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Synthetic studies on lemonomycin: construction of the tetracyclic core

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Abstract

A substrate-induced stereocontrol strategy was used to gain access to the tetracyclic core of (-)-lemonomycin. An advanced intermediate was prepared from a known substituted tyrosinol through a 16-step sequence, which involved a Pictet-Spengler reaction, a [3+2] dipolar cycloaddition and an enamide hydrogenation.

Keywords

(-)-Lemonomycin; Tetrahydroisoquinoline antitumor antibiotics; Pictet-Spengler reaction; [3+2] dipolar cycloaddition

1. Introduction

Lemonomycin (**1**) is a member of the tetrahydroisoquinoline (THIQ) family of antitumor antibiotics.¹ It was isolated from the fermentation broth of *Streptomyces candidus* (LL-AP191) in 1964,² and its structure was reported by He and coworkers in 2000.³ This compound showed significant *in vitro* antimicrobial activities against both gram-negative and gram-positive bacteria, including antibiotic-resistant strains, as well as against the human colon tumor cell line HCT116.^{2,3} Structurally, the compound contains the tetracyclic core found in quinocarcin⁴ and tetrazomine,⁵ which includes a 3,8-diazabicyclo ring system and a rare bis-desoxy aminosugar portion, which has only been found in a few natural products.⁶⁻¹⁰ The structural complexity and biological activities of this substance have made lemonomycin an attractive target for the synthetic community. To date, there are two total syntheses by Stoltz¹¹ and Fukuyama¹² and synthetic studies by Magnus,^{13,14} Zhu,^{15,16,17} Mulzer¹⁸ and our laboratory.¹⁹

As shown in Scheme 1, we envisioned that the final steps in the synthesis of lemonomycin (**1**) would involve a late-stage glycosylation reaction, and the formation of the quinone, hemiaminal and aldehyde hydrate functional groups. Compound **2** could be accessed through the epimerization of the southern benzylic position and the reduction of the enamide

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 Supplementary Material: ¹H and ¹³C NMR spectra of all compounds.

double bond found in tetracycle **3**. This key intermediate could be prepared from aldehyde **5** *via* azomethine ylide **4**, using a [3+2] dipolar cycloaddition approach previously developed by our group.¹⁹ This key reaction was also used for the construction of the [3,8]-diazabicyclo ring system in our total syntheses of (-)-tetrazomine²⁰ and (±)-quinocarcinamide.²¹ The tetra-hydroisoquinoline system of **5** could be formed through a Pictet-Spengler reaction involving a derivative of compound **6**, which is a known compound.²²

2. Results and discussion

Our synthetic sequence starts with substituted tyrosinol **6**, which can be prepared from commercially available L-tyrosine methyl ester according to the procedure described by Liao.²² We initially attempted to perform the direct conversion of **6** into bisilyl ether **8** using two equivalents of TBS-Cl, but the yields were inconsistent and low (<30%).^{23,24} By increasing the relative amount of TBS-Cl to six equivalents, compound **6** was converted into the tris-silylated compound **7**. Unexpectedly, the hydrolysis of the silylamine function required a prolonged vigorous stirring with aqueous NH₄Cl at room temperature (~2h) to form the bis-silyl ether **8** in 90% yield. The phenolic silyl ether was selectively cleaved with one equivalent of TBAF at 0 °C,²⁵ to afford compound **9** in 98% yield (Scheme 2).

The next step entailed the formation of the *trans*-tetrahydroisoquinoline ring *via* a Pictet Spengler reaction between **9** and ethyl glyoxalate. Previously, our group reported a similar transformation, which was performed by stirring a solution of the starting materials in acetonitrile for 3.5 days at 50°C, which afforded the *trans*- product stereospecifically.²⁶ A similar report by Zhu and coworkers involved the use of LiCl, hexafluoroisopropanol and molecular sieves, and stirring the suspension in toluene at room temperature for 48 h. Since none of these mild conditions led to the formation of the desired tetrahydroisoquinoline ring system, we decided to adapt the reaction conditions that were originally described by Zhu^{27,28} to our substrate. The amount of acetic acid was reduced from 2.5 equivalents to 0.2 equivalents to prevent cleavage of the *O*-TBS ether due to the prolonged exposure to the acid. In the present system, treatment of a solution of compound **9** and ethyl glyoxylate with CF₃CH₂OH, AcOH (0.2 eq.) and 4 Å MS afforded an 8:1 mixture of **10a** and **10b** in 82% yield. These two diastereomers were separated *via* flash chromatography and **10a** was subjected to selective acetylation,²⁹ followed by hydrogenolysis of the C-Br bond²² to afford compound **12** (Scheme 3).

Following the conditions described in our previous report,¹⁹ we converted THIQ **12** into the [3+2] dipolar cycloaddition adducts **20a** and **20b**. Thus, THIQ **12** and *N*-Boc-*N*-Bn-Gly were coupled using EDCI, and the resulting amide was treated with TBAF to cleave the *O*-TBS ether, followed by a Swern oxidation³⁰ to afford aldehyde **15** (Scheme 3).

As illustrated in Scheme 4, aldehyde **15** was dissolved in CHCl₃ and treated under aerobic conditions with TFA^{31,32,33} (50 eq.) and TEMPO (0.1 eq.), to generate iminium ion **16**, which tautomerizes to form ammonium ion **17**. This intermediate is autoxidized *in situ* to afford conjugated iminium ion **18**, which was concentrated to dryness and taken up in CHCl₃. Addition of triethylamine induces the formation of azomethine ylide **19**, which is

trapped *in situ* by *tert*-butyl acrylate to give a 2.4:1 mixture of tetracycles **20a** and **20b** in a combined 59% yield.³⁴

The deacetylation of the **20a/20b** mixture under standard methanolysis conditions provided a 5:1 mixture of **21a** and **21b** in 70% yield (Scheme 5). We suggest that **21b** decomposes under the reaction conditions at a higher rate than **21a**, which provides an explanation for both the moderate yield and the change in the diastereomeric ratio. The chemoselective reduction of the ethyl esters with one equivalent of LiAlH₄ at -10 °C, afforded a 3:1 mixture of aldehydes **22a** and **22b** in 55% yield.³⁵ We submit that the partial epimerization seen in this step is promoted by the slightly basic workup conditions. Treatment with BnBr and Na₂CO₃ formed the phenolic benzyl ethers and induced additional epimerization of the aldehyde's α carbon, to provide a 2.2:1 mixture of **23a** and **23b**³⁶ which was then reacted with DBN in THF to invert the epimeric ratio.^{20,21}

The 1:2.2 mixture of aldehydes **23a** and **23b** was then treated with sodium borohydride to afford a mixture of alcohols **24a** and **24b**, which were separated *via* flash chromatography to afford **24b** in 65% yield (Scheme 6). The sequence used to transform the **20a/20b** mixture into **24b** not only provided the desired configuration in the benzylic position but also furnished an unhindered substrate for the *N*-debenzylation of the piperazinone amine. Thus, hydrogenolysis of **24b** in glacial acetic acid (10% Pd/C, 1 atm.) effected the bis-debenzylation to afford **25** in 92% yield. Similarly, the removal of the *N*-benzyl group also provided an unhindered substrate for the hydrogenation of the enamide double bond from the *Re* face of C-3 (lemonomycin numbering). Gratifyingly, the hydrogenation of **25** with Raney[®] nickel at 100 psi²⁰ provided compound **26** in 73% yield.

3. Conclusion

In summary, we have accomplished the construction of the tetracyclic core of (-)-lemonomycin. Compound **26** was prepared from known bromotyrosinol **6** in sixteen steps. Efforts to gain access to (-)-lemonomycin through this advanced intermediate are currently under investigation.

4. Experimental section

4.1. General Methods

Unless otherwise noted, all materials were obtained from commercial sources and used without purification. All reactions requiring anhydrous conditions were performed under a positive pressure of argon using flame-dried glassware. Organic solvents were degassed with argon and dried through a solvent purification system (Pure Process Technology). Flash chromatography was performed on silica gel grade 60 (230 \times 400 mesh) from Sorbent Technologies. Thin layer chromatography was performed on glass plates coated with silica gel grade 60, from Merck. ¹H NMR and ¹³C NMR spectra were recorded on Varian 300 or 400 MHz spectrometers as indicated. Proton spectra in CDCl₃ were referenced to residual CHCl₃ at 7.26 ppm. Carbon spectra in CDCl₃ were referenced to 77.16 ppm. Proton spectra in DMSO-*d*₆ were referenced to residual CD₃SOCD₂H at 2.50 ppm. Infrared spectra were recorded on a Bruker Tensor FT-IR spectrometer. High-resolution mass spectra were

obtained using a TOF spectrometer using simultaneous electrospray (ESI) and atmospheric pressure chemical ionization (APCI). Optical rotations were recorded on a Rudolph Research Autopol polarimeter, at a wavelength of 589 nm.

4.2. (S)-1-(2-bromo-5-((tert-butyldimethylsilyloxy)-4-methoxy-3-methylphenyl)-3-((tert-butyldimethylsilyloxy)propan-2-amine (8)

To a stirred solution of compound **6** (1.55 g, 5.36 mmol, 1 eq.) (**6**) in CH₂Cl₂ (90 mL, 0.06 M), were added DMAP (327 mg, 2.68 mmol, 0.5 eq.), Et₃N (4.48 mL, 32.2 mmol, 6.00 eq.) and TBS-Cl (4.86 g, 32.2 mmol, 6 eq.). The reaction was stirred under Ar for 3 h at RT, and then aq. sat. aq. NH₄Cl (50 mL) was added and the mixture was stirred for 2h. The phases were separated, the aqueous layer was extracted with CH₂Cl₂ (2×50 mL) and the combined organic layers were rinsed with brine (50 mL), dried (Na₂SO₄), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexane/EtOAc 5:1) to give the title compound **8** (2.50 g, 90%) as a colorless oil. ¹H-NMR (400 MHz; CDCl₃): δ 6.65 (s, 1H), 3.72 (s, 3H), 3.61 (1/2 ABX, *J* = 9.7, 4.1 Hz, 1H), 3.47 (1/2 ABX, *J* = 9.7, 6.5 Hz, 1H), 3.20-3.14 (m, 1H), 2.87 (1/2 ABX, *J* = 13.4, 5.4 Hz, 1H), 2.57 (1/2 ABX, *J* = 13.4, 8.0 Hz, 1H), 2.35 (s, 3H), 1.00 (s, 9H), 0.91 (s, 9H), 0.17 (s, 6H), 0.07 (s, 3H), 0.06 (s, 3H); ¹³C-NMR (101 MHz, CDCl₃): δ 148.8, 147.6, 134.6, 133.1, 121.3, 119.4, 67.6, 60.2, 52.9, 41.3, 26.1, 25.8, 18.4, 18.4, 17.2, -4.4, -5.2; R_f (SiO₂, 2:1 hexanes/EtOAc) 0.35; [α]_D²⁵ = +0.9 ° (c=0.35, CHCl₃); IR (film, CH₂Cl₂), ν_{max} 2996, 2930, 2858, 2471, 839 cm⁻¹; HRMS (MH⁺), found 520.2103. C₂₃H₄₅BrNO₃Si₂ requires 520.2101.

4.3. (S)-5-(2-amino-3-((tert-butyldimethylsilyloxy)propyl)-4-bromo-2-methoxy-3-methylphenol (9)

To a stirred solution of compound **8** (1.59 g, 3.05 mmol, 1 eq.) in THF (100 mL, 0.03 M), under Ar, at 0 °C, was added a 1.0 solution M of TBAF in THF (3.05 mL, 3.05 mmol, 1 eq.). The reaction was stirred for 25 minutes and quenched with sat. aq. NH₄Cl (50 mL). The phases were allowed to warm to RT, the aqueous phase was extracted with EtOAc (2×50 mL) and the combined organic layers were rinsed with brine (50 mL), dried (Na₂SO₄), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, CHCl₃/MeOH 10:1) to give the title compound **9** (1.23 g, 98%) as a colorless oil. ¹H-NMR (400 MHz; CDCl₃): δ 6.77 (s, 1H), 3.73 (s, 3H), 3.71-3.66 (m, 1H), 3.56-3.50 (m, 1H), 3.27-3.24 (m, 1H), 2.92 (1/2 ABX, *J* = 13.5, 4.6 Hz, 1H), 2.62 (1/2 ABX, *J* = 13.5, 9.0 Hz, 1H), 2.34 (s, 3H), 0.92 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ¹³C-NMR (101 MHz, CDCl₃): δ 148.4, 145.0, 134.6, 132.2, 117.2, 116.1, 67.1, 60.8, 52.9, 52.7, 40.5, 26.1, 18.4, 17.2, -5.2, -5.2. R_f (SiO₂, CH₂Cl₂/MeOH 10:1) 0.4; [α]_D²⁵ = +8.3 ° (c=0.41, CHCl₃); IR (film, CH₂Cl₂), ν_{max} 3263 (br), 2954, 2928, 2856, 1578, 1471, 1092 cm⁻¹; HRMS (MH⁺), found 406.1233. C₁₇H₃₁BrNO₃Si requires 406.1236

4.4. 1S,3S)-ethyl 5-bromo-3-(((tert-butyldimethylsilyloxy)-methyl)-8-hydroxy-7-methoxy-6-methyl-1,2,3,4-tetrahydro-isoquinoline-1-carboxylate (10a) and (1R,3S)-ethyl 5-bromo-3-

(((tert-butylidimethylsilyl)oxy)methyl)-8-hydroxy-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (10b)

To a stirred solution of compound **9** (5.43 g, 13.4 mmol, 1.0 eq.) in CH₂Cl₂ (134 mL, 0.10 M), under Ar, were added, 4Å molecular sieves (2.72 g), CF₃CH₂OH (13.4 mL), AcOH (153 µL, 2.68 mmol, 0.20 eq.) and ethyl glyoxalate (50% solution in PhCH₃, 2.93 mL, 14.8 mmol, 1.1 eq.). The reaction was stirred overnight, diluted with CH₂Cl₂ (50 mL), filtered through Celite® and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 5:1) to give compound **10a** (4.78g, 73%) as a white solid and compound **10b** (610 mg, 9%) as a white solid. Compound **10a**: ¹H-NMR (400 MHz; CDCl₃): δ 6.25 (br s, 1H), 4.89 (s, 1H), 4.26-4.18 (m, 2H), 3.82 (1/2 ABX, *J* = 9.8, 3.5 Hz, 1H), 3.76 (s, 3H), 3.54 (1/2 ABX, *J* = 9.8, 8.5 Hz, 1H), 3.13-3.07 (m, 1H), 2.71 (1/2 ABX, *J* = 16.9, 4.1 Hz, 1H), 2.35 (s, 3H), 2.27 (1/2 ABX, *J* = 16.9, 11.3 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.93 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ¹³C-NMR (101 MHz, CDCl₃): δ 172.9, 145.6, 144.3, 130.8, 130.7, 120.0, 118.4, 66.9, 61.7, 61.2, 55.6, 51.6, 32.7, 26.0, 18.4, 17.0, 16.9, 14.4, 14.4, -5.1, -5.2, -5.2, -5.3; m.p. = 47 °C; R_f (SiO₂, hexanes/EtOAc 4:1) 0.40; [α]_D²⁵ = -24.3 ° (c = 0.885, CHCl₃); IR (film, CH₂Cl₂), ν_{max} 3284 (br), 2955, 2931, 2857, 1739, 1462, 1178 cm⁻¹; HRMS (MH⁺), found 490.1446. C₂₁H₃₅BrNO₅Si requires 490.1447. Compound **10b**: ¹H-NMR (400 MHz; CDCl₃): δ 5.86 (br s, 1H), 4.78 (s, 1H), 4.30-4.15 (m, 2H), 3.80 (1/2 ABX, *J* = 9.9, 4.1 Hz, 1H), 3.74 (s, 3H), 3.68 (1/2 ABX, *J* = 9.9, 6.6 Hz, 1H), 2.95 -2.89 (m, 1H), 2.77 (1/2 ABX, *J* = 16.6, 3.1 Hz, 1H), 2.44 (1/2 ABX, *J* = 16.6, 8.5 Hz, 2H), 2.36 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.92 (s, 9H), 0.09 (s, 6H); ¹³C-NMR (101 MHz, CDCl₃): δ 172.8, 145.1, 143.9, 132.0, 130.4, 120.3, 118.4, 66.7, 61.5, 61.4, 58.4, 54.5, 33.0, 26.1, 26.0, 18.5, 17.0, 14.2, -5.1, -5.2; m.p. = 95 °C; R_f (SiO₂, hexanes/EtOAc 4:1) 0.37; [α]_D²⁵ = -36.7 ° (c = 0.600, CHCl₃); IR (film, CH₂Cl₂), ν_{max} 3314 (br), 2955, 2931, 2858, 1738, 1463, 1257 cm⁻¹; HRMS (MH⁺), found 490.1456. C₂₁H₃₅BrNO₅Si requires 490.1447.

4.5. (1S,3S)-ethyl 8-acetoxy-5-bromo-3-(((tert-butylidimethyl-silyl)oxy)methyl)-7-methoxy-6-methyl-1,2,3,4-tetrahydro-isoquinoline-1-carboxylate (11)

To a stirred solution of compound **10a** (840 mg, 1.72 mmol, 1.0 eq.) in acetone (34 mL, 0.05 M), under Ar, were added K₂CO₃ (1.20 g, 8.64 mmol, 5.0 eq.) and acetic anhydride (162 µL, 1.72 mmol, 1.0 eq.). The suspension was stirred overnight, the solvent was evaporated and the residue was partitioned between water (25 mL) and EtOAc (25 mL). The aqueous phase was extracted with EtOAc (2×25 mL) and the combined organic layers were rinsed with brine (50 mL), dried (Na₂SO₄), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 5:1) to give the title compound **11** (800 mg g, 88%) as a colorless oil. ¹H-NMR (400 MHz; CDCl₃): δ 4.66 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.81 (1/2 ABX, *J* = 9.8, 3.5 Hz, 1H), 3.70 (s, 3H), 3.55 (1/2 ABX, *J* = 9.8, 7.6 Hz, 1H), 3.22-3.16 (m, 1H), 2.74 (1/2 ABX, *J* = 16.9, 4.1 Hz, 2H), 2.38 (s, 3H), 2.37-2.33 (m, 1H), 2.29 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.921 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); ¹³C-NMR (101 MHz, CDCl₃): δ 171.8, 167.9, 148.6, 141.0, 132.5, 131.5, 125.9, 125.8, 66.7, 61.5, 61.1, 55.8, 51.0, 32.6, 26.0, 20.6, 18.4, 17.1, 14.4, -5.2, -5.3. R_f (SiO₂, hexanes/EtOAc 4:1) 0.45; [α]_D²⁵ = -21.1 ° (c = 1.10, CHCl₃); IR (film, CH₂Cl₂),

ν_{\max} 2956, 2932, 2856, 1780, 1737, 1462, 1192 cm^{-1} ; HRMS (MH^+), found 532.1561. $\text{C}_{23}\text{H}_{37}\text{BrNO}_6\text{Si}$ requires 530.1574

4.6. (1S,3S)-ethyl 8-acetoxy-3-(((tert-butyl dimethylsilyl)oxy)methyl)-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (12)

A solution of compound **11** (2.90 mg, 5.46 mmol) in MeOH (110 mL, 0.05 M), and Pearlman's catalyst (20% $\text{Pd}(\text{OH})_2/\text{C}$, 580 mg) were placed in a Fisher-Porter bottle, under Ar. The mixture was sparged with Ar for 5 minutes and the vessel was filled with hydrogen gas at 50 psi. The reaction was vigorously stirred overnight and then filtered through Celite® and the vessel was rinsed with MeOH (50 mL) and EtOAc (50 mL). The solution was concentrated under vacuum to dryness and partitioned between sat. aq. NaHCO_3 (75 mL) and EtOAc (75 mL). The aqueous phase was extracted with EtOAc (2×75 mL) and the combined organic layers were rinsed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 5:1, 4:1 and 3:1) to give the title compound **12** (2.25 mg, 91%) as a colorless oil. $^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 6.85 (s, 1H), 4.65 (s, 1H), 4.17 (q, $J = 7.1$ Hz, 2H), 3.73 (1/2 ABX, $J = 9.8, 3.7$ Hz, 1H), 3.70 (s, 3H), 3.52 (1/2 ABX, $J = 9.8, 7.2$ Hz, 1H), 3.28-3.22 (m, 1H), 2.59 (1/2 ABX, $J = 16.1, 4.2$ Hz, 1H), 2.50 (1/2 ABX, $J = 16.1, 10.7$ Hz, 1H), 2.28 (s, 3H), 2.27 (s, 3H), 1.26 (t, $J = 7.1$ Hz, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 2H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ 172.2, 168.3, 148.2, 141.6, 131.5, 131.1, 129.2, 124.0, 66.7, 61.3, 60.6, 55.6, 50.7, 30.2, 26.0, 20.6, 18.4, 16.0, 14.4, -5.2, -5.3. R_f (SiO_2 , hexanes/EtOAc 4:1) 0.42; $[\alpha]_D^{25} = -17^\circ$ ($c = 0.42$, CHCl_3); IR (film, CH_2Cl_2), ν_{\max} 2954, 2929, 2857, 1775, 1737, 1197 cm^{-1} ; HRMS (MH^+), found 452.244. $\text{C}_{23}\text{H}_{38}\text{NO}_6\text{Si}$ requires 452.2468.

4.7. (1S,3S)-ethyl 8-acetoxy-2-(2-(benzyl(tert-butoxycarbonyl)amino)acetyl)-3-(((tert-butyl dimethylsilyl)oxy)methyl)-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (13)

A solution of compound **12** (2.20 g, 4.87 mmol, 1.0 eq.), *N*-Bn-*N*-Boc-glycine (2.58 g, 9.74 mmol, 2.0 eq.) and EDCI (1.40 g, 7.31 mmol, 1.5 eq.) in CH_2Cl_2 (2.5 mL, 2 M), under Ar, was stirred for 2.5 days. The reaction was diluted with EtOAc (200 mL), and the solution was extracted with water (100 mL), sat. aq. NaHCO_3 (2 × 100 mL) and brine (100 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 4:1, 3:1 and 2:1) to give the title compound **13** (3.15 g, 93%) as a colorless oil. $^1\text{H-NMR}$ (300 MHz; $\text{DMSO-}d_6$, 393 K, mixture of rotamers): δ 7.36-7.24 (m, 5H), 6.94 (s, 1H), 6.88 (s, 1H, minor rotamer), 5.48 (s, 1H), 4.49 (1/2 AB, $J = 15.6$ Hz, 1H), 4.39 (1/2 AB, $J = 15.6$ Hz, 1H), 4.33-4.27 (m, 2H), 4.13-3.87 (m, 3H), 3.69 (s, 3H), 3.66 (s, 1H, minor rotamer), 3.34-3.10 (br m, 2H), 3.07-2.91 (br m, 2H), 2.33 (s, 3H), 2.24 (s, 3H), 2.23 (s, 3H, minor rotamer), 2.23 (s, 1H, minor rotamer), 1.41 (s, 9H), 1.21 (t, $J = 7.0$ Hz, 3H, minor rotamer), 1.12 (t, $J = 7.1$ Hz, 3H), 0.92 (d, $J = 0.6$ Hz, 2H), 0.79 (s, 9H), 0.08 (s, 3H, minor rotamer), 0.04 (s, 3H, minor rotamer), 0.03 (m, 3H, minor rotamer), -0.11 (s, 3H), -0.14 (s, 3H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3 , mixture of rotamers): δ 170.1, 169.7, 168.1, 168.0, 156.1, 149.6, 129.2, 129.1, 128.7, 128.4, 127.8, 127.5, 127.5, 127.4, 121.6, 80.5, 80.4, 71.6, 61.9, 61.3, 60.7, 53.6, 53.6, 53.5, 53.0, 53.0, 52.9, 52.9, 50.9, 47.7, 29.5, 28.5, 28.4, 26.0, 26.0, 25.9, 20.9, 18.3, 16.1,

16.0, 14.0, 13.9, -5.3, -5.4, -5.4, -5.7. R_f (SiO₂, hexanes/EtOAc 3:1) 0.30; $[\alpha]_D^{25} = 26.8^\circ$ ($c = 0.995$, CHCl₃); IR (film, CH₂Cl₂), ν_{\max} 2956, 2931, 2857, 1781, 1743, 1703, 1668, 1199 cm⁻¹; HRMS (MH⁺), found 699.3666. C₃₇H₅₅N₂O₉Si requires 699.3677.

4.8. (1S,3S)-ethyl 2-(2-(benzyl(tert-butoxycarbonyl)amino)acetyl)-8-hydroxy-3-(hydroxymethyl)-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (14)

To a solution of compound **13** (765 mg, 1.09 mmol, 1.0 eq.) in THF (10 mL, 0.11 M), under Ar, were added MeOH (625 μ L) and TBAF (1.0 M solution in THF, 2.18 mL, 2.0 eq.). The reaction was stirred overnight and quenched with sat. aq. NH₄Cl (50 mL) and then diluted with EtOAc (100 mL). The phases were separated, the aqueous phase was extracted with EtOAc (2 \times 25 mL) and the combined organic layers were rinsed with brine (50 mL), dried (Na₂SO₄), filtered, and concentrated under vacuum. The crude material was dissolved in the minimal amount of CH₂Cl₂ and purified by flash chromatography (silica gel, hexanes/EtOAc 2:1, then 1:1) to give the title compound **14** (525 mg, 82%) as a white amorphous solid. ¹H-NMR (300 MHz; DMSO-*d*₆, 393 K): δ 7.36-7.26 (m, 5H), 6.96 (s, 1H), 5.50 (s, 1H), 4.49-4.40 (br m, 2H), 4.27-4.17 (br m, 2H), 4.07-3.89 (m, 3H), 3.70 (s, 3H), 3.19-3.03 (br m, 2H), 2.94-2.81 (m, 2H, overlapped with H₂O signal), 2.34 (s, 3H), 2.25 (s, 3H), 1.41 (s, 9H), 1.13 (t, $J = 7.1$ Hz, 3H); ¹³C-NMR (101 MHz, CDCl₃, mixture of rotamers): δ 170.2, 170.1, 168.0, 168.0, 156.4, 154.8, 152.8, 149.7, 145.0, 141.7, 141.5, 138.1, 138.1, 138.0, 132.9, 132.8, 130.2, 130.0, 128.7, 128.5, 128.4, 128.3, 128.1, 127.8, 127.8, 127.7, 127.5, 127.5, 127.1, 124.2, 121.2, 80.9, 80.4, 65.1, 63.8, 62.0, 60.6, 53.7, 53.5, 52.7, 52.0, 51.0, 47.9, 30.6, 30.0, 29.5, 28.5, 28.4, 20.9, 16.2, 13.8; m.p. 80 °C; R_f (SiO₂, hexanes/EtOAc 1:1) 0.35; $[\alpha]_D^{25} = 78^\circ$ ($c = 0.44$, CHCl₃); IR (film, CH₂Cl₂), ν_{\max} 3455 (br), 2977, 2935, 1780, 1742, 1698, 1663, 1200 cm⁻¹; HRMS (MH⁺), found 585.2816. C₃₁H₄₁N₂O₉ requires 585.2812.

4.9. (1S,3S)-ethyl 2-(2-(benzyl(tert-butoxycarbonyl)amino)-acetyl)-3-formyl-8-hydroxy-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (15)

A solution of oxalyl chloride (825 μ L, 9.75 mmol, 3.0 eq.) in CH₂Cl₂ (22.5 mL), under Ar, was cooled to -78 °C, and DMSO (921 μ L, 13.0 mmol, 4.0 eq.) was added dropwise. The resulting mixture was stirred an additional 30 min at -78 °C. A solution of compound **14** (1.90 mg, 3.25 mmol, 1.0 eq.) in CH₂Cl₂ (10 mL) at RT was then added slowly by cannula, and the mixture continued to stir at -78 °C for 30 min. Triethylamine (4.50 mL, 32.5 mmol, 10 eq.) was then added dropwise, and the solution was stirred for 15 min at -78 °C and an additional 30 min at 0 °C. The reaction was quenched with sat. aq. NH₄Cl (50 mL) and allowed to warm to RT. The layers were separated, the aqueous phase was extracted with CH₂Cl₂ (3 \times 50 mL) and the combined organic layers were rinsed with brine (50 mL), dried (Na₂SO₄), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 2:1, then 1:1) to give the title compound **15** (1.65 g, 87%) as a colorless oil, which solidifies upon standing to afford a colorless amorphous solid. ¹H-NMR (300 MHz; DMSO-*d*₆, 373 K, mixture of rotamers): δ 9.54 (s, 1H, minor rotamer), 9.28 (s, 1H), 7.35-7.23 (m, 5H), 7.08 (s, 1H, minor rotamer), 7.01 (s, 1H), 6.94 (s, 1H, minor rotamer), 6.91 (s, 1H, minor rotamer), 5.70 (s, 1H), 5.10-4.88 (m, 1H), 4.52-4.28 (m, 3H), 4.26-4.14 (m, 1H), 4.13-3.98 (m, 2H), 3.97-3.86 (m, 1H), 3.69 (s, 3H, minor rotamer), 3.68 (s, 3H, minor rotamer), 3.67 (s, 3H), 3.38-3.27 (m, 1H), 2.34 (s,

3H), 2.32 (s, 3H, minor rotamer), 2.25 (s, 3H, minor rotamer), 2.24 (s, 3H, minor rotamer), 2.22 (s, 3H), 1.41 (s, 9H, minor rotamer), 1.40 (s, 9H), 1.36 (s, 9H, minor rotamer), 1.34 (s, 9H, minor rotamer), 1.12 (t, $J = 7.2$ Hz, 3H). ^{13}C -NMR (101 MHz, CDCl_3 , mixture of rotamers): δ 201.2, 199.6, 199.2, 169.9, 167.8, 155.9, 155.8, 150.2, 149.7, 141.5, 141.0, 137.6, 137.5, 137.5, 133.6, 133.3, 128.6, 128.6, 128.5, 128.5, 128.4, 128.1, 128.0, 127.9, 122.6, 122.1, 81.0, 80.8, 62.7, 62.2, 60.9, 60.6, 60.6, 60.2, 53.7, 53.5, 53.3, 50.9, 47.8, 47.6, 47.1, 29.6, 28.5, 28.5, 28.4, 28.2, 20.9, 16.2, 13.8; m.p. 78 °C; R_f (SiO_2 , hexanes/EtOAc 1:1) 0.40; $[\alpha]_D^{25} = 35^\circ$ ($c = 0.23$, CHCl_3); IR (film, CH_2Cl_2), ν_{max} 2978, 2937, 1780, 1742, 1699, 1673, 1200 cm^{-1} ; HRMS (MH^+), found 583.2654. $\text{C}_{31}\text{H}_{39}\text{N}_2\text{O}_9$ requires 583.2656.

4.10. (5S,8S,10R,11S)-10-tert-butyl 5-ethyl 4-acetoxy-13-benzyl-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-b]isoquinoline-5,10-dicarboxylate (20a) and (5R,8S,10R,11S)-10-tert-butyl 5-ethyl 4-acetoxy-13-benzyl-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-b]isoquinoline-5,10-dicarboxylate (20b)

To solution of compound **15** (1.65 g, 2.83 mmol, 1.0 eq.) in CHCl_3 (28 mL, 0.1 M), under air, were added TEMPO (44 mg, 0.28 mmol, 0.10 eq.), and trifluoroacetic acid (10.8 mL, 142 mmol, 50 eq.) and the flask was loosely capped with a Teflon[®] stopper. The solution was stirred for 4h, the solvent was evaporated to dryness under vacuum and the residue was taken up in CHCl_3 . The solution was cooled to 0 °C and then *tert*-butyl acrylate (8.20 mL, 56.6 mmol, 20 eq.) and triethylamine (3.95 mL, 28.3 mmol, 10 eq.) were added. The reaction was allowed to warm to RT and stirred overnight. The solution was diluted with EtOAc (200 mL), rinsed with sat. aq. NH_4Cl (50 mL) and brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 4:1, 3:1) to afford a 2.4:1 mixture of the title compounds **20a** and **20b** (985 mg, 59%) as a yellow oil, which was used in the next step without further purification. ^1H -NMR (400 MHz; CDCl_3): δ 7.41-7.22 (m, 5H), 6.74 (s, 1H, minor diastereomer), 6.73 (s, 1H), 6.36 (s, 1H, minor diastereomer), 6.27 (s, 1H), 5.51 (s, 1H, minor diastereomer), 5.50 (s, 1H), 4.28-3.96 (m, 6H), 3.89-3.71 (m, 2H), 3.75 (s, 3H, minor diastereomer), 3.72 (s, 3H), 2.80-2.67 (m, 2H), 2.45 (dd, $J = 13.0, 9.8$ Hz, 1H, minor diastereomer), 2.40 (s, 3H), 2.39 (s, 3H, minor diastereomer), 2.28 (s, 3H, minor diastereomer), 2.26 (s, 3H), 2.13 (dd, $J = 13.3, 9.5$ Hz, 1H), 1.46 (s, 9H, minor diastereomer), 1.42 (s, 9H), 1.24 (t, $J = 7.1$ Hz, 3H), 1.20 (t, $J = 7.2$ Hz, 3H, minor diastereomer); ^{13}C -NMR (101 MHz, CDCl_3): δ 172.4, 171.7, 168.7, 167.9, 149.9, 141.6, 133.1, 129.0, 128.6, 128.4, 128.4, 127.4, 127.3, 126.6, 125.0, 124.8, 117.3, 116.7, 104.6, 103.1, 81.4, 81.3, 65.1, 64.1, 63.1, 62.6, 62.4, 62.3, 60.7, 60.6, 52.7, 51.8, 51.3, 50.7, 50.0, 48.0, 34.3, 31.9, 31.7, 28.2, 22.8, 21.0, 16.1, 14.2, 14.0; R_f (SiO_2 , hexanes/EtOAc 3:1) 0.5; $[\alpha]_D^{25} = -65.0^\circ$ ($c = 0.320$, CH_2Cl_2); IR (film, CH_2Cl_2), ν_{max} 2980, 2936, 1781, 1741, 1693, 1651 cm^{-1} ; HRMS (MH^+), found 591.2712. $\text{C}_{33}\text{H}_{39}\text{N}_2\text{O}_8$ requires 591.2706.

4.11. (5S,8S,10R,11S)-10-tert-butyl 5-ethyl 13-benzyl-4-hydroxy-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-b]isoquinoline-5,10-dicarboxylate (21a) and (5R,8S,10R,11S)-10-tert-butyl 5-ethyl 13-benzyl-4-hydroxy-3-methoxy-2-methyl-7-

oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-b]isoquinoline-5,10-dicarboxylate (21b)

To a stirred solution of a 2.6:1 mixture of compounds **20a** and **20b** (410 mg, 0.695 mmol, 1.0 eq.) in THF/MeOH 1:1 (14 mL, 0.05 M), under Ar, was added K₂CO₃ (192 mg, 1.39 mmol, 2.0 eq.). The suspension was stirred for 2.5 h, the solvent was evaporated and the residue was partitioned between phosphate buffer (0.1 M, pH = 7.5, 50 mL) and EtOAc (33 mL). The aqueous phase was extracted with EtOAc (2×33 mL) and the combined organic layers were rinsed with brine (50 mL), dried (Na₂SO₄), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 4:1) to afford a 5:1 mixture of the title compounds **21a** and **21b** (255 mg, 67%) as a pale yellow oil, which was used in the next step without further purification. ¹H-NMR (400 MHz; CDCl₃): δ 7.38-7.24 (m, 5H), 6.76 (s, 1H), 6.63 (s, 1H, minor diastereomer), 6.49 (s, 1H, minor diastereomer), 6.43 (s, 1H, minor diastereomer), 6.42 (s, 1H), 6.39 (s, 5H), 5.46 (s, 1H, minor diastereomer), 5.45 (s, 1H, minor diastereomer), 4.24 (q, *J* = 7.1 Hz, 2H), 4.19-3.9 (m, 5H), 4.07 (s, 1H), 3.86 (d, *J* = 7.5 Hz, 1H), 3.84 (s, 1H, minor diastereomer), 3.82 (s, 3H), 3.31 (dd, *J* = 9.8, 6.0 Hz, 1H, minor diastereomer), 2.79 (dd, *J* = 9.5, 4.6 Hz, 1H), 2.74-2.66 (m, 1H), 2.46 (dd, *J* = 13.0, 9.9 Hz, 1H, minor diastereomer), 2.26 (s, 3H, minor diastereomer), 2.24 (s, 3H), 2.13 (dd, *J* = 13.4, 9.6 Hz, 6H), 1.46 (s, 9H, minor diastereomer), 1.42 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H, minor diastereomer); ¹³C-NMR (101 MHz, CDCl₃): δ 172.4, 171.9, 170.7, 170.6, 170.4, 168.9, 146.9, 146.8, 146.2, 138.5, 138.0, 136.1, 134.2, 131.9, 131.7, 128.5, 127.4, 127.3, 126.6, 126.0, 119.1, 119.1, 110.8, 103.4, 81.3, 64.3, 62.7, 62.6, 60.8, 60.8, 52.2, 52.2, 52.1, 51.5, 50.8, 48.2, 32.1, 28.2, 28.1, 22.8, 15.9, 14.3; R_f (SiO₂, hexanes/EtOAc 2:1) 0.45; [α]_D²⁵ = -73.6 ° (c = 0.282, CH₂Cl₂); IR (film, CH₂Cl₂), ν_{max} 3374 (br), 2980, 2938, 1736, 1689, 1647, 1154 cm⁻¹; HRMS (MH⁺), found 549.2606. C₃₁H₃₇N₂O₇ requires 549.2601.

4.12. (5S,8S,10R,11S)-tert-butyl 13-benzyl-5-formyl-4-hydroxy-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epimino-azepino[1,2-b]isoquinoline-10-carboxylate (22a) and (5R,8S,10R,11S)-tert-butyl 13-benzyl-5-formyl-4-hydroxy-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-b]isoquinoline-10-carboxylate (22b)

A solution of LiAlH₄ in THF (1.0 M, 447 μL, 0.447 mmol, 1.0 eq.) was added dropwise to a solution of a 5:1 mixture of compounds **21a** and **21b** (245 mg, 0.447 mmol, 1.0 eq.) in THF (9 mL, 0.05 M), under Ar, at -10 °C. The solution was stirred for 10 minutes at this temperature, quenched with EtOAc (12 mL) and sat. aq. Rochelle's salt (12 mL) and allowed to warm to RT. The flask was covered with aluminum foil and stirred overnight under a stream of Ar. The solution was diluted with phosphate buffer (0.1 M, pH = 7.5, 50 mL), the phases were separated and aqueous phase was extracted with EtOAc (3×33 mL) and the combined organic layers were rinsed with brine (25 mL), dried (Na₂SO₄), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 4:1) to afford a 3:1 mixture of the title compounds **22a** and **22b** (124 mg, 55%) as a pale yellow oil, which was used in the next step without further purification. ¹H-NMR (400 MHz; CDCl₃): δ 9.48 (s, 1H), 9.38 (s, 1H, minor diastereomer), 7.41-7.23 (m, 5H), 6.58 (s, 1H), 6.57 (s, 1H, minor diastereomer), 6.43 (s, 1H, minor diastereomer), 6.41 (s, 1H), 6.18 (s, 1H, minor diastereomer), 6.17 (s, 1H, minor

diastereomer), 4.25 (1/2 AB, $J = 13.5$ Hz, 1H), 4.18 (1/2 AB, $J = 13.5$ Hz, 1H), 4.07 (s, 1H), 4.00 (s, 1H, minor diastereomer), 3.83 (s, 3H, minor diastereomer), 3.81 (s, 3H, minor diastereomer), 3.40 (dd, $J = 9.7, 6.0$ Hz, 1H, minor diastereomer), 2.81 (dd, $J = 9.5, 4.7$ Hz, 1H), 2.73-2.67 (m, 1H), 2.59 (dd, $J = 13.0, 9.8$ Hz, 1H, minor diastereomer), 2.28 (s, 3H, minor diastereomer), 2.26 (s, 3H), 2.15 (dd, $J = 13.4, 9.6$ Hz, 1H), 1.48 (s, 9H, minor diastereomer), 1.46 (s, 9H); $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ 192.1, 191.3, 172.5, 171.9, 170.1, 145.7, 144.6, 138.6, 138.0, 136.6, 135.3, 131.5, 128.8, 128.4, 127.5, 127.2, 119.4, 119.2, 107.3, 104.0, 102.7, 102.6, 81.4, 64.1, 64.0, 62.9, 62.8, 61.2, 61.1, 58.6, 58.5, 51.6, 50.8, 48.8, 34.7, 32.4, 31.7, 29.8, 28.1, 22.8, 16.0, 14.3; Rf (SiO_2 , hexanes/EtOAc 2:1) 0.42; $[\alpha]_{\text{D}}^{25} = -64.8^\circ$ ($c = 0.250$, CH_2Cl_2); IR (film, CH_2Cl_2), ν_{max} 3331 (br), 2977, 2935, 1733, 1679, 1642, 1154 cm^{-1} ; HRMS (MH^+), found 505.2345. $\text{C}_{29}\text{H}_{33}\text{N}_2\text{O}_6$ requires 505.2339.

4.13. (5S,8S,10R,11S)-tert-butyl 13-benzyl-4-(benzyloxy)-5-formyl-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-b]isoquinoline-10-carboxylate (23a) and (5R,8S,10R,11S)-tert-butyl 13-benzyl-4-(benzyloxy)-5-formyl-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-b]isoquinoline-10-carboxylate (5R,8S,10R,11S)-tert-butyl 13-benzyl-4-(benzyloxy)-5-formyl-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-b]isoquinoline-10-carboxylate (23b)

To a stirred solution of a 3:1 mixture of compounds **22a** and **22b** (115 mg, 0.228 mmol, 1.0 eq.) and benzyl bromide (108 μL , 0.912 mmol, 4.0 eq.) in DMF (7.6 mL, 0.03 M), under Ar, were added tetrabutylammonium iodide (9.0 mg, 0.023 mmol, 0.10 eq.) and finely ground anhydrous Na_2CO_3 (241 mg, 2.28 mmol, 10 eq.). The mixture was vigorously stirred for 2h and diluted with water (25 mL) and phosphate buffer (0.1 M, pH = 7.5, 25 mL). The aqueous phase was extracted with EtOAc (3 \times 33 mL) and the combined organic layers were rinsed with brine (25 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 6:1, 4:1) to afford a 2.2:1 mixture of compounds **23a** and **23b** (88 mg, 65%) as a pale yellow oil, which was used in the next step without further purification. $^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 9.32 (s, 1H), 9.19 (s, 1H minor diastereomer), 7.48-7.22 (m, 10H), 6.63 (s, 1H, minor diastereomer), 6.62 (s, 1H), 6.38 (s, 1H, minor diastereomer), 6.36 (s, 1H), 5.37 (s, 1H), 5.36 (s, minor diastereomer), 5.28 (1/2 AB, $J = 11.1$ Hz, 1H, minor diastereomer), 5.26 (1/2 AB, $J = 11.1$ Hz, 2H), 5.20 (1/2 AB, $J = 11.1$ Hz, 1H, minor diastereomer), 5.14 (1/2 AB, $J = 11.1$ Hz, 1H), 4.20 (1/2 AB, $J = 13.5$ Hz, 1H), 4.14 (1/2 AB, $J = 13.5$ Hz, 1H), 4.05 (s, 1H), 3.97 (s, 1H, minor diastereomer), 3.86 (s, 3H, minor diastereomer), 3.84 (s, 3H), 3.80 (1/2 AB, $J = 13.5$ Hz, 1H) 3.79 (d, $J = 7.4$ Hz, 1H), 3.75 (d, $J = 6.9$ Hz, minor diastereomer), 3.68 (1/2 AB, $J = 13.5$ Hz, 1H, minor diastereomer), 3.37 (dd, $J = 9.7, 6.1$ Hz, 1H, minor diastereomer), 2.78 (dd, $J = 9.6, 4.7$ Hz, 1H), 2.71-2.64 (m, 2H), 2.53 (1/2 ABX, $J = 13.1, 9.9$ Hz, 1H, minor diastereomer), 2.28 (s, 3H, minor diastereomer), 2.26 (s, 3H), 2.10 (dd, $J = 13.3, 9.7$ Hz, 1H), 1.45 (s, 9H minor diastereomer), 1.44 (s, 9H); $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ 192.5, 191.7, 171.9, 169.8, 168.8, 150.4, 150.3, 148.3, 148.1, 138.6, 138.1, 136.9, 136.9, 136.6, 135.3, 133.7, 128.9, 128.8, 128.8, 128.6, 128.6, 128.5, 128.5, 128.4, 128.3, 127.4, 127.2, 126.9, 123.1, 122.8, 115.0, 114.6, 103.9, 102.5, 81.4, 81.2, 75.0, 75.0, 65.0, 63.9, 63.1, 62.8, 60.5, 58.8, 57.3, 52.8, 51.6, 48.8, 34.7, 32.2, 28.2, 16.0, 16.0; Rf (SiO_2 , hexanes/EtOAc 4:1) 0.45; $[\alpha]_{\text{D}}^{25} = -64^\circ$ ($c = 0.32$, CH_2Cl_2); IR (film, CH_2Cl_2), ν_{max} 3030,

2976, 2934, 1733, 1688, 1646, 1154 cm^{-1} ; HRMS (MH^+), found 595.2801. $\text{C}_{36}\text{H}_{39}\text{N}_2\text{O}_6$ requires 595.2808.

To a stirred solution of a 2.2:1 mixture of compounds **23a** and **23b** (88 mg, 0.15 mmol, 1.0 eq.) in THF (2 mL, 0.08 M), under Ar, was added DBN (19 μL , 0.15 mmol, 1.0 eq.). The mixture was stirred for 30 minutes and then diluted with phosphate buffer (0.1 M, pH = 7.5, 50 mL) and water (50 mL). The aqueous phase was extracted with EtOAc (3 \times 33 mL) and the combined organic layers were rinsed with brine (25 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was dissolved in the minimal amount of EtOAc purified by flash chromatography (silica gel, hexanes/EtOAc 4:1) to afford a 1:2.2 mixture of compounds **23a** and **23b** (64 mg, 72%) as a pale yellow oil, which was used in the next step without further purification. $^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 9.32 (s, 1H, minor diastereomer), 9.19 (s, 1H), 7.48-7.24 (m, 10H), 6.63 (s, 1H), 6.62 (s, 1H, minor diastereomer), 6.38 (s, 1H), 6.36 (s, 1H, minor diastereomer), 5.37 (s, 1H, minor diastereomer), 5.36 (s, 1H), 5.28 (1/2 AB, $J = 11.1$ Hz, 1H), 5.26 (1/2 AB, $J = 11.1$ Hz, 1H, minor diastereomer), 5.19 (1/2 AB, $J = 11.1$ Hz, 1H), 5.13 (1/2 AB, $J = 11.2$ Hz, 2H, minor diastereomer), 4.20 (1/2 AB, $J = 13.4$ Hz, 1H, minor diastereomer), 4.14 (1/2 AB, $J = 13.5$ Hz, 1H minor diastereomer), 4.05 (s, 1H, minor diastereomer), 3.97 (s, 1H), 3.86 (s, 3H, minor diastereomer), 3.84 (s, 3H, minor diastereomer), 3.81 (1/2 AB, $J = 13.6$ Hz, 1H), 3.79 (d, $J = 6.2$ Hz, 4H), 3.75 (d, $J = 6.6$ Hz, 3H), 3.68 (1/2 AB, $J = 13.4$ Hz, 3H), 3.37 (dd, $J = 9.8, 6.0$ Hz, 1H), 2.78 (dd, $J = 9.5, 4.7$ Hz, 1H, minor diastereomer), 2.71-2.65 (m, 2H), 2.53 (1/2 ABX, $J = 13.0, 9.9$ Hz, 3H), 2.28 (s, 3H), 2.26 (s, 3H, minor diastereomer), 2.10 (dd, $J = 13.4, 9.5$ Hz, 1H, minor diastereomer), 1.45 (s, 9H), 1.44 (s, 9H, minor diastereomer); $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ 192.5, 191.7, 172.5, 171.9, 168.8, 150.4, 148.1, 138.0, 136.9, 135.3, 133.7, 128.9, 128.8, 128.8, 128.6, 128.5, 128.4, 128.3, 127.4, 127.2, 126.9, 123.1, 122.8, 115.0, 114.6, 103.9, 102.5, 81.4, 81.2, 75.0, 75.0, 65.0, 63.9, 63.1, 62.7, 60.4, 58.8, 57.3, 52.7, 51.6, 50.9, 48.8, 34.7, 32.2, 28.2, 28.1, 16.0, 16.0; R_f (SiO_2 , hexanes/EtOAc); $[\alpha]_D^{25} = +27^\circ$ ($c = 0.22$, CHCl_3); IR (film, CH_2Cl_2), ν_{max} 3029, 2969, 2935, 1732, 1688, 1647, 1154 cm^{-1} ; HRMS (MH^+), 595.2789. $\text{C}_{36}\text{H}_{39}\text{N}_2\text{O}_6$ requires 595.2808.

4.14. (5S,8S,10R,11S)-tert-butyl 13-benzyl-4-(benzyloxy)-5-(hydroxymethyl)-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-b]isoquinoline-10-carboxylate (24a) and (5R,8S,10R,11S)-tert-butyl 13-benzyl-4-(benzyloxy)-5-(hydroxymethyl)-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-b]isoquinoline-10-carboxylate (24b)

To a stirred solution of a mixture of compounds **23a** and **23b** (60 mg, 0.10 mmol) in EtOH (5 mL, 0.20 M), at 0 $^\circ\text{C}$, under Ar, was added NaBH_4 (30 mg, 0.80 mmol 8.0 eq.). The reaction was stirred at RT for 2 hours, quenched with 1N HCl (2.4 mL, 2.40 mmol, 24 eq.) and diluted with phosphate buffer (0.1 M, pH = 7.5, 50 mL). The aqueous phase was extracted with EtOAc (3 \times 25 mL) and the combined organic layers were rinsed with brine (25 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 4:1) to afford compounds **23a** (18 mg, 30%) as a colorless oil and compound **23b** (38 mg, 65%) as a colorless oil. Compound **23a**: $^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 7.50-7.22 (m, 10H), 6.62 (s, 1H), 6.14 (t, J

= 6.1 Hz, 1H), 5.48 (s, 1H), 5.18 (1/2 AB, $J = 11.1$ Hz, 1H), 5.09 (1/2 AB, $J = 11.1$ Hz, 1H), 4.10 (s, 1H), 3.97 (1/2 AB, $J = 13.3$ Hz, 1H), 3.87 (1/2 AB, $J = 13.3$ Hz, 1H), 3.79 (d, $J = 7.7$ Hz, 1H), 3.73 (s, 1H), 2.69 (ddt, $J = 27.0, 9.0, 4.6$ Hz, 2H), 2.25 (s, 3H), 2.06 (dd, $J = 13.3, 9.5$ Hz, 1H), 1.90 (br t, 6.0 Hz, 1H), 1.44 (s, 9H); $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ 171.9, 171.7, 150.5, 148.2, 138.3, 137.2, 135.6, 132.6, 128.7, 128.5, 128.4, 128.4, 127.6, 127.3, 122.1, 120.1, 103.7, 81.3, 75.1, 65.4, 64.2, 62.7, 60.4, 51.7, 51.3, 50.7, 31.6, 28.1, 28.1, 15.9, 14.3; R_f (SiO_2 , hexanes/EtOAc 4:1) 0.12; $[\alpha]_D^{25} = -60.0^\circ$ ($c = 0.895$, CHCl_3); IR (film, CH_2Cl_2), ν_{max} 3447 (br), 3063, 3030, 2934, 2870, 1730, 1676, 1636, 1154 cm^{-1} ; HRMS (MH^+), found 597.2971. $\text{C}_{36}\text{H}_{41}\text{N}_2\text{O}_6$ requires 597.2965. Compound **24b**: $^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 6.62 (s, 1H), 6.09 (dd, $J = 8.4, 4.4$ Hz, 1H), 5.45 (s, 1H), 5.17 (1/2 AB, $J = 11.1$ Hz, 1H), 5.14 (1/2 AB, $J = 11.1$ Hz, 1H), 3.95 (s, 1H), 3.83 (s, 3H), 3.78 (d, $J = 13.5$ Hz, 1H), 3.73 (d, $J = 6.6$ Hz, 1H), 3.63 (d, $J = 13.4$ Hz, 1H), 3.63-3.50 (m, 1H), 3.15 (dd, $J = 9.8, 6.1$ Hz, 1H), 2.63 (dt, $J = 12.8, 6.5$ Hz, 1H), 2.45 (dd, $J = 13.0, 9.8$ Hz, 1H), 1.77-1.74 (br m, 1H), 1.45 (s, 9H); $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ 172.3, 170.4, 150.6, 147.9, 138.1, 137.2, 134.0, 132.5, 128.7, 128.7, 128.6, 128.6, 128.5, 128.5, 128.4, 128.4, 127.3, 126.5, 122.8, 122.7, 120.6, 105.3, 105.3, 81.3, 75.0, 65.5, 65.5, 63.1, 63.0, 60.4, 52.7, 49.4, 49.4, 48.4, 34.8, 28.2, 16.0, 16.0; R_f (SiO_2 , hexanes/EtOAc 4:1) 0.10; $[\alpha]_D^{25} = +64^\circ$ ($c = 0.31$, CHCl_3); IR (film, CH_2Cl_2), ν_{max} 3444 (br), 3062, 3029, 2970, 2927, 1729, 1682, 1639, 1154 cm^{-1} ; HRMS (MH^+), found 597.2974. $\text{C}_{36}\text{H}_{41}\text{N}_2\text{O}_6$ requires 597.2965.

4.15. (5R,8S,10R,11S)-tert-butyl 4-hydroxy-5-(hydroxymethyl)-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epimino-azepino[1,2-b]isoquinoline-10-carboxylate (25)

A solution of compound **24b** (7.0 mg, 0.012 mmol) in glacial acetic acid (1 mL) and 10% Pd/C (7 mg) were placed in round bottom flask and sparged with Ar for 5 minutes. The vessel was evacuated and filled with hydrogen three times. The reaction was vigorously stirred overnight under hydrogen (1 atm). The suspension was diluted with CH_2Cl_2 (25 mL) and then filtered through Celite[®] and the flask was rinsed with CH_2Cl_2 (3 \times 5 mL). The solution was extracted with sat. aq. NaHCO_3 (3 \times 15 mL). The combined aqueous layers were diluted with phosphate buffer (0.1 M, pH = 7.5, 25 mL) and extracted with CH_2Cl_2 (3 \times 15 mL). The combined organic layers were rinsed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, $\text{CHCl}_3/\text{MeOH}$ 97:3) to afford compound **25** (4.6 mg, 92%) as a colorless oil. $^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 6.40 (s, 1H), 6.05 (dd, $J = 7.9, 4.1$ Hz, 1H), 5.53 (s, 1H), 4.30 (s, 1H), 4.09 (d, $J = 6.7$ Hz, 1H), 3.78-3.74 (m, 2H), 3.76 (s, 3H), 3.65-3.60 (m, 1H), 3.17 (dd, $J = 9.3, 6.2$ Hz, 1H), 2.61 (dd, $J = 13.1, 9.4$ Hz, 1H), 2.32 (dt, $J = 13.2, 6.6$ Hz, 1H), 2.24 (s, 3H), 1.47 (s, 9H); $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ 173.4, 171.1, 145.2, 144.7, 144.7, 136.9, 136.8, 130.3, 127.1, 119.1, 112.9, 112.9, 102.7, 81.6, 65.1, 62.4, 61.8, 61.0, 49.5, 48.1, 37.0, 29.8, 29.8, 28.2, 15.9; R_f (SiO_2 , $\text{CHCl}_3/\text{MeOH}$ 95:5) 0.17; $[\alpha]_D^{25} = +4.3^\circ$ ($c = 0.23$, CHCl_3); IR (film, CH_2Cl_2), ν_{max} 3262 (br), 2969, 2925, 2854, 1719, 1683, 1646, 1154 cm^{-1} ; HRMS (MH^+), found 417.2033. $\text{C}_{22}\text{H}_{29}\text{N}_2\text{O}_6$ requires 417.2026.

4.16. (5R,8S,10R,11S,11aS)-tert-butyl 4-hydroxy-5-(hydroxymethyl)-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11,11a, 12- octahydro-8,11-epiminoazepino[1,2-b]isoquinoline-10-carboxylate (26)

To a solution of compound **25** (4.6 mg, 0.011 mmol) in EtOH (1 mL) in a 5 mL vial, was added a slurry of Raney[®] nickel 2800 (500 μ L of commercially available water slurry, washed with EtOH (3 \times 1 mL) and suspended in EtOH (1 mL)). The vial was placed in a Fisher-Porter bottle, under Ar, the suspension was sparged with Ar for 5 minutes and the vessel was filled with hydrogen gas at 100 psi. The reaction was vigorously stirred overnight diluted with EtOAc (10 mL) and sat. aq. Rochelle's salt (10 mL), and stirred vigorously for 2 h. The biphasic suspension was filtered through Celite[®], the phases separated and the aqueous phase extracted with EtOAc (3 \times 10 mL). The combined organic phases were rinsed with brine (25 mL), dried (Na₂SO₄), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, CHCl₃/MeOH 97:3) to afford compound **26** (3.4 mg, 74%) as a colorless oil. ¹H-NMR (400 MHz; CDCl₃): δ 6.51 (s, 1H), 5.59 (dd, J = 5.6, 3.4 Hz, 1H), 3.96 (d, J = 6.1 Hz, 1H), 3.88 (dd, J = 10.9, 3.2 Hz, 1H), 3.78 (s, 3H), 3.77-3.76 (m, 1H), 3.67 (dt, J = 12.4, 2.6 Hz, 1H), 3.61 (dd, J = 11.1, 5.8 Hz, 1H), 3.16 (dd, J = 9.0, 6.4 Hz, 1H), 2.84 (t, J = 13.5 Hz, 1H), 2.54 (dd, J = 14.7, 2.2 Hz, 1H), 2.50 (dd, J = 13.2, 9.0 Hz, 1H), 2.27 (s, 3H), 2.18 (dt, J = 13.2, 6.6 Hz, 1H), 1.53-1.45 (m, 9H); ¹³C-NMR (101 MHz, CDCl₃): δ 174.4, 172.4, 145.7, 132.0, 129.7, 121.2, 120.2, 118.0, 81.5, 67.8, 63.0, 62.2, 61.0, 60.8, 52.6, 42.8, 38.8, 32.1, 29.9, 28.2, 15.9; Rf (SiO₂, CHCl₃/MeOH 95:5) 0.20; $[\alpha]_D^{25}$ = -36° (c = 0.080, CHCl₃); IR (film, CH₂Cl₂), ν_{\max} 3286 (br), 2958, 2925, 2855, 1729, 1652, 1456 cm⁻¹; HRMS (MH⁺), found 419.2174. C₂₂H₃₁N₂O₆ requires 419.2182.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

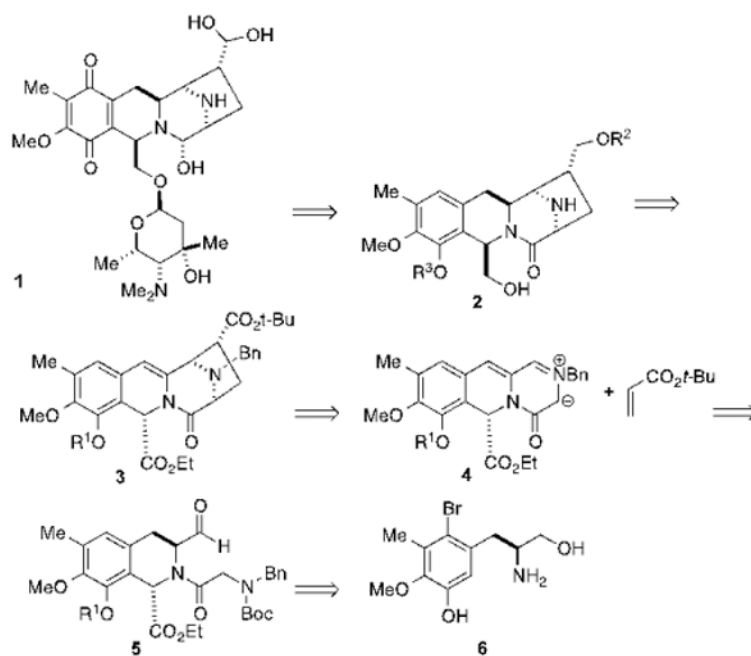
Acknowledgments

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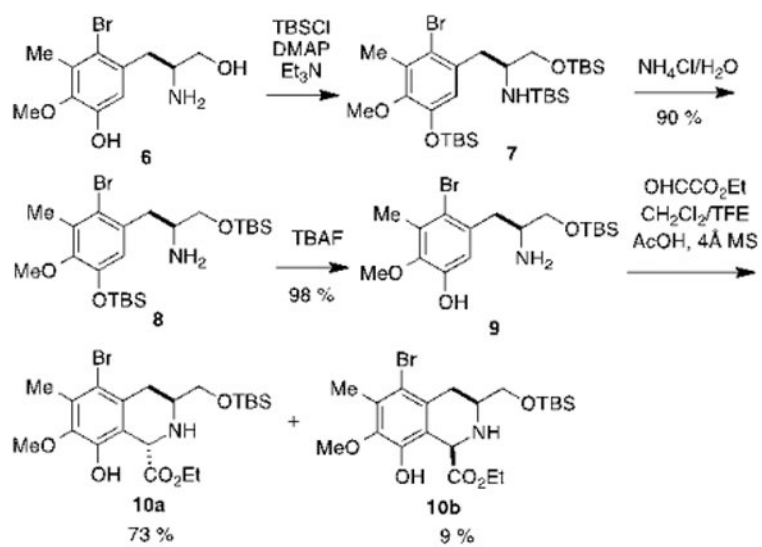
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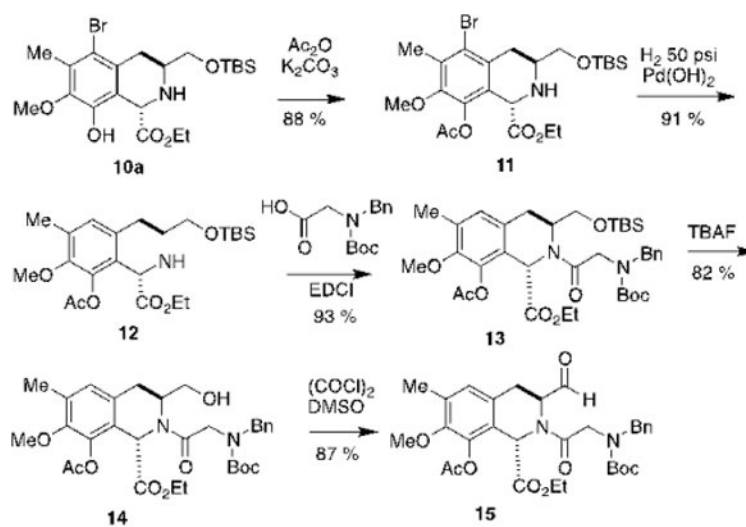
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23. The lack of reactivity of the primary hydroxyl of **7** is consistent with the regioselectivity observed in the reaction between TBS-Cl and diols bearing a β -aminoalcohol motif (ref. 24). We concur with the explanation provided by the authors, which stated that the nucleophilicity of the primary hydroxyl is reduced by internal hydrogen bonding to the neighboring amino group
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34. As illustrated in Scheme 4, we propose that the dipolarophile adds from the Re face of the iminium ion carbon to form **20a**, which epimerizes under the reaction conditions to form **20b**
35. We propose that the observed chemoselectivity can be explained by the initial formation of a phenoxyaluminum hydride species, which upon delivery of one hydride to the ester, forms a stable 7-membered ring alkoxy(phenoxy)aluminum hydride species
36. Compounds **23a** and **23b** are unstable to silica gel. Consequently, we did not attempt their separation for the purpose of recycling of **23a**



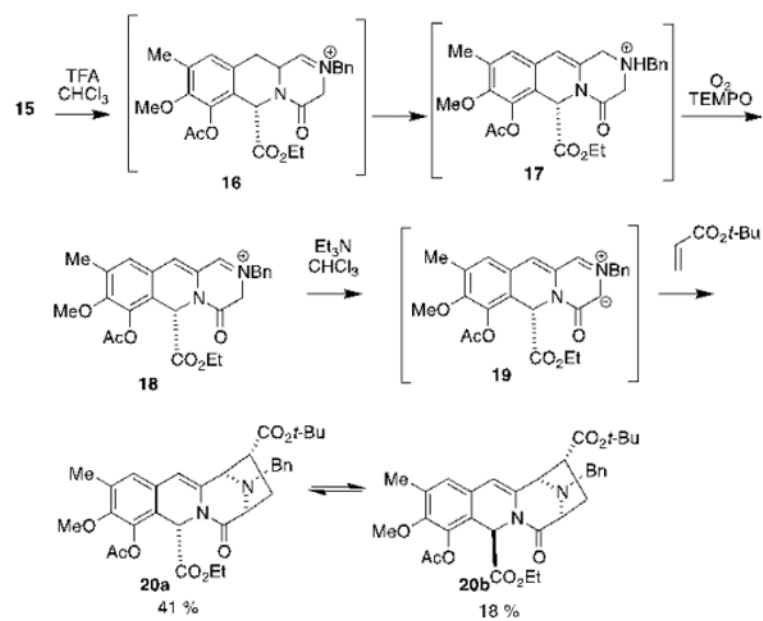
Scheme 1. Retrosynthetic analysis



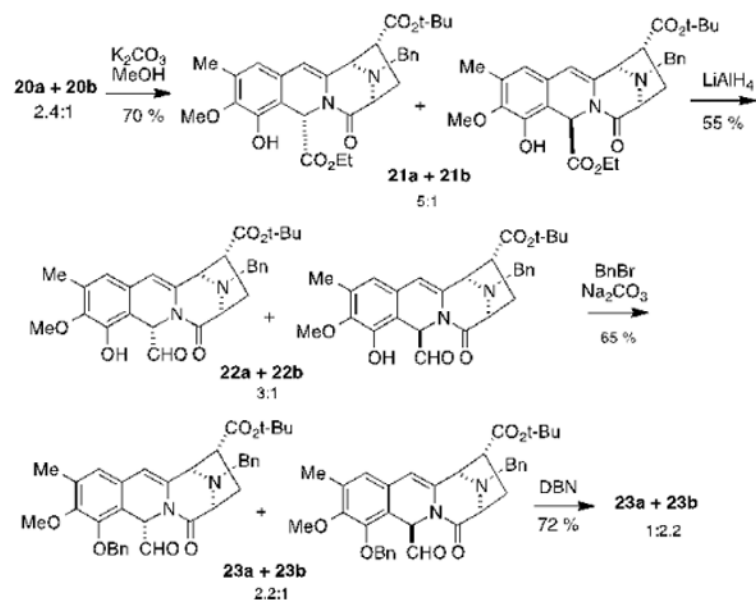
Scheme 2. Tetrahydroisoquinoline ring formation



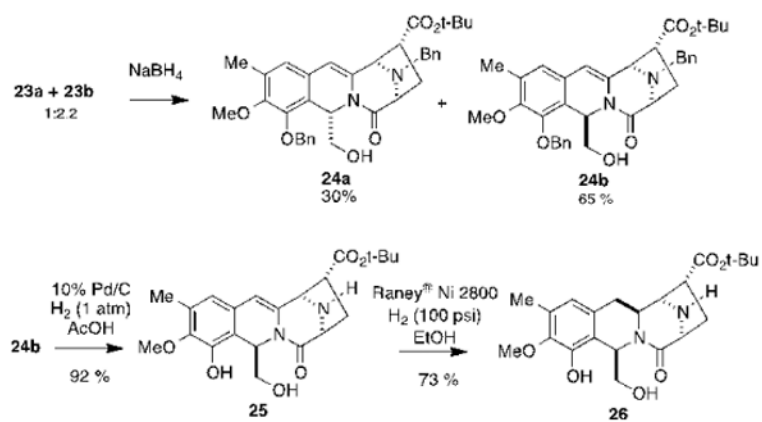
Scheme 3. Preparation of aldehyde 15



Scheme 4. Formation of cycloadducts 20a and 20b



Scheme 5.
Synthesis of aldehydes **23a** and **23b**.



Scheme 6.
Synthesis of compound **26**.