64–3.70 (m, 2 H), 3.62 (s, 3 H), 3.52 (s, 3 H), 3.10–3.16 (m, 1 H), 2.95 (br, 1 H), 2.27 (s, 3 H), 1.61 (s, 3 H), 1.43 (br, 1 H), 1.23 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.0, 155.3, 149.8, 149.4, 148.6, 147.7, 137.2, 136.8, 131.6, 130.5, 129.5, 128.6, 128.3, 128.1, 127.8, 124.9, 123.7, 105.7, 104.7, 99.2, 75.9, 75.6, 66.6, 65.7, 61.3, 60.5, 57.5, 57.4, 55.5, 54.9, 52.1, 42.7, 41.9, 29.4, 29.0, 24.9, 24.8, 16.0.

HRMS (ESI): *m*/*z* $[M - H]^+$ calcd for $C_{35}H_{41}ClN_3O_{11}S$: 746.2150; found: 746.2156.

(1*R*,3*S*)-2-Chloroethyl 1-[(*R*)-1-Amino-2-hydroxyethyl]-8-(benzyloxy)-3-(dimethoxymethyl)-7-methoxy-6-methyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (30)

To a solution of **29** (805 mg, 1.08 mmol) in MeCN (20 mL) at 0 °C were added 2-mercaptoethanol (0.12 mL, 1.71 mmol, 1.50 equiv) and DBU (0.25 mL, 1.7 mmol, 1.5 equiv), and the mixture was allowed to warm to r.t. and stirred for 2 h. The reaction mixture was diluted with EtOAc (20 mL), and quenched with sat. aq $NaHCO_3$ (10 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The organic phase was sequentially washed with sat. aq $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (MeOH–$CHCl_3$, 5%) to afford **30**.

Yield: 471 mg (0.901 mmol, 83%); pale-yellow foam; $[\alpha]_D^{23}$ 13 (*c* 0.27, $CHCl_3$).

IR (neat film): 2937, 2361, 2341, 1693, 1454, 1408, 1352, 1313, 1238, 1116, 1068, 999, 906, 808 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.54 (m, 2 H), 7.31–7.42 (m, 3 H), 6.82 (s, 1 H), 5.46 and 5.56 (d, *J* = 10.7 Hz, 1 H), 5.14 and 5.24 (d, *J* = 10.7 Hz, 1 H), 4.80–4.87 (m, 2 H), 4.36–4.41 and 4.53–4.58 (m, 1 H), 4.16–4.19 and 4.23–4.29 (m, 1 H), 3.92–3.99 (m, 1 H), 3.81 and 3.84 (s, 3 H), 3.59–3.79 (m, 4 H), 3.57 (s, 3 H), 3.51 and 3.53 (s, 3 H), 3.10 (dd, *J* = 15.3, 12.2 Hz, 1 H), 2.98–3.00 (m, 1 H), 2.80–2.89 (m, 1 H), 2.28 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5, 149.4, 147.8, 136.7, 131.5, 131.5, 130.0, 128.2, 127.8, 127.7, 127.5, 127.1, 125.4, 125.2, 105.2, 104.5, 74.7, 65.7, 65.3, 63.7, 63.4, 60.1, 57.4, 57.2, 55.7, 54.9, 54.8, 54.6, 53.2, 42.4, 41.9, 24.3, 24.0, 15.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{36}ClN_2O_7$: 523.2211; found: 523.2217.

(1*R*,3*S*)-2-Chloroethyl 8-(Benzyloxy)-3-(dimethoxymethyl)-7-methoxy-6-methyl-1-[(*R*)-6-oxomorpholin-3-yl]-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (32)

To a solution of **30** (606 mg, 1.16 mmol) in MeCN (12 mL) was added a solution of phenyl bromoacetate (**31**; 277 mg, 1.29 mmol, 1.10 equiv) and DIPEA (0.23 mL, 1.3 mmol, 1.1 equiv) in MeCN (12 mL) dropwise over 30 min at 0 °C. The mixture was allowed to warm to r.t. and stirred for 23 h. The solution was concentrated under reduced pressure and the residue was purified by column chromatography (neutral silica gel; EtOAc–hexane, 40%) to afford **32**.

Yield: 589 g (1.05 mmol, 91%); pale-yellow foam; $[\alpha]_D^{25}$ –17.3 (*c* 1.18, $CHCl_3$).

IR (neat film): 3348, 2939, 2837, 2363, 1743, 1697, 1585, 1485, 1454, 1406, 1356, 1309, 1236, 1211, 1138, 1113, 1070, 1033, 999, 912, 812, 754, 702 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.54 (m, 5 H), 6.82 (s, 1 H), 5.54 and 5.66 (d, *J* = 10.5 Hz, 1 H), 5.10 and 5.19 (d, *J* = 10.5 Hz, 1 H), 4.90 and 4.96 (d, *J* = 10.1 Hz, 1 H), 4.81 and 4.85 (br, 1 H), 4.55 and 4.58 (d, *J* = 3.6 Hz, 1 H), 4.15–4.53 (m, 3 H), 3.98 (ddd, *J* = 12.4, 6.9, 2.3 Hz, 1 H), 3.81 and 3.84 (s, 3 H), 3.52–3.77 (m,

3 H), 3.56 (s, 3 H), 3.52 and 3.54 (s, 3 H), 3.38–3.46 (m, 2 H), 3.07–3.16 (m, 1 H), 2.84–2.92 (m, 1 H), 2.26 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0, 156.2, 155.4, 149.7, 149.5, 148.3, 137.6, 137.2, 132.6, 132.4, 130.3, 130.2, 128.7, 128.4, 128.2, 127.6, 127.1, 126.4, 125.9, 125.8, 105.6, 104.5, 75.3, 74.8, 73.4, 72.6, 65.9, 65.6, 60.3, 57.6, 57.4, 55.6, 55.1, 53.4, 51.7, 51.4, 47.0, 42.6, 42.l, 24.4, 24.2, 15.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{36}ClN_2O_8$: 563.2160; found: 563.2144.

(1*R*,3*S*)-2-Chloroethyl 8-(Benzyloxy)-3-(dimethoxymethyl)-7-methoxy-6-methyl-1-[(*R*)-6-oxo-3,6-dihydro-2*H*-1,4-oxazin-3-yl]-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (33)

To a solution of **32** (566 mg, 1.01 mmol) in CH_2Cl_2 (12 mL) were added Et_3N (1.40 mL, 10.0 mmol, 10.0 equiv) and NBS (198 mg, 1.11 mmol, 1.10 equiv) at 0 °C. After stirring for 30 min, the reaction mixture was diluted with EtOAc (12 mL), and quenched with sat. aq $NaHCO_3$ (10 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with sat. aq NaCl (5 mL) , dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (neutral silica gel; EtOAc–hexane, 50%) to afford **33**.

Yield: 500 mg (0.891 mmol, 88%); pale-yellow foam; $[\alpha]_D^{24}$ –51 (*c* 0.54, $CHCl_3$).

IR (neat film): 2939, 2837, 2361, 2341, 1747, 1699, 1630, 1587, 1547, 1485, 1460, 1406, 1354, 1313, 1273, 1236, 1219, 1138, 1114, 1072, 1035, 999, 906, 868, 812, 771, 733, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 and 7.65 (br, 1 H), 7.29–7.45 (m, 5 H), 6.84 (s, 1 H), 5.66 and 5.78 (d, *J* = 11.0 Hz, 1 H), 5.11 (s, 1 H), 5.03 and 5.13 (d, *J* = 11.0 Hz, 1 H), 4.84 and 4.89 (br, 1 H), 4.57–4.60 (m, 1 H), 4.13–4.53 (m, 5 H), 4.04–4.09 (m, 1 H), 3.79 and 3.80 (s, 3 H), 3.58 (s, 3 H), 3.57–3.73 (m, 1 H), 3.53 and 3.55 (s, 3 H), 3.16 and 3.19 (d, *J* = 12.4 Hz, 1 H), 2.91–2.99 (m, 1 H), 2.28 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 155.3, 154.6, 152.6, 152.4, 149.7, 149.5, 148.6, 148.3, 138.2, 137.9, 132.6, 132.5, 129.8, 128.5, 127.8, 127.8, 127.0, 126.5, 125.5, 125.4, 74.3, 74.0, 68.9, 68.5, 65.9, 65.5, 60.1, 58.6, 58.4, 57.7, 57.6, 57.3, 57.2, 55.5, 55.0, 51.2, 50.8, 42.6, 42.1, 24.4, 24.1, 16.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{33}ClN_2O_8Na$: 583.1823; found: 583.1831.

(1*R*,3*S*)-2-Chloroethyl 8-(Benzyloxy)-1-{(3*R*,5*R*)-5-[6-(benzyloxy)-7-hydroxybenzo[*d*][1,3]dioxol-4-yl]-6-oxomorpholin-3-yl}-3-(dimethoxymethyl)-7-methoxy-6-methyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (35)

To a solution of **33** (483 mg, 0.861 mmol) and phenol **34** (315 mg, 1.29 mmol, 1.50 equiv) in CH_2Cl_2 (10 mL) was added TFA (1.28 mL, 17.4 mmol, 20.0 equiv) dropwise. After stirring for 25 min, the mixture was diluted with EtOAc (10 mL), and poured into sat. aq $NaHCO_3$ (10 mL). The resulting mixture was extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with brine (5 mL) , dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc–hexane, 50%) to afford **35**.

Yield: 564 mg (0.700 mmol, 81%); colorless foam; $[\alpha]_D^{23}$ –7.2 (*c* 0.84, $CHCl_3$).

IR (neat film): 3630, 3331, 2939, 2361, 2253, 1743, 1697, 1498, 1458, 1406, 1356, 1309, 1234, 1207, 1113, 1070, 1035, 999, 947, 912, 814, 733, 700.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 and 7.59 (d, *J* = 7.1 Hz, 2 H), 7.32–7.41 (m, 8 H), 6.80 and 6.84 (s, 1 H), 5.70–6.02 (m, 3 H), 5.66 (br, 1 H), 5.41 (br, 1 H), 4.91–5.19 (m, 3 H), 4.84 (m, 1 H), 4.70 (s, 2 H), 4.42–4.66 (m, 3 H), 4.23–4.28 (m, 1 H), 3.97–4.02 (m, 1 H), 3.78 and 3.79 (s, 3 H), 3.57 (s, 3 H), 3.49 and 3.52 (s, 3 H), 3.49–3.75 (m, 3 H), 2.96–3.05 (m, 1 H), 2.81–2.90 (m, 1 H), 2.26 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 168.7, 155.7, 155.0, 149.4, 149.2, 148.1, 141.9, 141.8, 140.5, 137.0, 136.7, 135.7, 133.6, 132.0, 131.8, 130.4, 130.0, 128.6, 128.3, 128.1, 128.0, 128.0, 127.9, 127.8, 127.7, 126.2, 125.6, 125.5, 110.1, 110.0, 105.2, 104.8, 104.6, 101.5, 75.5, 75.1, 71.9, 70.5, 70.3, 65.6, 65.4, 60.1, 60.0, 57.4, 56.9, 56.8, 55.3, 55.0, 54.9, 54.8, 51.3, 51.1, 50.8, 50.4, 42.5, 41.9, 24.2, 24.0, 15.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{42}H_{46}ClN_2O_{12}$: 805.2739; found: 805.2743.

(1*R*,3*S*)-2-Chloroethyl 8-(Benzyloxy)-1-{(4*R*,6*R*)-4-[6-(benzyloxy)-7-{[(trifluoromethyl)sulfonyl]oxy}benzo[*d*][1,3]dioxol-4-yl]-9,9,10,10-tetramethyl-3-oxo-2,8-dioxa-5-aza-9-silaundecan-6-yl}-3-(dimethoxymethyl)-7-methoxy-6-methyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (36)

To a solution of **35** (537 mg, 0.667 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added pyridine (0.08 mL, 1.0 mmol, 1.5 equiv) and Tf_2O (0.17 mL, 1.0 mmol, 1.5 equiv). After stirring for 0.5 h, the reaction mixture was diluted with EtOAc (10 mL), and quenched with sat. aq $NaHCO_3$ (10 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc–hexane, 40%) to afford the corresponding triflate.

Yield: 503 mg (0.537 mmol, 81%); colorless foam; $[\alpha]_D^{23}$ –13 (*c* 0.64, $CHCl_3$).

IR (neat film): 3319, 2939, 2837, 2363, 1743, 1699, 1498, 1460, 1425, 1408, 1377, 1358, 1309, 1288, 1211, 1138, 1087, 1001, 956, 912, 831, 734, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 and 7.58 (d, *J* = 7.1 Hz, 2 H), 7.33–7.43 (m, 8 H), 6.82 (s, 1 H), 5.85–6.08 (m, 3 H), 5.78 and 5.79 (br, 1 H), 4.85–5.18 (m, 4 H), 4.72 (s, 2 H), 4.45–4.69 (m, 3 H), 4.27–4.30 (m, 1 H), 3.99–4.04 (m, 1 H), 3.76 and 3.78 (s, 3 H), 3.68–3.74 (m, 2 H), 3.58 (s, 3 H), 3.50 and 3.52 (s, 3 H), 3.50–3.61 (m, 2 H), 2.97–3.06 (m, 1 H), 2.84–2.92 (m, 1 H), 2.26 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.2, 168.0, 156.0, 155.2, 149.6, 149.4, 148.3, 146.2, 146.1, 140.6, 140.2, 137.0, 136.7, 135.3, 132.4, 132.2, 132.1, 130.2, 128.9, 128.6, 128.3, 128.2, 128.1, 128.0, 127.3, 126.9, 126.2, 125.9, 125.8, 124.0, 123.0, 122.5, 119.8, 119.0, 118.8, 116.6, 105.5, 105.4, 104.2, 103.0, 75.8, 75.5, 71.7, 70.4, 70.3, 60.2, 57.6, 57.0, 56.9, 55.5, 55.0, 54.8, 54.7, 51.7, 51.5, 50.9, 50.5, 42.7, 42.2, 24.4, 24.2, 15.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{43}H_{45}ClF_3N_2O_{14}S$: 937.2232; found: 937.2235.

To a solution of the above triflate (179 mg, 0.191 mmol) in MeOH (8 mL) was added Et_3N (0.06 mL, 0.4 mmol, 2 equiv) at r.t., and the reaction was stirred for 1 h. The reaction mixture was concentrated under reduced pressure. To a solution of the residue in DMF (8 mL) at 0 °C were added TBSCl (44.0 mg, 0.29 mmol, 1.5 equiv) and imidazole (19.5 mg, 0.286 mmol, 1.50 equiv), and the mixture was allowed to warm to r.t. and stirred for 1 h. TBSCl (22.0 mg, 0.146 mmol, 0.80 equiv) and imidazole (10.0 mg, 0.147 mmol, 0.80 equiv) were added at r.t. and the mixture was stirred for an additional 1 h. The reaction mixture was diluted with EtOAc (15 mL), and washed with brine (15 mL). The aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organic phase was washed with 20% aq NaCl (3 × 5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc–*n*-hexane, 20%) to afford **36**.

Yield: 187 mg (0.173 mmol, 91% over 2 steps); colorless foam; $[\alpha]_D^{23}$ –16 (*c* 0.42, $CHCl_3$).

IR (neat film): 2953, 2932, 2856, 2363, 2341, 1741, 1699, 1643, 1496, 1458, 1427, 1406, 1358, 1311, 1271, 1249, 1213, 1138, 1078, 1005, 956, 902, 835, 773, 736, 696 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.52 (m, 2 H), 7.29–7.38 (m, 8 H), 6.80 (s, 1 H), 6.42 (s, 1 H), 5.95 (s, 1 H), 5.86 and 5.86 (s, 1 H), 5.60 and 5.75 (d, *J* = 10.5 Hz, 1 H), 5.11–5.20 (m, 1 H), 5.02 and 5.05 (s, 1 H), 4.84–4.86 (m, 2 H), 4.68 and 4.76 (br, 1 H), 4.18–4.23 (m, 2 H), 3.94–3.98 (m, 1 H), 3.39–3.79 (m, 6 H), 3.76 (s, 3 H), 3.53 (s, 3 H), 3.42 (s, 3 H), 3.14–3.21 (m, 2 H), 2.78–2.82 (m, 1 H), 2.26 (s, 3 H), 0.84 (s, 9 H), 0.01 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 155.6, 149.3, 148.0, 146.1, 140.7, 139.3, 137.9, 135.3, 132.4, 131.1, 130.5, 128.0, 127.9, 127.7, 127.2, 126.8, 124.9, 124.6, 121.9, 119.7, 119.0, 118.9, 116.5, 105.9, 104.8, 103.9, 102.5, 73.9, 71.4, 65.1, 65.0, 60.0, 57.4, 57.1, 56.9, 56.7, 55.3, 51.8, 51.3, 41.7, 25.8, 24.0, 18.3, 15.8, –5.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{50}H_{63}ClF_3N_2O_{15}SSi$: 1083.3359; found: 1083.3356.

(1*R*,3*S*)-2-Chloroethyl 8-(Benzyloxy)-1-[(*R*)-1-({(*R*)-1-[6-(benzyloxy)-7-{[(trifluoromethyl)sulfonyl]oxy}benzo[*d*][1,3]dioxol-4-yl]-2-hydroxyethyl}amino)-2-{(*tert*-butyldimethylsilyl)oxy}ethyl]-3-(dimethoxymethyl)-7-methoxy-6-methyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (37)

To a mixture of **36** (245 mg, 0.226 mmol) and LiCl (96.0 mg, 2.26 mmol, 10.0 equiv) in THF (3.75 mL) were added $NaBH_4$ (86.0 mg, 2.27 mmol, 10.0 equiv) and EtOH (7.5 mL) at 0 °C, and the mixture was allowed to warm to r.t. and stirred for 2 d. The reaction mixture was diluted with EtOAc (10 mL), and quenched with 1 M aq HCl (10 mL) at 0 °C, and the mixture was neutralized with sat. aq $NaHCO_3$ (10 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc–*n*-hexane, 30%) to afford **37**.

Yield: 217 mg (0.206 mmol, 91%); colorless foam; $[\alpha]_D^{23}$ 9.7 (*c* 0.42, $CHCl_3$).

IR (neat film): 3476, 2932, 2858, 2361, 2341, 1699, 1647, 1498, 1456, 1425, 1406, 1358, 1311, 1286, 1249, 1211, 1138, 1078, 1003, 951, 835, 773, 736, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.57 (m, 2 H), 7.28–7.38 (m, 8 H), 6.84 (s, 1 H), 6.29 and 6.32 (br, 1 H), 5.83–5.91 (m, 2 H), 5.09–5.78 (m, 1 H), 4.70–4.95 (m, 4 H), 4.02–4.48 (m, 2 H), 3.83 (br, 3 H), 3.56 (s, 3 H), 3.06–3.77 (m, 12 H), 2.85–2.87 (m, 1 H), 2.28 (s, 3 H), 0.81 (s, 9 H), –0.01 (s, 3 H), –0.08 (br, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.7, 148.2, 146.3, 140.1, 139.5, 137.9, 137.7, 135.4, 131.2, 129.7, 129.2, 128.5, 128.2, 128.0, 127.6, 127.4, 126.9, 125.6, 121.9, 119.9, 116.7, 106.2, 105.0, 104.4, 104.2, 102.5, 71.7, 65.4, 63.5, 62.0, 61.0, 60.3, 58.8, 57.9, 57.7, 57.4, 57.2, 57.0, 56.0, 55.5, 51.6, 51.3, 42.8, 41.7, 25.9, 24.3, 18.5, 16.0, –5.4, –5.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{49}H_{63}ClF_3N_2O_{14}SSi$: 1055.3410; found: 1055.3413.

(3*R*,5*R*,6*R*,12*S*,12a*S*)-2-chloroethyl 7-(benzyloxy)-3-[6-(benzyloxy)-7-{[(trifluoromethyl)sulfonyl]oxy}benzo[*d*][1,3]dioxol-4-yl]-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-8-methoxy-9-methyl-3,5,6,11,12,12a-hexahydro-2*H*-6,12-epiminobenzo[*e*]oxazolo[3,2-*a*]azocine-13-carboxylate (38)

To a solution of **37** (124 mg, 0.117 mmol) in CH_2Cl_2 (4 mL) was added a solution of $BF_3{\cdot}OEt_2$ (0.075 mL, 0.59 mmol, 5.0 equiv) in CH_2Cl_2 (1 mL) at 0 °C, and the reaction was stirred for 1 h. To the reaction mixture was added a solution of $BF_3{\cdot}OEt_2$ (0.075 mL, 0.52 mmol, 5.0 equiv) in CH_2Cl_2 (1 mL) at 0 °C, and the mixture was stirred for an additional 55 min. The reaction mixture was diluted with EtOAc (10 mL), and quenched with sat. aq $NaHCO_3$ (10 mL) at 0 °C. The organic layer was separated at r.t., and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc–*n*-hexane, 25%) to afford **38**.

Yield: 85.2 mg (0.0859 mmol, 73%); white foam; $[\alpha]_D^{23}$ –31 (*c* 0.43, $CHCl_3$).

IR (neat film): 2953, 2930, 2887, 2856, 2361, 2341, 1707, 1635, 1489, 1452, 1427, 1344, 1325, 1286, 1251, 1215, 1138, 1093, 1020, 906, 835, 773, 736, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 7.1 Hz, 1 H), 7.53 (d, *J* = 6.6 Hz, 1 H), 7.26–7.44 (m, 8 H), 6.75 and 6.77 (s, 1 H), 6.55 (s, 1 H), 5.98 (d, *J* = 1.2 Hz, 1 H), 5.87 and 5.88 (d, *J* = 1.2 Hz, 1 H), 5.46 and 5.48 (d, *J* = 2.2 Hz, 1 H), 5.37 and 5.41 (dd, *J* = 8.1, 4.2 Hz, 1 H), 5.20 and 5.25 (d, *J* = 10.5 Hz, 1 H), 4.73–4.91 (m, 4 H), 4.22–4.45 (m, 4 H), 4.11 (dd, *J* = 7.3, 1.0 Hz, 1 H), 3.86 and 3.87 (s, 3 H), 3.60–3.71 (m, 3 H), 3.18–3.26 (m, 2 H), 3.08 and 3.11 (d, *J* = 8.3 Hz, 1 H), 2.69 (d, *J* = 17.3 Hz, 1 H), 2.21 and 2.21 (s, 3 H), 0.63 and 0.65 (s, 9 H), –0.28 and –0.25 (s, 3 H), –0.36 and –0.33 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.0, 153.4, 149.2, 149.0, 147.7, 147.5, 145.3, 139.4, 139.4, 137.0, 136.9, 135.4, 131.2, 131.0, 129.8, 129.5, 128.2, 128.1, 127.8, 127.8, 127.7, 127.1, 125.2, 125.1, 124.8, 124.4, 123.6, 121.2, 119.7, 116.5, 103.1, 103.1, 102.5, 92.1, 75.3, 75.1, 71.0, 68.1, 68.0, 66.8, 66.7, 65.3, 64.9, 60.1, 60.0, 59.8, 59.6, 47.9, 47.4, 47.1, 46.1, 42.1, 41.8, 30.5, 30.2, 25.4, 17.8, 17.7, 15.7, –5.9, –5.9, –6.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{47}H_{55}ClF_3N_2O_{12}SSi$: 991.2886; found: 991.2887.

(3*R*,5*R*,6*R*,12*S*,12a*S*)-2-Chloroethyl 7-(benzyloxy)-3-[6-(benzyloxy)-7-methylbenzo[d][1,3]dioxol-4-yl]-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-8-methoxy-9-methyl-3,5,6,11,12,12a-hexahydro-2*H*-6,12-epiminobenzo[*e*]oxazolo[3,2-*a*]azocine-13-carboxylate (39)

To a degassed solution of **38** (76.7 mg, 0.0774 mmol) in THF (3 mL) at 0 °C was added MeZnCl (2.0 M in THF, 0.15 mL, 0.30 mmol, 3.0 equiv), and the mixture was allowed to warm to r.t. To the mixture was added [$PdCl_2$(dppf)] (6.3 mg, 0.0086 mmol, 10 mol%), and the resulting mixture was heated to reflux. After stirring for 1 h, [$PdCl_2$(dppf)] (6.0 mg, 0.0082 mmol, 10 mol%) and MeZnCl (2.0 M in THF, 0.60 mL, 1.2 mmol, 12 equiv) were added to the mixture and heating was continued for an additional 2.5 h. The reaction mixture was diluted with EtOAc (5 mL) and quenched with sat. aq $NaHCO_3$ (5 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc–*n*-hexane, 25%) to afford **39**.

Yield: 50.3 mg (0.0587 mmol, 76%); colorless foam; $[\alpha]_D^{23}$ –34.3 (*c* 1.57, $CHCl_3$).

IR (neat film): 3065, 3032, 2953, 2930, 2885, 2856, 2361, 2251, 1950, 1707, 1610, 1581, 1485, 1427, 1379, 1342, 1325, 1284, 1257, 1224, 1195, 1114, 1072, 1020, 939, 908, 839, 775, 734, 698, 667 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 6.8 Hz, 1 H), 7.54 (d, *J* = 7.1 Hz, 1 H), 7.29–7.48 (m, 8 H), 6.73 and 6.75 (s, 1 H), 6.40 and 6.41 (s, 1 H), 5.85 and 5.86 (s, 1 H), 5.77 and 5.77 (s, 1 H), 5.48 and 5.50 (d, *J* = 1.7 Hz, 1 H), 5.35 and 5.41 (dd, *J* = 7.3, 3.4 Hz, 1 H), 5.18 and 5.23 (d, *J* = 10.7 Hz, 1 H), 4.70–4.90 (m, 4 H), 4.22–4.45 (m, 5 H), 3.85 and 3.87 (s, 3 H), 3.61–3.75 (m, 3 H), 3.14–3.25 (m, 3 H), 2.69 (d, *J* = 17.3 Hz, 1 H), 2.21 (s, 3 H), 2.08 (s, 3 H), 0.67 and 0.69 (s, 9 H), –0.24 and –0.27 (s, 3 H), –0.29 and –0.32 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.0, 153.4, 151.4, 149.1, 148.9, 147.7, 147.4, 146.1, 137.8, 137.0, 130.9, 130.8, 130.1, 129.8, 128.2,

128.2, 128.0, 127.9, 127.7, 127.4, 127.1, 126.9, 125.2, 125.1, 125.0, 124.5, 120.5, 107.6, 101.7, 101.6, 100.4, 92.0, 91.9, 75.3, 75.1, 70.2, 68.1, 67.9, 66.6, 66.5, 65.2, 64.9, 60.2, 60.1, 60.1, 60.0, 59.8, 59.7, 48.1, 47.5, 47.1, 46.2, 42.1, 41.8, 30.5, 30.2, 25.5, 17.8, 17.8, 15.7, 8.7, –5.8, –5.8, –5.9, –5.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{47}H_{58}ClN_2O_9Si$: 857.3600; found: 857.3588.

(3*R*,5*R*,6*R*,12*S*,12a*S*)-2,2,2-Trichloroethyl 7-(Benzyloxy)-3-[6-(benzyloxy)-7-methylbenzo[*d*][1,3]dioxol-4-yl]-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-8-methoxy-9-methyl-3,5,6,11,12,12a-hexahydro-2*H*-6,12-epiminobenzo[*e*]oxazolo[3,2-*a*]azocine-13-carboxylate (7)

To a solution of **39** (8.7 mg, 0.010 mmol) in DMF (1 mL) was added NaI (30.0 mg, 0.200 mmol, 20.0 equiv) at r.t., and the resulting mixture was heated at 110 °C with stirring for 18 h. The reaction mixture was diluted with EtOAc (5 mL) at r.t., and quenched with H_2O (5 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with 20% aqueous NaCl (3 × 5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc–*n*-hexane, 25%) to afford the iodide.

Yield: 9.1 mg (0.0096 mmol, 96%); colorless oil; $[\alpha]_D^{23}$ –32 (*c* 0.46, $CHCl_3$).

IR (neat film): 2951, 2928, 2883, 2856, 1707, 1608, 1548, 1485, 1425, 1379, 1342, 1323, 1284, 1259, 1222, 1195, 1111, 1068, 1012, 939, 906, 839, 773, 734, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 6.8 Hz, 1 H), 7.53 (d, *J* = 6.9 Hz, 1 H), 7.30–7.44 (m, 8 H), 6.73 and 6.74 (s, 1 H), 6.39 and 6.40 (s, 1 H), 5.85 and 5.86 (s, 1 H), 5.76 and 5.77 (s, 1 H), 5.46 and 5.48 (br, 1 H), 5.35 and 5.41 (dd, *J* = 7.4, 3.2 Hz, 1 H), 5.18 and 5.26 (d, *J* = 11.0 Hz, 1 H), 4.70–4.89 (m, 4 H), 4.22–4.44 (m, 5 H), 3.84 and 3.86 (s, 3 H), 3.69–3.74 (m, 1 H), 3.32 and 3.33 (d, *J* = 6.8 Hz, 1 H), 3.13–3.27 (m, 4 H), 2.67 (d, *J* = 17.4 Hz, 1 H), 2.20 (s, 3 H), 2.08 (s, 3 H), 0.67 and 0.70 (s, 9 H), –0.21 and –0.27 (s, 3 H), –0.27 and –0.32 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.3, 153.7, 151.9, 149.5, 149.3, 148.2, 148.0, 146.5, 138.3, 137.6, 137.5, 137.4, 131.4, 131.2, 130.5, 130.2, 128.7, 128.6, 128.5, 128.2, 128.1, 127.8, 127.3, 125.6, 125.4, 124.9, 120.9, 107.9, 102.0, 101.9, 100.8, 92.3, 75.6, 75.4, 70.5, 68.4, 68.2, 66.9, 66.7, 65.8, 65.5, 60.4, 60.4, 60.2, 60.0, 60.0, 48.3, 47.7, 47.3, 46.4, 30.8, 30.4, 25.7, 25.7, 18.0, 17.9, 15.8, 8.8, 1.7, –5.7, –5.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{47}H_{58}IN_2O_9Si$: 949.2956; found: 949.2964.

To a solution of the above iodide (9.1 mg, 0.00959 mmol) in THF (1.0 mL) at r.t. were added an excess of zinc powder, and acetic acid (0.03 mL). After stirring for 1 h, additional acetic acid (0.03 mL) and excess zinc powder were added to the mixture, which was stirred for another 1 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. To a mixture of the residue in CH_2Cl_2 (1.0 mL) at 0 °C were added pyridine (0.5 mL, large excess) and 2,2,2-trichloroethyl chloroformate (0.25 mL, large excess). After stirring for 1 h, the reaction mixture was diluted with EtOAc (5 mL), and quenched with sat. aq $NaHCO_3$ (5 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc–hexane, 30%) to afford **7**.

Yield: 3.9 mg (0.0042 mmol, 44% over 2 steps); colorless oil; $[\alpha]_D^{23}$ –32 (*c* 0.16, $CHCl_3$).

IR (neat film): 3726, 3626, 3586, 2928, 2883, 2854, 2361, 2341, 1720, 1485, 1427, 1377, 1342, 1323, 1282, 1259, 1222, 1195, 1116, 1072, 1022, 939, 906, 839, 775, 667 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 8.0 Hz, 1 H), 7.50 (d, *J* = 6.8 Hz, 1 H), 7.26–7.49 (m, 8 H), 6.77 and 6.73 (s, 1 H), 6.41 and 6.40 (s, 1 H), 5.86 (s, 1 H), 5.77 (s, 1 H), 5.57 and 5.51 (s, 1 H), 5.41 (br, 1 H), 5.21 (dd, *J* = 10.4, 10.4 Hz, 1 H), 4.93 (dd, *J* = 7.2, 6.0 Hz, 1 H), 4.69–5.02 (m, 5 H), 4.20–4.35 (m, 3 H), 3.87 and 3.83 (s, 3 H), 3.74 (m, 1 H), 3.14–3.35 (m, 3 H), 2.73 (dd, *J* = 17.6, 6.0 Hz, 1 H), 2.21 (s, 3 H), 2.09 (s, 3 H), 0.71 and 0.69 (s, 9 H), –0.21 and –0.26 (s, 3 H), –0.27 and –0.31 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1, 153.5, 151.8, 149.5, 149.4, 148.1, 147.6, 146.5, 138.2, 137.4, 137.3, 131.4, 131.2, 130.2, 129.9, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.7, 127.2, 127.2, 125.5, 125.0, 124.4, 120.7, 120.6, 107.9, 101.9, 101.7, 100.7, 100.6, 95.4, 62.1, 62.1, 75.5, 75.2, 75.0, 74.8, 70.3, 68.9, 68.3, 68.1, 66.7, 66.6, 60.5, 60.3, 60.2, 60.1, 60.0, 59.9, 48.5, 48.1, 47.5, 46.7, 30.7, 30.5, 25.6, 17.8, 15.7, 15.7, 8.7, –5.9, –5.9, –6.0, –6.0.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{47}H_{56}Cl_3N_2O_9Si$: 927.2791; found: 927.2787.

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