# Enantioselective Synthesis of the AB-Ring System of the Antitumor Antibiotic Tetrazomine

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The synthesis of the 1,2,3,4-tetrahydroisoquinoline moiety of tetrazomine was accomplished in 18 steps and in 3% overall yield from commercially available *o*-anisaldehyde. The reaction sequence utilizes a Sharpless asymmetric dihydroxylation to install the stereocenter and an intramolecular Friedel−Crafts hydroxyalkylation with an *N*-protected 2-oxo-acetamide to close the heterocyclic ring.

## Introduction

Tetrazomine was isolated from *Saccharothrix mutabilis* in 1991 and is part of the naphthyridinomycin/bioxalomycin class of antitumor antibiotics that includes the Cdc25 inhibitor dnacin $A_1$ (Figure 1).[1] Preliminary biological testing of tetrazomine indicated cytotoxic activity against a P388 leukemia cell line as well as significant antimicrobial activity.[1d,e,i] To date, synthetic efforts toward tetrazomine have been limited and include approaches toward the racemic AB-ring system as well as studies to determine the absolute stereochemistry of the amino acid side-chain and lipase-resolution of this building block.[2] Herein, we report our efforts toward the asymmetric synthesis of the isoquinoline AB-ring system of tetrazomine.

The key step in our retrosynthetic approach toward this natural product is an intramolecular Heck annulation of enamide **1** to give the core 3,8-diaza-bicyclo[3.2.1]-octane scaffold (Figure 2). This strategy requires the preparation of an enol triflate or a related electrophile from isoquinoline amide **2**. In earlier studies, we have reported an application of the Moore−Liebeskind quinone synthesis toward the preparation of 1,4-dihydro-2*H*-isoquinoline-3,5,8-triones.[3] Unfortunately, we were unable to extend this approach to include the functionalities necessary for the AB-ring system of tetrazomine. Accordingly, we decided to construct the isoquinoline ring by an intramolecular Friedel−Crafts hydroxyalkylation of a 2-oxo-acetamide derivative of **3**.

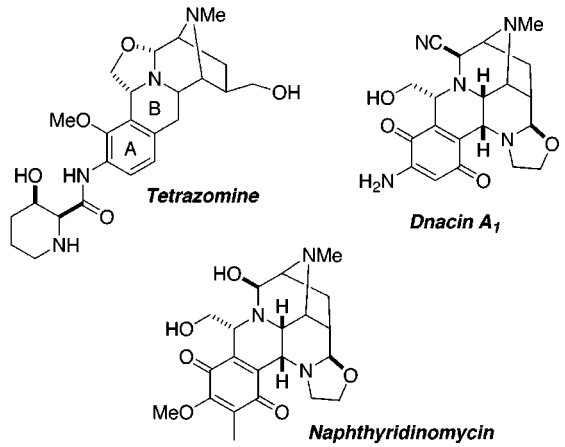


**Figure 1.** Structures of the polycyclic alkaloids tetrazomine, dnacin $A_1$ and naphthyridinomycin.

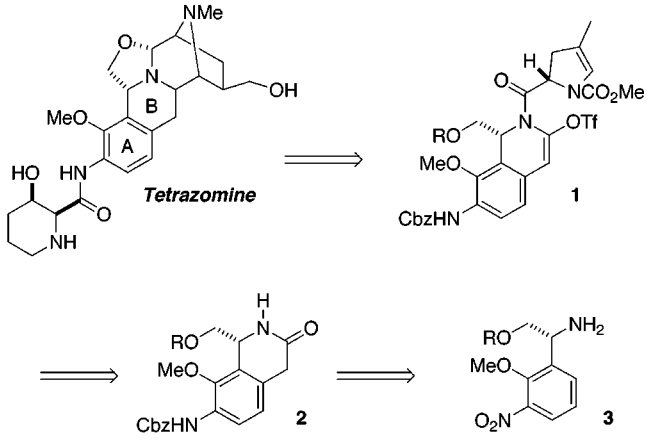


**Figure 2.** Retrosynthetic approach toward tetrazomine.

## Results and Discussion

Wittig olefination of *o*-anisaldehyde followed by dihydroxylation of the resulting styrene derivative with Sharpless's AD-Mix-α installed the desired benzylic stereocenter in diol **5** in 76% yield and 94% enantioselectivity as determined by Mosher ester analysis (Scheme 1).[4−6] Diacetylation of **5** with $Ac_2O$ and pyridine proceeded in 94% yield and allowed subsequent nitration

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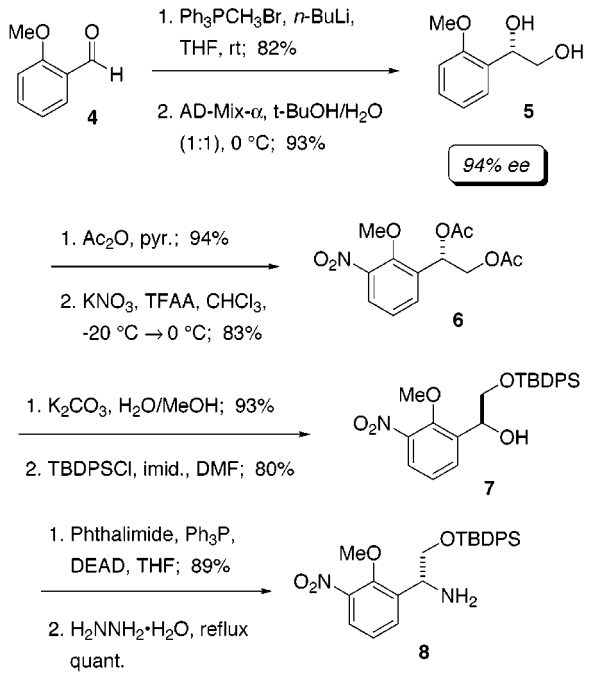
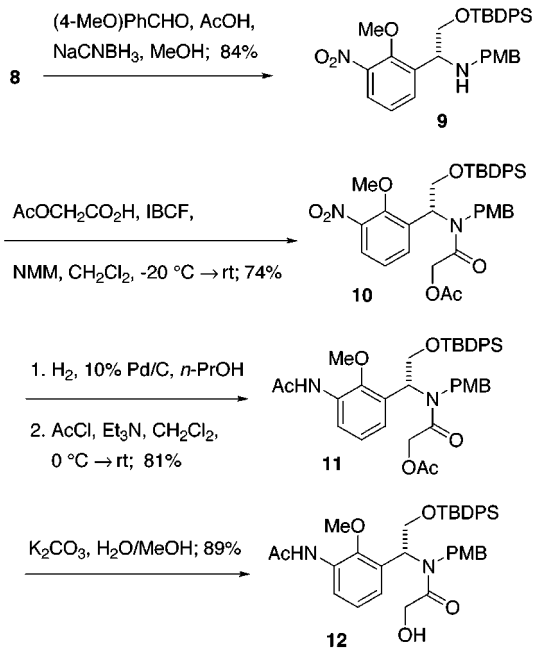
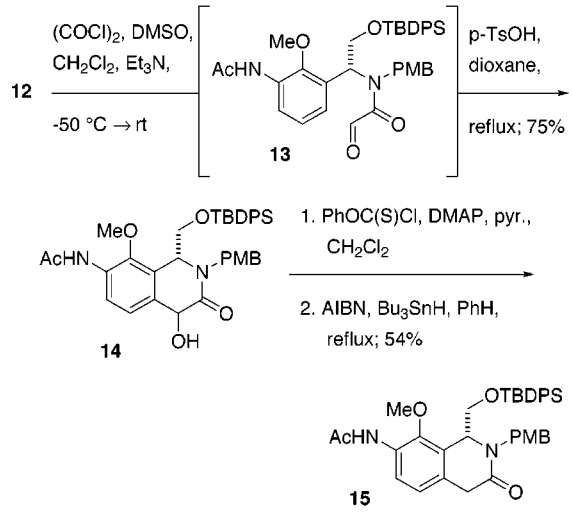
**Scheme 1**




**Scheme 2**




**Scheme 3**




under mild conditions ($KNO_3$, TFAA, $CHCl_3$) to give the *ortho*-nitrated product **6** as the sole product in 83% yield.[7] Nitrodiacetate **6** was then converted to the primary silyl ether **7** by saponification and selective silylation with TBDPS-Cl and imidazole in DMF in 74% overall yield. Conversion to the benzylic amine and concomitant inversion of the stereochemistry in **7** was accomplished in 89% yield by a Mitsunobu reaction with phthalimide, DEAD, and triphenylphosphine.[8] Hydrazinolysis of the imide provided the primary amine **8** in quantitative yield.[9]

Conversion of the primary amine **8** to the *N*-protected tertiary amide **10** was necessary to effect ring closure to the isoquinolinone (Scheme 2). Attempts to cyclize secondary amides had failed, presumably because the required (*Z*)-amide conformation was sterically significantly destabilized. After conversion of **8** to the *p*-methoxybenzyl-protected secondary amine **9** in 84% yield by reductive amination, mixed anhydride coupling with acetoxyacetic acid/isobutyl chloroformate (IBCF) led to amide **10** in 74% yield.[10] From this intermediate, the cyclization precursor alcohol **12** was readily obtained in three steps and 72% yield by catalytic reduction of the nitroarene, *N*-acetylation, and finally ester saponification with $K_2CO_3$ in aqueous MeOH.

After extensive experimentation with a variety of methods to effect direct ring closure of **12** and derivatives thereof, we decided to abandon plans for a Friedel−Crafts alkylation in favor of a hydroxyalkylation sequence, even though the latter required an additional deoxygenation step (Scheme 3). Swern oxidation of **12** to the sensitive α-formyl amide **13** followed by treatment with pTsOH in dioxane yield the desired isoquinoline **14** in 75% overall yield as a single diastereomer.[11] Our first attempt to deoxygenate the benzylic carbon utilized the $SmI_2$ protocol optimized by Simpkins et al. for α-functionalized amides.[12] Thus, **14** was converted to the requisite benzoate ester and then subjected to $SmI_2$ in THF in the presence of LiCl; however, we were unable to drive this reaction to completion and product isolation was hampered by unreacted starting material as well as significant amounts of saponified product. In contrast, after conversion of alcohol **14** to the corresponding thionocarbonate with PhOC(S)Cl, DMAP, and pyridine, Barton

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(6) Diol **5** was converted to the terminal silyl ether with TBDMS-Cl and imidazole in DMF and converted to the Mosher ester with (*R*)-MTPA. The enantiomeric excess of this derivative was determined to be 94% by integration of the methine 500 MHz $^1$H NMR signals. (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (c) Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *32*, 7165.
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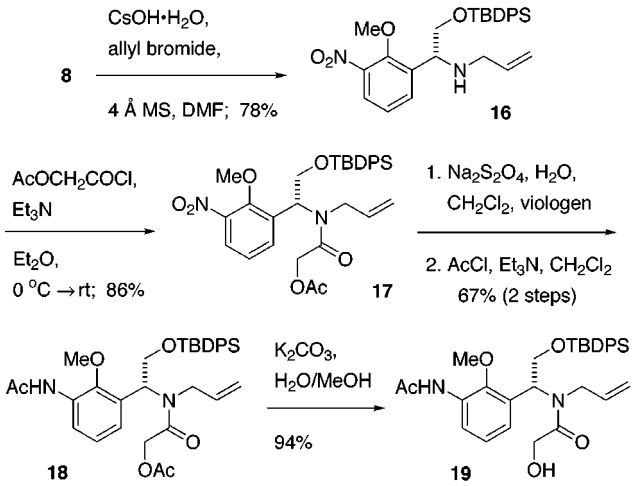
**Scheme 4**

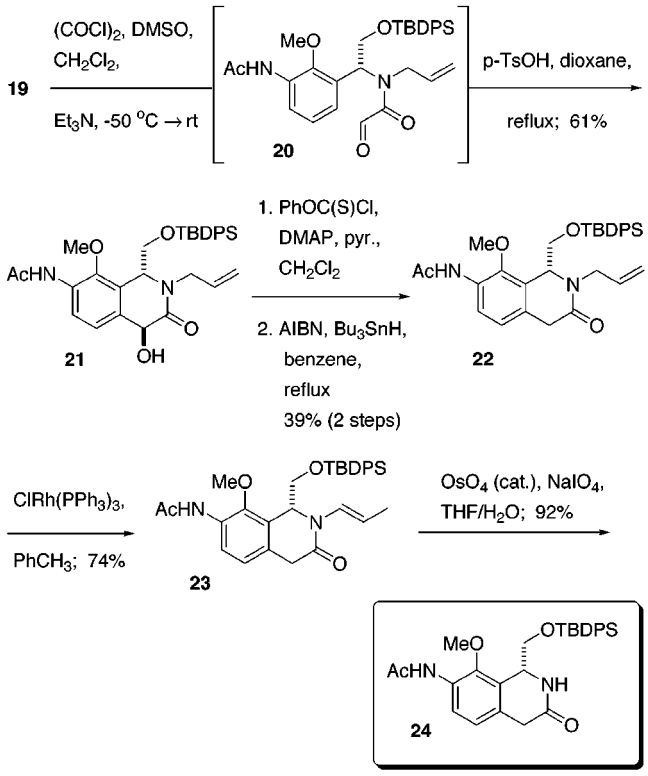



radical deoxygenation provided the PMB-protected tetrazomine segment **15** in 54% yield over the two steps.

While only deprotection of the lactam remained to convert **15** into the desired AB-ring segment of tetrazomine, we were unable to remove the PMB group despite extensive experimentation (hydrogenolysis,[13,14] dissolving metal reduction,[15] Pd(II),[16] CAN-,[17] and DDQ-oxidation,[18] as well as acidic conditions,[19] etc.). Several alternative amide protective groups, including Boc, (trimethylsilyl)-ethane sulfonyl (Ses),[20] Ts, benzyl, and 3,4-dimethoxybenzyl, failed either because of premature cleavage or substrate decomposition during forcing deprotection conditions. In the absence of a protecting group, the secondary amide did not undergo cyclization to the isoquinoline.

We finally turned our attention to the *N*-allyl function.[21] Primary amine **8** was allylated in 78% yield with allyl bromide in the presence of CsOH (Scheme 4).[22] Only small amounts (~5%) of diallylated amine were detected under these conditions. The secondary amine **16** was converted with acetoxyacetyl chloride in 86% yield into the tertiary amide **17**. Reduction of the aromatic nitro group with $Na_2S_2O_4$ and ethyl viologen dibromide (1,1′-diethyl-4,4′-bipyridinium dibromide) in aqueous $CH_2Cl_2$,[23]

**Scheme 5**




followed by aniline acetylation and ester saponification provided alcohol **19** in 63% overall yield. It is noteworthy that nitroarene reduction by the sodium dithionate/viologen protocol was somewhat batch-dependent and gave variable yields ranging from 45% to 75%.

Oxidation of alcohol **19** and acid-mediated cyclization of the intermediate aldehyde **20** proceeded uneventfully to give isoquinolinone **21** in 61% overall yield and as a single diastereomer by $^1$H NMR (Scheme 5). The (*S*)-configuration at C(4) of **21** was tentatively assigned based on MM2 calculations which showed that the alternative (4*R*)-stereoisomer was ca. 1.5 kcal/mol higher in energy. Barton deoxygenation of **21** led to the bicyclic lactam **22** in 39% yield. The allyl group was stable to the radical conditions used in the deoxygenation and also resisted initial attempts for deprotection under Pd(II) reaction conditions as well as treatment with trimethylalane in the presence of Ni-catalysts.[24,25] In contrast, isomerization of the allyl amide to the enamide with Wilkinson's catalyst followed by cleavage of **23** under Weinreb's conditions with ozone and hydrolysis of the resulting *N*-formyl compound gave the desired isoquinoline **24** in 45% yield from the allyl lactam, along with 20% of the intermediate *N*-formyl derivative.[26,27] In an attempt to improve this sequence, we attempted a Johnson–Lemieux cleavage of enamide **23**.[28] The enamide was treated with catalytic $OsO_4$ in the presence of stoichio-

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metric $NaIO_4$ in aqueous THF to give the desired lactam **24** directly in 66% yield along with 30% of the intermediate *N*-formyl amide that was readily converted to the lactam under basic conditions ($NaHCO_3$, MeOH) and provided an additional 26% of **24**.

In conclusion, we have developed a scalable enantioselective synthesis of the AB-ring system of the novel antitumor antibiotic tetrazomine. Key aspects of our approach include the use of Sharpless asymmetric dihydroxylation conditions to install a benzylic stereocenter in 94% ee in an *o*-methoxy styrene unit and an intramolecular Friedel−Crafts hydroxyalkylation of an *N*-allylated α-oxo acetamide to close the isoquinolinone ring. Extensive experimentation was necessary to identify a suitable amide protective group for this sequence. The target heterocycle was obtained in an overall yield of 3% over 18 synthetic steps; the only comparable literature sequence proceeded in 15−16 steps and in comparable overall yield to a racemic analogue of **21**.[2a] Efforts to elaborate key intermediate **24** toward the natural product tetrazomine by a novel Heck annulation are ongoing in our labs and will be disclosed in due course.

## Experimental Section

**General.** All moisture-sensitive reactions were performed under an atmosphere of $N_2$ or Ar and all glassware was dried in an oven at 140 °C prior to use. THF and $Et_2O$ were dried by distillation over Na/benzophenone and LAH under a nitrogen atmosphere, respectively. Dry $CH_2Cl_2$ and toluene were obtained by distillation from $CaH_2$. Unless otherwise stated, solvents or reagents were used without further purification. NMR spectra were recorded at either 300 MHz/75 MHz ($^1H/^{13}C$ NMR) or 500 MHz/125 MHz ($^1H/^{13}C$ NMR) in $CDCl_3$ unless stated otherwise. Chemical shifts ($\delta$) are reported in parts per million and the residual solvent peak was used as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), integration, and coupling constants.

**1-Methoxy-2-vinylbenzene.** A suspension of 44.4 g (124 mmol) of methyl triphenylphosphonium bromide in 250 mL of dry THF was treated at room temperature with 84.0 mL of n-BuLi (1.6 M solution in cyclohexane; 134 mmol). The resulting orange solution was stirred for 4 h. Then, a solution of 15.8 g (116 mmol) of *o*-anisaldehyde in 80 mL of dry THF was added dropwise. Upon addition a white precipitate formed. The suspension was stirred for 1 h and concentrated in vacuo to give a viscous orange oil that was purified by passing through a short column of $SiO_2$ (hexanes) to yield 12.7 g (94.6 mmol, 82%) of 1-methoxy-2-vinyl-benzene as a faint yellow liquid: IR (neat) 3003, 1625, 1598 $cm^{-1}$; $^1H$ NMR $\delta$ 7.41 (dd, 1 H, $J$ = 7.6, 1.5 Hz), 7.17 (td, 1 H, $J$ = 8.2, 1.6 Hz), 7.00 (dd, 1 H, $J$ = 17.7, 11.1 Hz), 6.87 (t, 1 H, $J$ = 7.5 Hz), 6.80 (d, 1 H, $J$ = 8.2 Hz), 5.68 (dd, 1 H, $J$ = 17.9, 1.6 Hz), 5.20 (dd, 1 H, $J$ = 11.1, 1.5 Hz), 3.77 (s, 3 H); $^{13}C$ NMR $\delta$ 156.9, 131.8, 129.0, 126.9, 126.7, 120.8, 114.6, 111.0, 55.6; MS (EI) *m*/*z* (rel intensity) 134 ($M^+$, 27), 91 (100), 65 (26); HRMS (EI) *m*/*z* calcd for $C_9H_{10}O$ 134.0732, found 134.0727.

**(*S*)-1-(2-Methoxyphenyl)ethane-1,2-diol (5).** To a suspension of 72.2 g of AD-Mix-α [37.5 mg (0.101 mmol) of $K_2OsO_2(OH)_4$, 398 mg (0.555 mmol) of $(DHQ)_2PHAL$, 50.5 g (154 mmol) of $K_3Fe(CN)_6$, 21.2 g (155 mmol) of $K_2CO_3$] in 250 mL of *t*-BuOH and 250 mL of $H_2O$ was added at 0 °C 7.00 g (52.2 mmol) of 2-vinylanisole. The reaction mixture was stirred vigorously for 3 h, treated with 76.5 g (0.607 mmol) of sodium sulfite, warmed to room temperature, and stirred for an additional 45 min. After addition of EtOAc, the aqueous layer was extracted with EtOAc, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a yellow oil that was purified by chromatography on $SiO_2$ (hexanes/EtOAc; 3:7) to afford 8.198 g (48.74 mmol, 93%) of diol **5** as an oil: $[\alpha]_D$ +48.1 (c 1.1, $CHCl_3$); IR (neat) 3381, 2938, 1602 $cm^{-1}$; $^1H$ NMR $\delta$ 7.41 (d, 1 H, $J$ = 7.2 Hz), 7.25 (t, 1 H, $J$ = 7.6 Hz), 6.96 (t, 1 H, $J$ = 7.5 Hz), 6.85 (d, 1 H, $J$ = 8.2 Hz), 5.11−5.09 (m, 1 H), 3.94−3.92 (m, 1 H), 3.85 (bs, 4 H), 3.65−3.50 (m, 2 H); $^{13}C$ NMR $\delta$ 156.4, 128.7, 127.2, 120.9, 110.3, 70.8, 66.7, 55.3; MS (EI) *m*/*z* (rel intensity)168 ($M^+$, 42), 121 (66), 91 (100); HRMS (EI) *m*/*z* calcd for $C_9H_{12}O_3$ 168.0786, found 168.0793.

**(*S*)-Acetic Acid 2-Acetoxy-2-(2-Methoxyphenyl)ethyl Ester.** To a solution of 8.046 g (47.84 mmol) of diol **5** in 80.0 mL (0.989 mol) of pyridine was added at 0 °C 64.0 mL (69.2 g, 0.678 mol) of $Ac_2O$. The reaction mixture was warmed to room temperature, stirred for 8 h, poured onto ice, and stirred for 1 h. The solution was extracted with $CH_2Cl_2$, and the combined organic extracts were washed with 3 N HCl, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on $SiO_2$ (hexanes/EtOAc; 7:3) to give 11.32 g (44.87 mmol, 94%) of (*S*)-acetic acid 2-acetoxy-2-(2-methoxyphenyl)ethyl ester as a light yellow liquid that solidified upon standing at −20 °C: $[\alpha]_D$ +40.0 (*c* 0.99, $CHCl_3$); IR (neat) 2954, 1743, 1604 $cm^{-1}$; $^1H$ NMR $\delta$ 7.35−7.27 (m, 2 H), 6.96 (t, 1 H, $J$ = 6.8 Hz), 6.87 (d, 1 H, $J$ = 8.1 Hz), 6.40 (dd, 1 H, $J$ = 7.1, 3.6 Hz), 4.36−4.24 (m, 2 H), 3.84 (s, 3 H), 2.13 (s, 3 H), 2.03 (s, 3 H); $^{13}C$ NMR $\delta$ 170.8, 170.0, 156.3, 129.5, 126.9, 124.8, 120.6, 110.6, 68.7, 65.2, 55.5, 21.2, 20.9; MS (EI) *m*/*z* (rel intensity) 252 ($M^+$, 52), 137 (100); HRMS (EI) *m*/*z* calcd for $C_{13}H_{16}O_5$ 252.0998, found 252.0997.

**(*S*)-Acetic Acid 2-Acetoxy-2-(2-methoxy-3-nitrophenyl)ethyl Ester (6).** A solution of 19.91 g (78.94 mmol) of (*S*)-acetic acid 2-acetoxy-2-(2-methoxyphenyl)ethyl ester in 100 mL of $CHCl_3$ was treated at −20 °C with 8.40 g (83.1 mmol) of $KNO_3$ and 39.0 mL (0.276 mol) of TFAA. The reaction mixture was warmed to 0 °C, stirred for 2 d at 0 °C, quenched with $H_2O$, and warmed to room temperature. The aqueous layer was extracted with $CH_2Cl_2$, and the combined organic extracts were dried ($Na_2SO_4$) and concentrated to give a yellow oil that was purified by chromatography on $SiO_2$ (hexanes/EtOAc; 4:1) to give 19.47 g (65.50 mmol, 83%) of **6** as a yellow oil: $[\alpha]_D$ −17.6 (*c* 1.62, $CHCl_3$); IR (neat) 2956, 1747 $cm^{-1}$; $^1H$ NMR $\delta$ 7.82 (dd, 1 H, $J$ = 8.0, 1.5 Hz), 7.62 (dd, 1 H, $J$ = 7.9, 1.5 Hz), 7.24 (t, 1 H, $J$ = 8.0 Hz), 6.33 (t, 1 H, $J$ = 5.2 Hz), 4.31−4.27 (m, 2 H), 3.97 (s, 3 H), 2.11 (s, 3 H), 2.01 (s, 3 H); $^{13}C$ NMR $\delta$ 170.6, 170.0, 151.2, 143.7, 133.5, 132.3, 125.9, 124.3, 68.0, 65.0, 63.1, 21.1, 20.9; MS (EI) *m*/*z* (rel intensity) 297 (7, $M^+$), 182 (100), 166 (46); HRMS (EI) *m*/*z* calcd for $C_{13}H_{15}NO_7$ 297.0849, found 297.0843.

**(*S*)-1-(2-Methoxy-3-nitrophenyl)ethane-1,2-diol.** To a solution of 19.47 g (65.50 mmol) of diacetate **6** in 300 mL of MeOH was added a solution of 18.34 g (132.7 mmol) of $K_2CO_3$ in 100 mL $H_2O$. After 30 min, the reaction mixture was diluted with EtOAc and $H_2O$, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated to afford 12.97 g (60.85 mmol, 93%) of (*S*)-1-(2-methoxy-3-nitrophenyl)ethane-1,2-diol as an orange oil: $[\alpha]_D$ +10.8 (*c* 1.21, $CHCl_3$); IR (neat) 3384, 1604, 1529 $cm^{-1}$; $^1H$ NMR $\delta$ 7.76−7.73 (m, 2 H), 7.21 (t, 1 H, $J$ = 7.6 Hz), 5.20−5.10 (m, 1 H), 3.90−3.80 (m, 5 H), 3.57 (br t, 1 H, $J$ = 9.8 Hz), 3.30 (br s, 1 H); $^{13}C$ NMR $\delta$ 150.7, 143.3, 136.8, 132.5, 125.2, 124.4, 69.2, 66.9, 63.0; MS (EI) *m*/*z* (rel intensity) 182 (100); HRMS (EI) *m*/*z* calcd for $C_8H_8NO_4$ (M-$CH_3O$) 182.0453, found 182.0449;

**(*R*)-2-(*tert*-Butyldiphenylsilanyloxy)-1-(2-methoxy-3-nitrophenyl)ethanol (7).** To a solution of 4.324 g (20.29 mmol) of (*S*)-1-(2-methoxy-3-nitrophenyl)ethane-1,2-diol in 25 mL of dry DMF was added 2.78 g (40.8 mmol) of imidazole followed by 5.30 mL (5.56 g, 20.2 mmol) of TBDPSCl. The reaction mixture was stirred at room temperature for 4 h, poured onto $H_2O$, and extracted with $Et_2O$. The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give a yellow oil that was purified by chromatography on $SiO_2$ (hexanes/EtOAc; 9:1) to afford 1.611 g (2.338 mmol, 12%) of the di-TBDPS-protected compound and 6.684 g (14.81 mmol, 73%) of **7** as a viscous yellow oil: $[\alpha]_D$ +38.5 (*c* 1.31, $CHCl_3$); IR (neat) 3566, 3073, 2253 $cm^{-1}$; $^1H$ NMR $\delta$ 7.83−7.76 (m, 2 H), 7.69−7.66 (m, 2 H), 7.59−7.57 (m,

2 H), 7.46−7.38 (m, 6 H), 7.25 (t, 1 H, $J$ = 8.0 Hz), 5.19−5.12 (m, 1 H), 3.97 (dd, 1 H, $J$ = 10.3, 6.7 Hz), 3.69 (s, 3 H), 3.63 (dd, 1 H, $J$ = 10.2, 7.7 Hz), 3.24 (d, 1 H, $J$ = 3.4 Hz), 1.10 (s, 9 H); $^{13}$C NMR $\delta$ 136.6, 135.7, 135.6, 132.7, 130.2, 130.1, 128.1, 128.0, 125.0, 124.1, 69.0, 68.0, 62.7, 27.0, 19.4; MS (EI) *m*/*z* (rel intensity) 434 (6), 394 (26), 199 (100); HRMS (EI) *m*/*z* calcd for $C_{21}H_{20}NO_5Si$ (M − $C_4H_9$) 394.1111, found 394.1119.

**(*S*)-2-[2-(*tert*-Butyldiphenylsilanyloxy)-1-(2-methoxy-3-nitrophenyl)ethyl]isoindole-1,3-dione**. To a solution of 6.658 g (14.76 mmol) of alcohol **7** in 90 mL of dry THF were added 4.66 g (17.8 mmol) of $Ph_3P$, 2.607 g (17.69 mmol) of phthalimide, and 2.80 mL (3.10 g, 17.8 mmol) of DEAD. The reaction mixture was stirred for 90 min, concentrated in vacuo to give a viscous orange oil, and purified by chromatography on $SiO_2$ (hexanes/EtOAc; 4:1) to afford 7.663 g (13.20 mmol, 89%) of (*S*)-2-[2-(*tert*-butyl-diphenylsilanyloxy)-1-(2-methoxy-3-nitrophenyl)ethyl]isoindole-1,3-dione as a viscous oil: $[\alpha]_D$ +32.4 (*c* 0.96, $CHCl_3$); IR (neat) 3071, 2858, 1776, 1713 cm$^{-1}$; $^1$H NMR $\delta$ 7.96−7.60 (m, 11 H), 7.40−7.20 (m, 6 H), 7.18 (t, 1 H, $J$ = 7.7 Hz), 6.01−5.92 (m, 1 H), 4.67 (t, 1 H, $J$ = 9.8 Hz), 4.20−4.15 (m, 1 H), 3.89 (s, 3 H), 0.93 (s, 9 H); $^{13}$C NMR $\delta$ 168.6, 152.1, 143.7, 135.7, 135.6, 134.9, 134.3, 133.0, 131.9, 130.1, 130.0, 127.9, 125.6, 123.9, 123.5, 63.2, 62.0, 50.4, 26.7, 19.1; MS (EI) *m*/*z* (rel intensity) 565 (16), 523 (100), 328 (55); HRMS (EI) *m*/*z* calcd for $C_{29}H_{23}N_2O_6Si$ (M − $C_4H_9$) 523.1325, found 523.1318.

**(*S*)-2-(*tert*-Butyldiphenylsilanyloxy)-1-(2-methoxy-3-nitrophenyl)ethylamine (8).** A solution of 7.663 g (13.20 mmol) of (*S*)-2-[2-(*tert*-butyldiphenylsilanyloxy)-1-(2-methoxy-3-nitrophenyl)ethyl]isoindole-1,3-dione and 2.3 mL (40 mmol) of hydrazine mono hydrate in 70 mL of EtOH was heated at reflux for 3 h. The reaction mixture was cooled to room temperature, diluted with $Et_2O$, and filtered. The solid was washed with $Et_2O$, and the filtrate was concentrated in vacuo, redissolved in $Et_2O$, and washed with 1 N HCl. The organic layer was dried ($Na_2SO_4$) and concentrated to afford 5.940 g (13.19 mmol, 100%) of **8** as an orange, amorphous solid: mp 59−60 °C; $[\alpha]_D$ −6.6 (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 2932, 2860 cm$^{-1}$; $^1$H NMR $\delta$ 9.27 (bs, 1 H) 7.90 (d, 1 H, $J$ = 7.2 Hz), 7.74 (d, 1 H, $J$ = 7.8 Hz), 7.55 (d, 2 H, $J$ = 6.6 Hz), 7.40−7.25 (m, 8 H), 6.95 (t, 1 H, $J$ = 8.0 Hz), 4.82 (br s, 1 H), 4.10 (dd, 1 H, $J$ = 10.8, 4.2 Hz), 3.88 (dd, 1 H, $J$ = 10.6, 4.5 Hz), 3.58 (s, 3 H), 1.0 (s, 9 H); $^{13}$C NMR $\delta$ 151.4, 143.1, 136.0, 135.7, 135.6, 133.5, 132.2, 130.4, 130.3, 130.2, 128.1, 128.0, 126.3, 123.9, 64.3, 62.8, 51.0, 26.9, 19.3; MS (EI) *m*/*z* (rel intensity) 393 (15), 198 (100), 181 (91); HRMS (EI) *m*/*z* calcd for $C_{21}H_{21}N_2O_4Si$ (M − $C_4H_9$) 393.1271, found 393.1253.

**(*S*)-[2-(*tert*-Butyldiphenylsilanyloxy)-1-(2-methoxy-3-nitrophenyl)ethyl]-(4-methoxybenzyl)amine (9).** To a solution of 5.031 g (11.17 mmol) of amine **8** in 13 mL of MeOH was added at 0 °C 712.7 mg (11.34 mmol) of $NaBH_3CN$ followed by 1.50 mL (1.68 g, 12.3 mmol) of *p*-anisaldehyde and 0.5 mL of AcOH. The reaction mixture was warmed to room temperature, stirred overnight, and quenched with $H_2O$ and solid $Na_2CO_3$. The viscous suspension was transferred to a separatory funnel and extracted with $CH_2Cl_2$. The combined organic extracts were dried ($Na_2SO_4$) and concentrated in vacuo to give a bright yellow oil that was purified by chromatography on $SiO_2$ (hexanes/EtOAc; 9:1) to afford 5.324 g (9.336 mmol, 84%) of amine **9** as a light yellow oil: $[\alpha]_D$ −37.3 (*c* 0.74, $CHCl_3$); IR (neat) 2859, 1611 cm$^{-1}$; $^1$H NMR $\delta$ 7.91 (dd, 1 H, $J$ = 7.7, 1.6 Hz), 7.73 (dd, 1 H, $J$ = 8.1, 1.6 Hz), 7.63−7.55 (m, 4 H), 7.45−7.30 (m, 6 H), 7.25−7.15 (m, 3 H), 6.89 (d, 2 H, $J$ = 8.5 Hz), 4.33 (dd, 1 H, $J$ = 8.1, 3.9 Hz), 3.83−3.79 (m, 4 H), 3.68−3.56 (m, 6 H), 2.50 (bs, 1 H), 1.06 (s, 9 H); $^{13}$C NMR $\delta$ 158.8, 152.2, 143.9, 137.2, 135.8, 135.7, 133.8, 133.3, 133.2, 132.5, 130.0, 129.4, 127.9, 124.5, 124.1, 114.0, 67.5, 62.9, 56.7, 55.5, 51.0, 27.0, 19.4; MS (EI) *m*/*z* (rel intensity) 513 (36), 121 (100); HRMS (EI) *m*/*z* calcd for $C_{29}H_{29}N_2O_5Si$ (M − $C_4H_9$) 513.1846, found 513.1844.

**(*R*)-Acetic Acid [[2-(*tert*-Butyldiphenylsilanyloxy)-1-(2-methoxy-3-nitrophenyl)ethyl]-(4-methoxybenzyl)carbamoyl]methyl Ester (10).** To a solution of 1.439 g (12.19 mmol) of acetoxyacetic acid and 2.00 mL (1.84 g; 18.2 mmol) of NMM in 25 mL of dry $CH_2Cl_2$ was added at −20 °C 1.66 mL (1.75 g; 12.8 mmol) of isobutyl chloroformate. After 15 min, a solution of 5.324 g (9.336 mmol) of amine **9** in 15 mL of dry $CH_2Cl_2$ was added dropwise via cannula. The reaction mixture was warmed to room temperature, stirred for 12 h, diluted with $CH_2Cl_2$, and washed with 1 N $NaH_2PO_4$ and brine. The organic layer was dried ($MgSO_4$) and concentrated to give a yellow oil that was purified by chromatography on $SiO_2$ (hexanes/EtOAc; 7:3) to afford 4.660 g (6.952 mmol, 74%) of **10** as a viscous oil: $[\alpha]_D$ +38.0 (*c* 0.9, $CHCl_3$); IR (neat) 3016, 2859, 1750, 1667 cm$^{-1}$; $^1$H NMR $\delta$ 7.76 (d, 1 H, $J$ = 8.0 Hz), 7.61−7.27 (m, 12 H), 7.17−7.09 (m, 2 H), 6.85−6.75 (m, 2 H), 6.63 (d, 1 H, $J$ = 8.1 Hz), 5.75−5.65 (m, 0.4 H); 5.26−5.13 (m, 1 H), 4.90−3.90 (m, 6 H), 3.85, 3.80, 3.73, 3.62 (4 s, 6 H), 2.24, 2.16 (2 s, 3 H), 1.02, 0.93 (2 s, 9 H); $^{13}$C NMR $\delta$ 170.8, 170.7, 168.0, 167.8, 159.2, 158.7, 135.8, 135.6, 134.9, 134.3, 132.8, 132.6, 130.3, 130.0, 129.4, 128.4, 128.2, 127.9, 127.4, 126.2, 125.1, 123.7, 123.1, 114.5, 114.2, 113.7, 62.9, 62.7, 62.1, 61.7, 55.7, 55.5, 55.4, 54.9, 48.7, 44.9, 26.9, 20.9, 20.8, 19.2; MS (EI) *m*/*z* (rel intensity) 671 ([M + H]$^+$, 10), 613 (40), 121 (100); HRMS (EI) *m*/*z* calcd for $C_{33}H_{33}N_2O_8Si$ (M − $C_4H_9$) 613.2006, found 613.2025.

**(*R*)-Acetic Acid [[1-(3-Acetylamino-2-methoxyphenyl)-2-(*tert*-butyldiphenylsilanyloxy)ethyl]-(4-methoxybenzyl)-carbamoyl]methyl Ester (11).** To a solution of 4.511 g (6.279 mmol) of nitroarene **10** in 50 mL of *n*-PrOH was added 843.2 mg of 10% Pd/C. The suspension was stirred under $H_2$ (1 atm) for 4 h, filtered through Celite (EtOAc), and concentrated to give the crude aniline as a maroon, amorphous solid. A solution of this aniline in 30 mL of dry $CH_2Cl_2$ was treated with 1.88 mL (1.36 g, 13.5 mmol) of $Et_3N$ followed by 718 $\mu$L (793 mg, 10.1 mmol) of AcCl. The reaction mixture was stirred at room temperature for 12 h, diluted with $CH_2Cl_2$, and washed with $H_2O$ and brine. The organic layer was dried ($MgSO_4$) and chromatographed on $SiO_2$ (hexanes/EtOAc; 1:1) to afford 2.432 g (3.565 mmol, 53%) of **11** as a light tan, viscous oil in addition to 1.450 g (2.264 mmol, 34%) of the intermediate aniline which was resubjected to acetylation to yield at total of 3.732 g (5.470 mmol, 81%) of amide **11**: $[\alpha]_D$ −34.4 (*c* 1.08, $CHCl_3$); IR (neat) 3305, 2859, 2250, 1748, 1663 cm$^{-1}$; $^1$H NMR $\delta$ 8.29−8.15 (m, 1 H), 7.75−7.20 (m, 11 H), 7.12−6.88 (m, 3 H), 6.82−6.61 (m, 2 H), 6.09−5.99 (m, 0.3 H), 5.37 (d, 0.6 H, $J$ = 14.8 Hz), 5.15−5.06 (m, 0.5 H), 5.00 (d, 0.5 H, $J$ = 14.3 Hz), 4.63−4.39 (m, 2 H), 4.07−3.61 (m, 8 H), 2.26−2.05 (m, 6 H), 1.01, 0.96 (2 s, 9 H); $^{13}$C NMR $\delta$ 171.0, 168.5, 167.9, 167.7, 158.6, 148.4, 135.7, 135.6, 132.7, 132.5, 132.0, 130.6, 130.1, 129.8, 129.4, 128.9, 128.8, 128.1, 127.8, 127.4, 124.8, 123.2, 122.5, 120.7, 114.2, 113.6, 63.1, 62.2, 61.7, 61.5, 61.2, 55.3, 54.2, 47.2, 44.7, 26.9, 25.0, 24.9, 21.0, 20.8, 19.2; MS (EI) *m*/*z* (rel intensity) 651 (28), 625 (11), 121 (100); HRMS (EI) *m*/*z* calcd for $C_{35}H_{37}N_2O_7Si$ (M − $C_4H_9$) 625.2370, found 625.2375**.**

**(*R*)-*N*-[1-(3-Acetylamino-2-methoxyphenyl)-2-(*tert*-butyldiphenylsilanyloxy)ethyl]-2-hydroxy-*N*-(4-methoxybenzyl)acetamide (12).** To a solution of 2.432 g (3.565 mmol) of diacetate **11** in 25 mL of MeOH was added 655.0 mg (4.739 mmol) of $K_2CO_3$ in 5 mL of $H_2O$. After 90 min, the mixture was diluted with EtOAc and $H_2O$, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to give an orange oil that was purified by chromatography on $SiO_2$ ($CH_2Cl_2$/EtOAc; 7:3) to afford 2.024 g (3.177 mmol, 89%) of **12** as a viscous oil: $[\alpha]_D$ −28.3 (*c* 1.24, $CHCl_3$); IR (neat) 3420, 3313, 2859, 2250, 1683, 1643 cm$^{-1}$; $^1$H NMR $\delta$ 8.26−8.20 (m, 1 H), 7.69−7.27 (m, 11 H), 7.11−6.63 (m, 6 H), 6.07 (bt, 0.3 H, $J$ = 6.1 Hz), 4.99 (dd, 0.6 H, $J$ = 8.3, 5.1 Hz), 4.68, 4.54 (2 d, 1 H, $J$ = 14.8 Hz), 4.40−3.68 (m, 9 H), 3.46 (s, 3 H), 2.22, 2.21 (2s, 3 H), 1.02, 1.00 (2 s, 9 H); $^{13}$C NMR $\delta$ 173.5, 173.3, 168.6, 159.1, 158.6, 148.2, 135.8, 135.7, 135.6, 132.7, 132.5, 132.1, 129.9, 129.3, 128.6, 128.5, 128.0, 127.8, 127.5, 124.9, 124.8, 123.2, 122.6, 114.2, 113.6, 62.8, 61.5, 60.9, 60.3, 55.4, 55.3, 54.6, 46.5, 45.2, 26.9, 25.0, 24.9, 19.2, 19.1; MS (EI) *m*/*z* (rel intensity) 640 (M$^+$, 7), 583 (12), 121 (100); HRMS (EI) *m*/*z* calcd for $C_{33}H_{35}N_2O_6Si$ (M−$C_4H_9$) 583.2264, found 583.2258**.**

**(*R*)-*N*-[1-(*tert*-Butyldiphenylsilanyloxymethyl)-4-hydroxy-8-methoxy-2-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]acetamide (14).** A solution of 157

μL (1.70 mmol) of oxalyl chloride in 5 mL of dry $CH_2Cl_2$ was treated at −60 to −50 °C with a solution of 272 μL (3.34 mmol) of DMSO in 2 mL of $CH_2Cl_2$ followed by a solution of 1.020 g (1.593 mmol) of **12** in 2 mL of $CH_2Cl_2$. After 45 min, 1.09 mL (791 mg, 7.80 mmol) of $Et_3N$ were added, and the reaction mixture was warmed to room temperature, stirred for 2 h, and quenched with $H_2O$. The aqueous layer was extracted with $CH_2Cl_2$. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give 953.7 mg (1.494 mmol, 94%) of crude aldehyde **13**. A solution of this compound in 14 mL of dioxane was treated with 340.5 mg (1.987 mmol) of anhydrous pTsOH, heated at reflux for 90 min, cooled to room temperature, diluted with $H_2O$, and extracted with $Et_2O$. The combined organic extracts were dried ($MgSO_4$) and purified by chromatography on $SiO_2$ ($CH_2Cl_2$/EtOAc; 7:3) to afford 760.5 mg (1.191 mmol, 75%) of **14** as a light yellow glass: $[\alpha]_D$ −41.0 (*c* 1.03, $CHCl_3$); IR (neat) 3422, 2859, 2250, 1651 $cm^{-1}$; $^1H$ NMR δ 8.26 (d, 1 H, *J* = 8.2 Hz), 7.60−7.27 (m, 13 H), 7.09 (d, 2 H, *J* = 7.8 Hz), 6.78 (d, 2 H, *J* = 7.8 Hz), 5.60 (d, 1 H, *J* = 14.6 Hz), 5.06 (s, 1 H), 4.70 (bs, 1 H), 4.30 (d, 1 H, *J* = 14.5 Hz), 4.21 (s, 1 H), 3.85−3.66 (m, 5 H), 3.12 (s, 3 H), 2.17 (s, 3 H), 1.05 (s, 9 H); $^{13}C$ NMR δ 172.1, 168.3, 159.3, 144.4, 135.7, 135.6, 133.1, 132.6, 132.5, 130.3, 130.1, 129.7, 128.5, 128.0, 123.8, 121.7, 121.3, 114.2, 66.6, 65.5, 60.7, 55.9, 55.4, 49.4, 27.0, 24.9, 19.2; MS (EI) *m*/*z* (rel intensity) 581 (21), 121 (100); HRMS (EI) *m*/*z* calcd for $C_{33}H_{33}N_2O_6Si$ (M − $C_4H_9$) 581.2108, found 581.2105.

**(*R*)-*N*-[1-(*tert*-Butyldiphenylsilanyloxymethyl)-8-methoxy-2-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]acetamide (15).** To a solution of 358.7 mg (0.5619 mmol) of alcohol **14** in 6 mL of dry $CH_2Cl_2$ were added 4.2 mg (0.034 mmol) of DMAP, 79.0 μL (77.3 mg, 0.976 mmol) of pyridine, and 135 μL (168 mg, 0.972 mmol) of phenyl thionochloroformate. The reaction mixture was stirred for 6 h, concentrated, and passed through a short plug of $SiO_2$ ($CH_2Cl_2$/EtOAc; 9:1) to give 305.6 mg (0.3946 mmol) of the crude thiocarbonate as a light yellow, sticky solid. A solution of this compound in 30 mL of dry, degassed benzene was heated at reflux and treated over a 2.5 h period with a solution of 7.1 mg (0.043 mmol) of AIBN and 138 μL (0.512 mmol) of $Bu_3SnH$ in 5 mL of dry, degassed benzene. After 24 h, an additional solution of 7.1 mg (0.043 mmol) of AIBN in 5 mL of benzene was added. The reaction mixture was heated at reflux for an additional 36 h, cooled to room temperature, and concentrated in vacuo. The residue was purified by chromatography on $SiO_2$ ($CH_2Cl_2$/EtOAc; 3:1) through a plug of KF to afford 190.2 mg (0.3056 mmol, 54%) of **15** as a light yellow, viscous oil: $[\alpha]_D$ −19.2 (*c* 1.09, $CHCl_3$); IR (neat) 3421, 3289, 2247, 1642 $cm^{-1}$; $^1H$ NMR δ 8.15 (d, 1 H, *J* = 8.3 Hz), 7.57−7.52 (m, 2 H), 7.46−7.27 (m, 10 H), 7.12 (d, 2 H, *J* = 8.5 Hz), 6.92 (d, 1 H, *J* = 8.2 Hz), 6.79 (d, 2 H, *J* = 8.6 Hz), 5.66 (d, 1 H, *J* = 14.8 Hz), 4.66−4.61 (m, 1 H), 4.18 (d, 1 H, *J* = 14.8 Hz), 3.84−3.61 (m, 7 H), 3.18 (s, 3 H), 2.18 (s, 3 H), 1.03 (s, 9 H); $^{13}C$ NMR δ 169.8, 168.4, 159.2, 144.9, 135.7, 135.6, 132.8, 132.7, 130.5, 130.0, 129.7, 129.6, 129.4, 128.0, 126.1, 123.7, 121.3, 114.2, 65.9, 60.7, 56.4, 55.4, 48.2, 37.5, 27.0, 24.9, 19.2; MS (EI) *m*/*z* (rel intensity) 622 ($M^+$, 10), 565 (30), 121 (100); HRMS (EI) *m*/*z* calcd for $C_{37}H_{42}N_2O_5Si$ 622.2863, found 622.2842.

**(*R*)-Allyl-[2-(*tert*-butyldiphenylsilanyloxy)-1-(2-methoxy-3-nitrophenyl)ethyl]amine (16).** A suspension of 980 mg of 4 Å MS in 16 mL of dry DMF was treated with 553 mg (3.36 mmol) of $CsOH·H_2O$. After 10 min of vigorous stirring, a solution of 1.513 g (3.360 mmol) of amine **8** in 5 mL of dry DMF was added. The reaction mixture was stirred for 30 min, treated with 344 μL (478 mg, 3.95 mmol) of allyl bromide, and stirred overnight. The suspension was filtered, and the filtrate was diluted with $H_2O$ and extracted with $Et_2O$. The combined organic extracts were dried ($Na_2SO_4$) and purified by chromatography on $SiO_2$ (hexanes/EtOAc; 85:15) to yield 1.293 g (2.636 mmol, 78%) of amine **16** as an orange oil: $[\alpha]_D$ −45.1 (*c* 1.06, $CHCl_3$); IR (neat) 3073, 2254 $cm^{-1}$; $^1H$ NMR δ 7.82 (d, 1 H, *J* = 7.7 Hz), 7.72 (d, 1 H, *J* = 8.1 Hz), 7.68−7.64 (m, 2 H), 7.60−7.55 (m, 2 H), 7.46−7.34 (m, 6 H), 7.19 (t, 1 H, *J* = 7.7 Hz), 5.98−5.85 (m, 1 H), 5.31−5.12 (m, 2 H), 4.35 (dd, 1 H, *J* = 7.5, 3.9 Hz), 3.84 (dd, 1 H, *J* = 10.0, 3.2 Hz), 3.69−3.60 (m, 4 H), 3.21 (dd, 1 H, *J* = 14.3, 4.9 Hz), 3.09 (dd, 1 H, *J* = 14.3, 5.9 Hz), 2.20 (bs, 1 H), 1.07 (s, 9 H); $^{13}C$ NMR δ 152.2, 143.9, 137.3, 136.9, 135.8, 135.7, 133.7, 133.3, 133.2, 130.1, 130.0, 128.0, 124.5, 124.1, 116.1, 67.4, 63.0, 56.9, 50.2, 27.0, 19.4; MS (EI) *m*/*z* (rel intensity) 433 (82), 221 (100); HRMS (EI) *m*/*z* calcd for $C_{24}H_{25}N_2O_4Si$ (M − $C_4H_9$) 433.1584, found 433.1576.

**(*R*)-Acetic Acid {Allyl-[2-(*tert*-butyldiphenylsilanyloxy)-1-(2-methoxy-3-nitrophenyl)ethyl]carbamoyl}methyl Ester (17).** To a solution of 838.7 mg (1.711 mmol) of allylamine **16** in 10 mL of dry $Et_2O$ were added at 0 °C 430 μL (312 mg, 3.09 mmol) of $Et_3N$ and 276 μL (351 mg, 2.57 mmol) of acetoxyacetyl chloride. The reaction mixture was slowly warmed to room temperature, stirred overnight, and filtered. The residue was washed with $Et_2O$, and the filtrate was concentrated and purified by chromatography on $SiO_2$ (hexanes/EtOAc; 3:2) to yield 864.1 mg (1.464 mmol, 86%) of the desired amide **17** as a yellow oil: $[\alpha]_D$ +33.8 (*c* 1.29, $CHCl_3$); IR (neat) 3073, 2251, 1751, 1668 $cm^{-1}$; $^1H$ NMR δ 7.80 (bt, 1 H, *J* = 9.2 Hz), 7.68−7.55 (m, 3 H), 7.50−7.27 (m, 8 H), 7.16 (bt, 1 H, *J* = 7.9 Hz), 5.73−5.50 (m, 1.5 H), 5.20−5.10 (m, 2 H), 4.83−4.56 (m, 2.5 H), 4.20−3.50 (m, 7 H), 2.21, 2.17 (2 s, 3 H), 1.03, 0.99 (2 s, 9 H); $^{13}C$ NMR δ 170.7, 170.6, 167.6, 167.2, 152.9, 152.2, 143.8, 142.8, 135.7, 135.6, 135.3, 134.7, 134.5, 134.1, 133.7, 132.8, 132.7, 132.4, 132.3, 131.9, 130.3, 130.2, 130.0, 128.1, 127.9, 126.1, 125.0, 123.6, 123.1, 117.3, 116.7, 62.9, 62.8, 62.6, 62.5, 61.7, 60.4, 55.3, 54.5, 47.9, 45.1, 26.8, 20.7, 19.1; MS (EI) *m*/*z* (rel intensity) 533 (70), 199 (100); HRMS (EI) *m*/*z* calcd for $C_{28}H_{29}N_2O_7Si$ (M − $C_4H_9$) 533.1744, found 533.1743.

**(*R*)-Acetic Acid {[1-(3-Acetylamino-2-methoxyphenyl)-2-(*tert*-butyldiphenylsilanyloxy)ethyl]allylcarbamoyl}methyl Ester (18).** To a solution of 586.3 mg (0.9932 mmol) of allyl amide **17** and 18.6 mg (0.0497 mmol) of ethyl viologen dibromide in 7.5 mL of $CH_2Cl_2/H_2O$ (8:1) was added dropwise a solution of 685 mg (4.95 mmol) of $K_2CO_3$ and 808 mg (4.59 mmol) $Na_2S_2O_4$ in 3.5 mL of $H_2O$. The reaction mixture was stirred for 24 h, diluted with $H_2O$, and extracted with $CH_2Cl_2$, EtOAc, and $Et_2O$. The combined organic extracts were dried ($Na_2SO_4$), concentrated, and passed through a short plug of $SiO_2$ (hexanes/EtOAc, 1:1) to yield 420.3 mg (0.7500 mmol, 76%) of the desired aniline as a yellow, sticky solid. A solution of this aniline was then dissolved in 7 mL of dry $CH_2Cl_2$ was treated with 210 μL (152 mg, 1.51 mmol) of $Et_3N$ and 93.0 μL (103 mg, 1.31 mmol) of acetyl chloride. The reaction mixture was stirred at room temperature for 12 h, concentrated in vacuo, and purified by chromatography on $SiO_2$ (hexanes/EtOAc; 1:1) to yield 402.1 mg (0.6675 mmol, 67% from **17**) of **18** as a viscous oil: $[\alpha]_D$ −45.0 (*c* 1.02, $CHCl_3$); IR (neat) 3302, 3072, 2248, 1750, 1664 $cm^{-1}$; $^1H$ NMR δ 8.28−8.19 (m, 1 H), 7.75−7.55 (m, 5 H), 7.45−7.27 (m, 6 H), 7.09−7.02 (m, 1.5 H), 6.78 (d, 0.5 H, *J* = 7.4 Hz), 6.07 (t, 0.4 H, *J* = 5.9 Hz), 5.58−5.45 (m, 1 H), 5.33 (d, 0.6 H, *J* = 14.6 Hz), 5.10−5.00 (m, 1.5 H), 4.95−4.68 (m, 3 H), 4.14−3.97 (m, 2 H), 3.82−3.64 (m, 5 H), 2.23−2.16 (m, 6 H), 1.05, 1.00 (2 s, 9 H); $^{13}C$ NMR δ 170.9, 170.6, 168.6, 168.5, 167.4, 167.1, 148.4, 147.9, 135.7, 135.6, 134.0, 133.9, 133.1, 130.2, 130.1, 129.9, 128.0, 127.8, 124.7, 124.6, 123.7, 123.0, 122.4, 120.8, 117.1, 116.8, 62.8, 62.7, 61.8, 61.5, 61.3, 54.9, 53.3, 46.4, 44.8, 26.8, 24.9, 24.8, 20.8, 19.1; MS (EI) *m*/*z* (rel intensity) 545 (100), 388 (54); HRMS (EI) *m*/*z* calcd for $C_{30}H_{33}N_2O_6Si$ (M − $C_4H_9$) 545.2108, found 545.2104.

**(*R*)-*N*-[1-(3-Acetylamino-2-methoxyphenyl)-2-(*tert*-butyldiphenylsilanyloxy)ethyl]-*N*-allyl-2-hydroxyacetamide (19).** To a solution of 2.369 g (3.933 mmol) of the diacetate **18** in 30 mL of MeOH was added a solution of 761 mg (5.51 mmol) of $K_2CO_3$ in 5 mL of $H_2O$. After 2 h, the reaction mixture was diluted with $H_2O$ and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to yield 2.080 g (3.713 mmol, 94%) of the primary alcohol **19** as a viscous oil: $[\alpha]_D$ −47.8 (*c* 1.14, $CHCl_3$); IR (neat) 3422, 3308, 3073, 2250, 1644 $cm^{-1}$; $^1H$ NMR δ 8.30−8.23 (m, 1 H), 7.66−7.29 (m, 11 H), 7.10−6.97 (m, 1.6 H), 6.80 (bd, 0.5 H, *J* = 7.5 Hz), 6.08 (bt, 0.4 H, *J* = 6.4 Hz), 5.52−5.32 (m, 1 H), 5.04−4.79 (m, 2.5 H), 4.52 (dq, 1 H, *J* = 10.5, 3.7 Hz), 4.17−3.95 (m, 3 H), 3.82−3.56 (m, 7 H), 2.24, 2.22 (2 s, 3 H), 1.04, 1.02 (2 s, 9 H); $^{13}C$ NMR δ 172.8, 172.7,

168.8, 168.6, 148.4, 148.0, 135.8, 135.7, 135.6, 133.6, 133.1, 132.7, 132.5, 132.0, 130.3, 130.2, 129.9, 128.6, 128.0, 127.9, 124.8, 124.7, 123.0, 122.7, 117.3, 116.9, 62.5, 61.4, 61.1, 60.5, 60.1, 54.2, 53.8, 45.8, 45.0, 26.8, 24.9, 24.7, 19.2, 19.1; MS (EI) *m*/*z* (rel intensity) 503 (42), 388 (24), 295 (100); HRMS (EI) *m*/*z* calcd for $C_{28}H_{31}N_2O_5Si$ (M−$C_4H_9$) 503.2002, found 503.2021.

***N*-[(1*R*,4*S*)-2-Allyl-1-(*tert*-butyldiphenylsilanyloxymethyl)-4-hydroxy-8-methoxy-3-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]acetamide (21).** A solution of 387 $\mu$L (4.01 mmol) of oxalyl chloride in 8 mL of dry $CH_2Cl_2$ was treated at −50 to −60 °C with a solution of 671 $\mu$L (8.44 mmol) of DMSO in 8 mL $CH_2Cl_2$ followed by a solution of 2.080 g (3.713 mmol) of **19** in 8 mL of $CH_2Cl_2$. After 45 min, 2.69 mL (1.95 g, 19.3 mmol) of $Et_3N$ was added, and the reaction mixture was allowed to warm to room temperature, stirred for 2 h, and diluted with $H_2O$. The aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give crude aldehyde **20**. A solution of this compound in 30 mL of dioxane was treated with 833.1 mg (4.837 mmol) of anhydrous pTsOH and heated at reflux. After 90 min, the reaction mixture was cooled to room temperature, diluted with $H_2O$, and extracted with $Et_2O$. The combined organic extracts were dried ($MgSO_4$) and purified by chromatography on $SiO_2$ (hexanes/EtOAc; 45:55) to afford 1.269 g (2.273 mmol, 61%) of **21** as a light yellow glass: $[\alpha]_D$ −34.6 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3422, 3311, 3072, 2250, 1658 $cm^{-1}$; $^1H$ NMR $\delta$ 8.27 (d, 1 H, $J$ = 8.4 Hz), 7.70−7.25 (m, 12 H), 5.80−5.65 (m, 1 H, 5.16−5.03 (m, 3 H), 4.92−4.79 (m, 1 H), 4.13 (s, 1 H), 3.90−3.80 (m, 2 H), 3.73−3.63 (m, 7 H), 2.21 (s, 3 H), 1.01 (s, 9 H); $^{13}C$ NMR $\delta$ 171.8, 168.5, 144.7, 135.6, 135.5, 135.0, 133.2, 132.6, 132.4, 130.4, 130.1, 128.0, 127.7, 123.8, 122.0, 121.3, 117.8, 67.2, 66.6, 65.6, 61.2, 56.9, 49.4, 26.9, 24.8, 19.2; MS (EI) *m*/*z* (rel intensity) 558 ($M^+$, 9), 199 (100); HRMS (EI) *m*/*z* calcd for $C_{32}H_{38}N_2O_5Si$ 558.2550, found 558.2555.

**(*R*)-*N*-[2-Allyl-1-(*tert*-butyldiphenylsilanyloxymethyl)-8-methoxy-3-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]acetamide (22).** To a solution of 200.2 mg (0.3586 mmol) of alcohol **21** in 2.7 mL of dry $CH_2Cl_2$ was added 12.1 mg (0.0990 mmol) of DMAP, 51.0 $\mu$L (50.0 mg, 0.630 mmol) of pyridine, and 86.0 $\mu$L (108 mg, 0.613 mmol) of PhOC(S)Cl. The reaction flask was wrapped in aluminum foil, and the solution was stirred at room temperature. After 1 h, 12.1 mg (0.0990 mmol) of DMAP and 24.0 $\mu$L (30.1 mg, 0.171 mmol) of PhOC(S)Cl were added. The reaction mixture was stirred for an additional 16 h, concentrated, and passed through a short plug of $SiO_2$ (hexanes/EtOAc; 1:1) to yield 181.3 mg (0.2611 mmol) of the crude thionocarbonate as a yellow, sticky solid. A solution of this compound in 15 mL of dry, degassed benzene was treated with a solution of 3 mg (0.02 mmol) of AIBN and 91.0 $\mu$L (99.1 mg, 0.338 mmol) of $Bu_3SnH$ in 3 mL of dry, degassed benzene over a 2.5 h period. After 24 h, an additional 3 mg (0.02 mmol) of AIBN in 3 mL of benzene was added. The reaction mixture was heated at reflux for an additional 36 h, cooled to room temperature, and concentrated in vacuo. The residue was purified by chromatography on $SiO_2$ ($CH_2Cl_2$/EtOAc; 4:1) through a plug of KF to afford 76.4 mg (0.141 mmol, 39%) of lactam **22** as a white, amorphous solid: mp 170.5−172.1 °C; $[\alpha]_D$ −10.9 (*c* 1.17, $CHCl_3$); IR ($CHCl_3$) 3423, 2860, 1685, 1638 $cm^{-1}$; $^1H$ NMR $\delta$ 8.18 (d, 1 H, $J$ = 8.3 Hz), 7.56−7.26 (m, 11 H), 6.91 (d, 1 H, $J$ = 8.3 Hz), 5.84−5.72 (m, 1 H), 5.15−4.95 (m, 3 H), 4.80−4.75 (m, 1 H), 3.87 (dd, 1 H, $J$ = 10.5, 3.3 Hz), 3.78−3.64 (m, 6 H), 3.51 (d, 1 H, $J$ = 19.2 Hz), 2.22 (s, 3 H), 1.00 (s, 9 H); $^{13}C$ NMR $\delta$ 169.5, 168.4, 145.0, 135.6, 135.5, 133.3, 132.8, 132.7, 130.5, 130.0, 129.8, 128.0, 126.0, 123.7, 121.5, 117.1, 66.0, 61.2, 57.3, 48.3, 37.3, 27.0, 24.9, 19.2; MS (EI) *m*/*z* (rel intensity) 542 ($M^+$, 17), 485 (11), 273 (100); HRMS (EI) *m*/*z* calcd for $C_{32}H_{38}N_2O_4Si$ 542.2601, found 542.2578.

**(*R*)-*N*-[1-(*tert*-Butyldiphenylsilanyloxymethyl)-8-methoxy-3-oxo-2-propenyl-1,2,3,4-tetrahydroisoquinolin-7-yl]-acetamide (23).** To a solution of 329.2 mg (0.6070 mmol) of the allyl amide **22** in 1.2 mL of dry toluene was added 44.6 mg (0.0482 mmol; 8 mol %) of $ClRh(PPh_3)_3$. The reaction mixture was heated at reflux for 14 h, cooled to room temperature, concentrated, and passed through a short plug of $SiO_2$ ($CH_2Cl_2$/EtOAc; 4:1) to yield 242.3 mg (0.4467 mmol, 74%) of enamide **23** as a light tan, viscous oil that was carried on without further purification: $^1H$ NMR $\delta$ 8.22 (d, 1 H, $J$ = 8.3 Hz), 7.49−7.27 (m, 12 H), 6.93 (d, 1 H, $J$ = 8.3 Hz), 5.27−5.18 (m, 2 H), 4.01 (dd, 1 H, $J$ = 10.4, 3.6 Hz), 3.86 (d, 1 H, $J$ = 19.5 Hz), 3.74−3.68 (m, 4 H), 3.53 (d, 1 H, $J$ = 19.6 Hz), 2.24 (s, 3 H), 1.76 (dd, 3 H, $J$ = 6.6, 1.4 Hz), 0.94 (s, 9 H); $^{13}C$ NMR $\delta$ 168.4, 168.2, 145.3, 135.6, 135.5, 132.7, 129.9, 129.8, 127.9, 126.4, 125.8, 123.5, 121.6, 107.2, 65.1, 61.3, 55.1, 37.6, 26.8, 24.9, 19.1, 15.7.

**(*R*)-*N*-[1-(*tert*-Butyldiphenylsilanyloxymethyl)-8-methoxy-3-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]acetamide (24).** To a solution of 58.4 mg (0.108 mmol) of enamide **23** in 1 mL of THF was added 1.8 mg (0.0071 mmol) of $OsO_4$ followed by a solution of 36.5 mg (0.171 mmol) of $NaIO_4$ in 1 mL of $H_2O$. The reaction mixture was stirred at room-temperature overnight, diluted with $H_2O$, and extracted with $CH_2Cl_2$. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography on $SiO_2$ ($CH_2Cl_2$/EtOAc; 1:1) to afford 17.2 mg (0.0324 mmol, 30%) of *N*-formyl amide and 35.6 mg (0.0709 mmol, 66%) of **24** as a light yellow glass: $[\alpha]_D$ +9.2 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3253, 3072, 2247, 1669 $cm^{-1}$; $^1H$ NMR $\delta$ 8.15 (d, 1 H, $J$ = 8.2 Hz), 7.62−7.55 (m, 3 H), 7.45−7.28 (m, 8 H), 7.13 (bs, 1 H), 6.88 (d, 1 H, $J$ = 8.2 Hz), 4.75 (bs, 1 H); 3.88 (d, 1 H, $J$ = 9.7 Hz), 3.72−3.60 (m, 5 H), 3.45 (d, 1 H, $J$ = 20.1 Hz), 2.21 (s, 3 H), 1.02 (s, 9 H); $^{13}C$ NMR $\delta$ 171.7, 168.5, 145.7, 135.6, 135.4, 133.0, 132.9, 130.0, 129.9, 129.5, 127.9, 127.8, 124.4, 124.1, 121.7, 67.8, 61.1, 54.4, 35.9, 26.9, 26.6; 24.8, 19.2; MS (EI) *m*/*z* (rel intensity) 445 (95), 233 (100), 199 (91); HRMS (EI) *m*/*z* calcd for $C_{25}H_{25}N_2O_4Si$ (M − $C_4H_9$) 445.1584, found 445.1587. To a solution of 73.3 mg (0.138 mmol) of the *N*-formyl amide side product in 3 mL of MeOH was added 15.5 mg (0.185 mmol) of $NaHCO_3$. After 2 h, the solution was diluted with $H_2O$ and extracted with $CH_2Cl_2$. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give 60.4 mg (87%) of **24**.

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**Supporting Information Available:** $^1H$ and $^{13}C$ NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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