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Synthetic studies on lemonomycin: construction of the tetracyclic core

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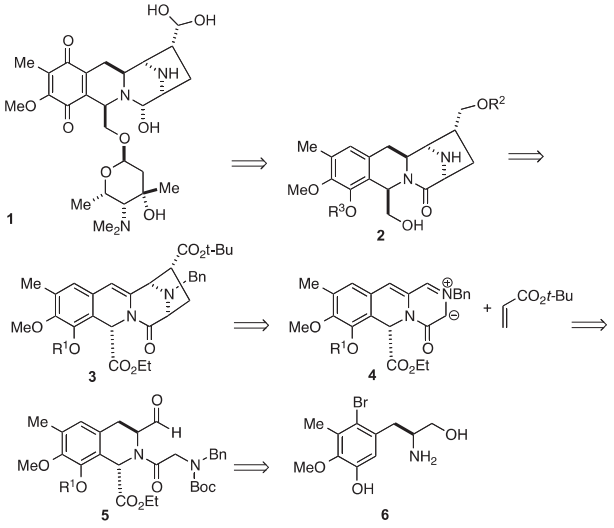
ABSTRACT

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.

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 co-workers in 2000.[4] 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.[2,4] Structurally, the compound contains the tetracyclic core found in quinocarcin[5] and tetrazomine,[6] 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.[7–11] 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 Stoltz[12] and Fukuyama[13] and synthetic studies by Magnus,[14,15] Zhu,[16–18] Mulzer,[19] and our laboratory.[20]

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 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.[20] This key reaction was also used for the construction of the [3,8]-diazabicyclo ring system in our total syntheses of (−)-tetrazomine[21] and (±)-quinocarcinamide.[22] The tetrahydroisoquinoline system of **5** could be formed through a Pictet–Spengler reaction involving a derivative of compound **6**, which is a known compound.[23]



Scheme 1. Retrosynthetic analysis.

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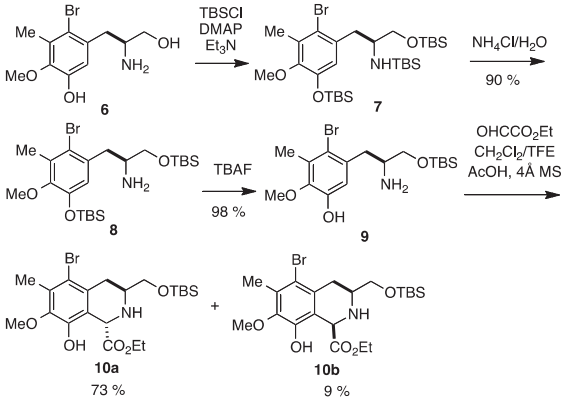
2. Results and discussion

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.[23] We initially attempted to perform the direct conversion of **6** into bis-silyl ether **8** using 2 equiv of TBS-Cl, but the yields were inconsistent and low (<30%).[24,25] By increasing the relative amount of TBS-Cl to 6 equiv, compound **6** was converted into the tris-silylated compound **7**. Unexpectedly, the hydrolysis of the silyl-amine function required a prolonged vigorous stirring with aq NH_4Cl at rt (~2 h) to form the bis-silyl ether **8** in 90% yield. The phenolic silyl ether was selectively cleaved with 1 equiv of TBAF at 0 °C,[26] to afford compound **9** in 98% yield (Scheme 2).

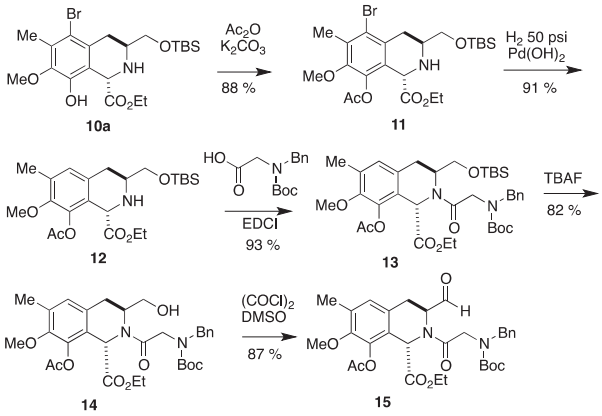


Scheme 2. Tetrahydroisoquinoline ring formation.

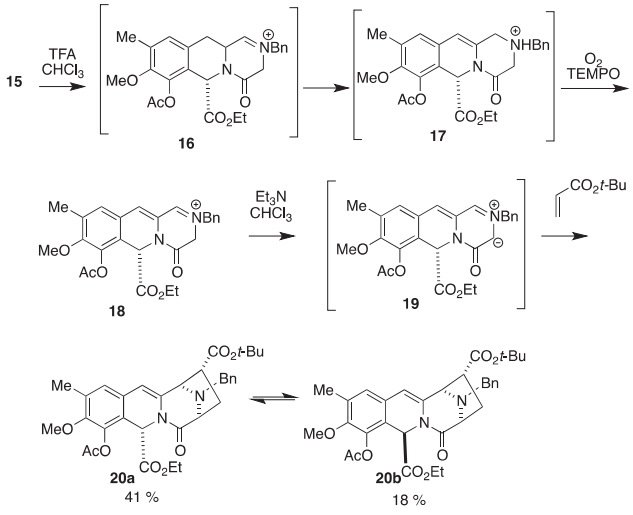
The next step entailed the formation of the *trans*-tetrahydroisoquinoline ring via a Pictet–Spengler reaction between **9** and ethyl glyoxalate. Previously, our group reported a similar transformation, which was performed by stirring a solution of the starting materials in acetonitrile for 3.5 days at 50 °C, which afforded the trans-product stereospecifically.[27] A similar report by Zhu and co-workers involved the use of LiCl, hexafluoroisopropanol and molecular sieves, and stirring the suspension in toluene at rt 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[28,29] to our substrate. The amount of acetic acid was reduced from 2.5 equiv to 0.2 equiv 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 CF_3CH_2OH, AcOH (0.2 equiv), 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,[30] followed by hydrogenolysis of the C–Br bond[23] to afford compound **12** (Scheme 3).

Following the conditions described in our previous report,[20] 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 oxidation[31] to afford aldehyde **15** (Scheme 3).

As illustrated in Scheme 4, aldehyde **15** was dissolved in $CHCl_3$ and treated under aerobic conditions with TFA[32–34] (50 equiv) and TEMPO (0.1 equiv), 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 $CHCl_3$. 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.[35]

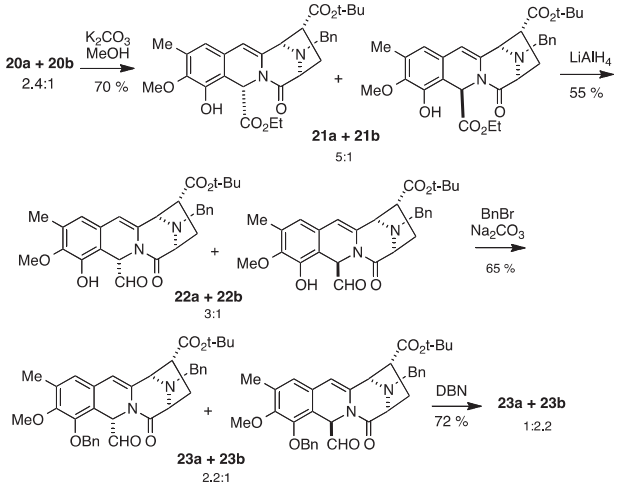


Scheme 3. Preparation of aldehyde **15**.



Scheme 4. Formation of cycloadducts **20a** and **20b**.

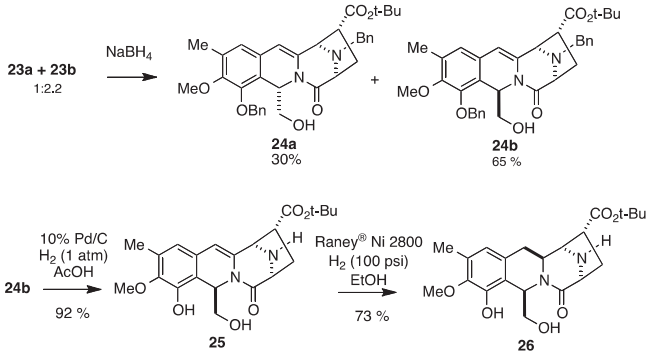
The deacetylation of the **20a**/**20b** mixture under standard methanolysis conditions provided a 5:1 mixture of **21a** and **21b** in 70% yield (Scheme 5). We suggest that **21b** decomposes under the reaction conditions at a higher rate than **21a**, which provides an explanation for both the moderate yield and the change in the diastereomeric ratio. The chemoselective reduction of the ethyl esters with 1 equiv of $LiAlH_4$ at −10 °C, afforded a 3:1 mixture of aldehydes **22a** and **22b** in 55% yield.[36] We submit that the partial



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

epimerization seen in this step is promoted by the slightly basic workup conditions. Treatment with BnBr and Na_2CO_3 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**,[37] which was then reacted with DBN in THF to invert the epimeric ratio.[21,22]

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 psi[21] provided compound **26** in 73% yield.



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

3. Conclusion

In summary, we have accomplished the construction of the tetracyclic core of (−)-lemonomycin. Compound **26** was prepared from known bromotyrosinol **6** in 16 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 (230×400 mesh) from Sorbent Technologies. Thin layer chromatography was performed on glass plates coated with silica gel grade 60, from Merck. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 300 or 400 MHz spectrometers as indicated. Proton spectra in $CDCl_3$ were referenced to residual $CHCl_3$ at 7.26 ppm. Carbon spectra in $CDCl_3$ were referenced to 77.16 ppm. Proton spectra in DMSO-d_6 were referenced to residual CD_3SOCD_2H 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*-butyldimethylsilyl)oxy)-4-methoxy-3-methylphenyl)-3-((*tert*-butyldimethylsilyl)oxy) propan-2-amine (8)

To a stirred solution of compound **6** (1.55 g, 5.36 mmol, 1 equiv) (**6**) in CH_2Cl_2 (90 mL, 0.06 M), were added DMAP (327 mg, 2.68 mmol, 0.5 equiv), Et_3N (4.48 mL, 32.2 mmol, 6.00 equiv), and TBS-Cl (4.86 g, 32.2 mmol, 6 equiv). The reaction was stirred under Ar for 3 h at rt, and then satd aq NH_4Cl (50 mL) was added and the mixture was stirred for 2 h. The phases were separated, the aqueous layer was extracted with CH_2Cl_2 (2×50 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, hexane/EtOAc 5:1) to give the title compound **8** (2.50 g, 90%) as a colorless oil. ^{1}H NMR (400 MHz; $CDCl_3$): 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); ^{13}C NMR (101 MHz, $CDCl_3$): 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 (SiO_2, 2:1 hexanes/EtOAc) 0.35; $[\alpha]_D^{25}$ +0.9 (*c* 0.35, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 2996, 2930, 2858, 2471, 839 cm^{-1}; HRMS (MH^+), found 520.2103. $C_{23}H_{45}BrNO_3Si_2$ requires 520.2101.

4.3. (*S*)-5-(2-Amino-3-((*tert*-butyldimethylsilyl)oxy)propyl)-4-bromo-2-methoxy-3-methylphenol (9)

To a stirred solution of compound **8** (1.59 g, 3.05 mmol, 1 equiv) 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 equiv). The reaction was stirred for 25 min and quenched with satd aq NH_4Cl (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 (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, $CHCl_3$/MeOH 10:1) to give the title compound **9** (1.23 g, 98%) as a colorless oil. ^{1}H NMR (400 MHz; $CDCl_3$): 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); ^{13}C NMR (101 MHz, $CDCl_3$): 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 (SiO_2, CH_2Cl_2/MeOH 10:1) 0.4; $[\alpha]_D^{25}$ +8.3 (*c* 0.41, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 3263 (br), 2954, 2928, 2856, 1578, 1471, 1092 cm^{-1}; HRMS (MH^+), found 406.1233. $C_{17}H_{31}BrNO_3Si$ requires 406.1236.

4.4. (1*S*,3*S*)-Ethyl 5-bromo-3-(((*tert*-butyldimethylsilyl)oxy)-methyl)-8-hydroxy-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (10a) and (1*R*,3*S*)-ethyl 5-bromo-3-(((*tert*-butyldimethylsilyl)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 equiv) in CH_2Cl_2 (134 mL, 0.10 M), under Ar, were added, 4 Å molecular sieves (2.72 g), CF_3CH_2OH (13.4 mL), AcOH (153 μL, 2.68 mmol, 0.20 equiv), and ethyl glyoxalate (50% solution in $PhCH_3$, 2.93 mL, 14.8 mmol, 1.1 equiv). The reaction was stirred overnight, diluted with CH_2Cl_2 (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** (4.78 g, 73%) as a white solid and compound **10b** (610 mg, 9%) as a white solid. Compound **10a**: ^{1}H NMR (400 MHz; $CDCl_3$): 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); ^{13}C NMR (101 MHz, $CDCl_3$): 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; mp=47 °C; R_f (SiO_2, hexanes/EtOAc 4:1) 0.40; $[\alpha]_D^{25}$ −24.3 (*c* 0.885, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 3284 (br), 2955, 2931, 2857, 1739, 1462, 1178 cm^{-1}; HRMS (MH^+), found 490.1446. $C_{21}H_{35}BrNO_5Si$ requires 490.1447. Compound **10b**: ^{1}H NMR (400 MHz; $CDCl_3$): 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); ^{13}C NMR (101 MHz, $CDCl_3$): 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; mp=95 °C; R_f (SiO_2, hexanes/EtOAc 4:1) 0.37; $[\alpha]_D^{25}$ −36.7 (*c* 0.600, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 3314 (br), 2955, 2931, 2858, 1738, 1463, 1257 cm^{-1}; HRMS (MH^+), found 490.1456. $C_{21}H_{35}BrNO_5Si$ requires 490.1447.

4.5. (1*S*,3*S*)-Ethyl 8-acetoxy-5-bromo-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (11)

To a stirred solution of compound **10a** (840 mg, 1.72 mmol, 1.0 equiv) in acetone (34 mL, 0.05 M), under Ar, were added K_2CO_3 (1.20 g, 8.64 mmol, 5.0 equiv) and acetic anhydride (162 μL, 1.72 mmol, 1.0 equiv). 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 (Na_2SO_4), 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, 88%) as a colorless oil. ^{1}H NMR (400 MHz; $CDCl_3$): 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); ^{13}C NMR (101 MHz, $CDCl_3$): 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 (SiO_2, hexanes/EtOAc 4:1) 0.45; $[\alpha]_D^{25}$ −21.1 (*c* 1.10, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 2956, 2932, 2856, 1780, 1737, 1462, 1192 cm^{-1}; HRMS (MH^+), found 532.1561. $C_{23}H_{37}BrNO_6Si$ requires 530.1574.

4.6. (1*S*,3*S*)-Ethyl 8-acetoxy-3-(((*tert*-butyldimethylsilyl)oxy)-methyl)-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (12)

A solution of compound **11** (2.90 g, 5.46 mmol) in MeOH (110 mL, 0.05 M), and Pearlman's catalyst (20% $Pd(OH)_2$/C, 580 mg) were placed in a Fisher–Porter bottle, under Ar. The mixture was sparged with Ar for 5 min 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 satd 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 g, 91%) as a colorless oil. ^{1}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}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 (*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. $C_{23}H_{38}NO_6Si$ requires 452.2468.

4.7. (1*S*,3*S*)-Ethyl 8-acetoxy-2-(2-(benzyl(*tert*-butoxycarbonyl)-amino)acetyl)-3-(((*tert*-butyldimethylsilyl)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 equiv), *N*-Bn-*N*-Boc-glycine (2.58 g, 9.74 mmol, 2.0 equiv), and EDCI (1.40 g, 7.31 mmol, 1.5 equiv) 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), satd 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}H NMR (300 MHz; 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=15.6.0 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}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 (SiO_2, hexanes/EtOAc 3:1) 0.30; $[\alpha]_D^{25}$ +26.8 (*c* 0.995, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 2956, 2931, 2857, 1781, 1743, 1703, 1668, 1199 cm^{-1}; HRMS (MH^+), found 699.3666. $C_{37}H_{55}N_2O_9Si$ requires 699.3677.

4.8. (1*S*,3*S*)-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 equiv) in THF (10 mL, 0.11 M), under Ar, were added MeOH (625 μL) and TBAF (1.0 M solution in THF, 2.18 mL, 2.0 equiv). The reaction was stirred overnight and quenched with satd aq NH_4Cl (50 mL) and then diluted with EtOAc (100 mL). The phases were separated, the aqueous phase was extracted with EtOAc (2×25 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 dissolved in the minimal amount of CH_2Cl_2 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. ^{1}H 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 H_2O signal), 2.34 (s, 3H), 2.25 (s, 3H), 1.41 (s, 9H),

1.13 (t, J=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, 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; mp 80 °C; R_f (SiO_2, hexanes/EtOAc 1:1) 0.35; $[\alpha]_D^{25}$ +78 (*c* 0.44, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 3455 (br), 2977, 2935, 1780, 1742, 1698, 1663, 1200 cm^{-1}; HRMS (MH^+), found 585.2816. $C_{31}H_{41}N_2O_9$ requires 585.2812.

4.9. (1*S*,3*S*)-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 μL, 9.75 mmol, 3.0 equiv) in CH_2Cl_2 (22.5 mL), under Ar, was cooled to −78 °C, and DMSO (921 μL, 13.0 mmol, 4.0 equiv) 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 equiv) in CH_2Cl_2 (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 equiv) 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 satd aq NH_4Cl (50 mL) and allowed to warm to rt. The layers were separated, the aqueous phase was extracted with CH_2Cl_2 (3×50 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 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. ^{1}H 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; mp 78 °C; R_f (SiO_2, hexanes/EtOAc 1:1) 0.40; $[\alpha]_D^{25}$ +35 (*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. $C_{31}H_{39}N_2O_9$ requires 583.2656.

4.10. (5*S*,8*S*,10*R*,11*S*)-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 (5*R*,8*S*,10*R*,11*S*)-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 equiv) in $CHCl_3$ (28 mL, 0.1 M), under air, were added TEMPO (44 mg, 0.28 mmol, 0.10 equiv), and trifluoroacetic acid (10.8 mL, 142 mmol, 50 equiv) and the flask was loosely capped with a Teflon® stopper. The solution was stirred for 4 h, 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 equiv) and triethylamine (3.95 mL, 28.3 mmol, 10 equiv) were added. The reaction was allowed to warm to rt and stirred overnight. The solution was diluted with EtOAc (200 mL), rinsed with satd 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. ^{1}H 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 (*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. $C_{33}H_{39}N_2O_8$ requires 591.2706.

4.11. (5*S*,8*S*,10*R*,11*S*)-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 (5*R*,8*S*,10*R*,11*S*)-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 equiv) in THF/MeOH 1:1 (14 mL, 0.05 M), under Ar, was added K_2CO_3 (192 mg, 1.39 mmol, 2.0 equiv). 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 (Na_2SO_4), 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. ^{1}H NMR (400 MHz; $CDCl_3$): 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); ^{13}C NMR (101 MHz, $CDCl_3$): 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 (SiO_2, hexanes/EtOAc 2:1) 0.45; $[\alpha]_D^{25}$ −73.6 (*c* 0.282, CH_2Cl_2); IR (film, CH_2Cl_2), ν_{max} 3374 (br), 2980, 2938, 1736, 1689, 1647, 1154 cm^{-1}; HRMS (MH^+), found 549.2606. $C_{31}H_{37}N_2O_7$ requires 549.2601.

4.12. (5*S*,8*S*,10*R*,11*S*)-*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 (22a) and (5*R*,8*S*,10*R*,11*S*)-*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 $LiAlH_4$ in THF (1.0 M, 447 μL, 0.447 mmol, 1.0 equiv) was added dropwise to a solution of a 5:1 mixture of compounds **21a** and **21b** (245 mg, 0.447 mmol, 1.0 equiv) in THF (9 mL, 0.05 M), under Ar, at −10 °C. The solution was stirred for 10 min at this temperature, quenched with EtOAc (12 mL) and satd 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 (Na_2SO_4), 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. ^{1}H NMR (400 MHz; $CDCl_3$): 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}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; R_f (SiO_2, hexanes/EtOAc 2:1) 0.42; $[\alpha]_D^{25}$ −64.8 (*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. $C_{29}H_{33}N_2O_6$ requires 505.2339.

4.13. (5*S*,8*S*,10*R*,11*S*)-*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 (5*R*,8*S*,10*R*,11*S*)-*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 (5*R*,8*S*,10*R*,11*S*)-*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 equiv) and benzyl bromide (108 μL, 0.912 mmol, 4.0 equiv) in DMF (7.6 mL, 0.03 M), under Ar, were added tetrabutylammonium iodide (9.0 mg, 0.023 mmol, 0.10 equiv) and finely ground anhydrous Na_2CO_3 (241 mg, 2.28 mmol, 10 equiv). The mixture was vigorously stirred for 2 h and diluted with water (25 mL) and phosphate buffer (0.1 M, pH=7.5, 25 mL). The aqueous phase was extracted with EtOAc (3×33 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}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}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; R_f (SiO_2, hexanes/EtOAc 4:1) 0.45; $[\alpha]_D^{25}$ −64 (*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. $C_{36}H_{39}N_2O_6$ 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 equiv) in THF (2 mL, 0.08 M), under Ar, was added DBN (19 μL, 0.15 mmol, 1.0 equiv). The mixture was stirred for 30 min 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 (3×33 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}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}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 (*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. $C_{36}H_{39}N_2O_6$ requires 595.2808.

4.14. (5*S*,8*S*,10*R*,11*S*)-*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 (5*R*,8*S*,10*R*,11*S*)-*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 °C, under Ar, was

added $NaBH_4$ (30 mg, 0.80 mmol 8.0 equiv). The reaction was stirred at rt for 2 h, quenched with 1 N HCl (2.4 mL, 2.40 mmol, 24 equiv) and diluted with phosphate buffer (0.1 M, pH=7.5, 50 mL). The aqueous phase was extracted with EtOAc (3×25 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}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}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 (*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. $C_{36}H_{41}N_2O_6$ requires 597.2965. Compound **24b**: ^{1}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}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 (*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. $C_{36}H_{41}N_2O_6$ requires 597.2965.

4.15. (5*R*,8*S*,10*R*,11*S*)-*tert*-Butyl 4-hydroxy-5-(hydroxymethyl)-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[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 min. 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 (3×5 mL). The solution was extracted with satd aq $NaHCO_3$ (3×15 mL). The combined aqueous layers were diluted with phosphate buffer (0.1 M, pH=7.5, 25 mL) and extracted with CH_2Cl_2 (3×15 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, $CHCl_3$/MeOH 97:3) to afford compound **25** (4.6 mg, 92%) as a colorless oil. ^{1}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}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, $CHCl_3$/MeOH 95:5) 0.17; $[\alpha]_D^{25}$ +4.3 (*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. $C_{22}H_{29}N_2O_6$ requires 417.2026.

4.16. (5*R*,8*S*,10*R*,11*S*,11a*S*)-*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 μL of commercially available water slurry, washed with EtOH (3×1 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 min and the vessel was filled with hydrogen gas at 100 psi. The reaction was vigorously stirred overnight, diluted with EtOAc (10 mL) and satd 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 (3×10 mL). The combined organic phases 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, $CHCl_3$/MeOH 97:3) to afford compound **26** (3.4 mg, 74%) as a colorless oil. ^{1}H NMR (400 MHz; $CDCl_3$): 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); ^{13}C NMR (101 MHz, $CDCl_3$): 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; R_f (SiO_2, $CHCl_3$/MeOH 95:5) 0.20; $[\alpha]_D^{25}$ −36 (*c* 0.080, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 3286 (br), 2958, 2925, 2855, 1729, 1652, 1456 cm^{-1}; HRMS (MH^+), found 419.2174. $C_{22}H_{31}N_2O_6$ requires 419.2182.

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Supplementary data

^{1}H and ^{13}C NMR spectra of all compounds. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.05.009.

References and notes

1. Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669–1730.
2. Whaley, H. A.; Patterson, E. L.; Dann, M.; Shay, A. J.; Porter, J. N. In *Antimicrobial Agents and Chemotherapy*, 1964: Proceedings of the Fourth Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, NY, October 26–28, 1964; pp 83–86.
4. He, H. Y.; Shen, B.; Carter, G. T. *Tetrahedron Lett.* **2000**, *41*, 2067–2071.
5. Takahashi, K.; Tomita, F. *J. Antibiot.* **1983**, *36*, 468–470.
6. Suzuki, K.; Sato, T.; Morioka, M.; Nagai, K.; Abe, K.; Yamaguchi, H.; Saito, T.; Ohmi, Y.; Susaki, K. *J. Antibiot.* **1991**, *44*, 479–485.
7. Hegde, V. R.; Patel, M. G.; Das, P. R.; Pramanik, B.; Puar, M. S. *J. Antibiot.* **1997**, *50*, 126–134.
8. Li, W. Y.; Leet, J. E.; Ax, H. A.; Gustavson, D. R.; Brown, D. M.; Turner, L.; Brown, K.; Clark, J.; Yang, H.; Fung-Tomc, J.; Lam, K. S. *J. Antibiot.* **2003**, *56*, 226–231.
9. Northcote, P. T.; Siegel, M.; Borders, D. B.; Lee, M. D. *J. Antibiot.* **1994**, *47*, 901–908.
10. Sasaki, T.; Otani, T.; Matsumoto, H.; Unemi, N.; Hamada, M.; Takeuchi, T.; Hori, M. *J. Antibiot.* **1998**, *51*, 715–721.
11. Zhang, C. W.; Herath, K.; Jayasuriya, H.; Ondeyka, J. G.; Zink, D. L.; Occi, J.; Birdsall, G.; Venugopal, J.; Ushio, M.; Burgess, B.; Masurekar, P.; Barrett, J. F.; Singh, S. B. *J. Nat. Prod.* **2009**, *72*, 841–847.
12. Ashley, E. R.; Cruz, E. G.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 15000–15001.
13. Yoshida, A.; Akaiwa, M.; Asakawa, T.; Hamashima, Y.; Yokoshima, S.; Fukuyama, T.; Kan, T. *Chem.—Eur. J.* **2012**, *18*, 11192–11195.
14. Magnus, P.; Matthews, K. S. *J. Am. Chem. Soc.* **2005**, *127*, 12476–12477.
15. Magnus, P.; Matthews, K. S. *Tetrahedron* **2012**, *68*, 6343–6360.
16. Couturier, C.; Schlama, T.; Zhu, J. P. *Synlett* **2006**, 1691–1694.

17. Wu, Y. C.; Bernadat, G.; Masson, G.; Couturier, C.; Schlama, T.; Zhu, J. P. *J. Org. Chem.* **2009**, *74*, 2046–2052.
18. Bernadat, G.; George, N.; Couturier, C.; Masson, G.; Schlama, T.; Zhu, J. P. *Synlett* **2011**, 576–578.
19. Siengalewicz, P.; Brecker, L.; Mulzer, J. *Synlett* **2008**, 2443–2446.
20. Vincent, G.; Chen, Y. Y.; Lane, J. W.; Williams, R. M. *Heterocycles* **2007**, *72*, 385–398.
21. Scott, J. D.; Williams, R. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1463–1465.
22. Flanagan, M. E.; Williams, R. M. *J. Org. Chem.* **1995**, *60*, 6791–6797.
23. Liao, X. W.; Liu, W.; Dong, W. F.; Guan, B. H.; Chen, S. Z.; Liu, Z. Z. *Tetrahedron* **2009**, *65*, 5709–5715.
24. 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.
25. Sales, M.; Charette, A. B. *Org. Lett.* **2005**, *7*, 5773–5776.
26. Frie, J. L.; Jeffrey, C. S.; Sorensen, E. J. *Org. Lett.* **2009**, *11*, 5394–5397.
27. Lane, J. W.; Chen, Y. Y.; Williams, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 12684–12690.
28. Chen, J. C.; Chen, X. C.; Bois-Choussy, M.; Zhu, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 87–89.
29. Zhu's conditions were also used by Liao (Ref. 22) to convert compound **6** into a *trans*-THIQ system, using 2-benzyloxyacetaldehyde.
30. Fukuyama, T.; Nunes, J. J. *J. Am. Chem. Soc.* **1988**, *110*, 5196–5198.
31. Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.
32. Vishnetskaya, M. V.; Yakimova, I. Y.; Sidorenkova, I. A. *Russ. J. Phys. Chem.* **2006**, *80*, 176–180.
33. Vishnetskaya, M. V.; Yakimova, I. Y.; Sidorenkova, I. A. *Russ. J. Phys. Chem.* **2006**, *80*, 173–175.
34. Vishnetskaya, M. V.; Ivanova, M. S.; Solkan, V. N.; Zhidomirov, G. M.; Mel'nikov, M. Y. *Russ. J. Phys. Chem. A* **2012**, *86*, 889–891.
35. 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**.
36. 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 seven-membered ring alkoxy(phenoxy) aluminum hydride species.
37. Compounds **23a** and **23b** are unstable to silica gel. Consequently, we did not attempt their separation for the purpose of recycling of **23a**.