Optically Active Cyclobutanone Chemistry: Synthesis of (−)-Cyclobut-A and (±)-3′-*Epi*-Cyclobut-A

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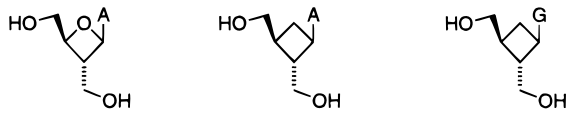
The carbocyclic nucleoside analogues (−)-cyclobut-A and (±)-3′-*epi*-cyclobut-A were synthesized utilizing photolysis of the (benzyloxymethyl)(methoxy) chromium carbene complex **4** with optically active ene-carbamate **5** to produce the corresponding optically active α,α-disubstituted cyclobutanone **6**. Stereoselective removal of the α-ethoxy group with inversion gave cyclobutanone **7**, which was converted by existing methodology to the title compounds.

Introduction

Recent methodology developed in these laboratories provides efficient access to optically active cyclobutanones.[1] These cyclobutanones underwent Baeyer−Villiger oxidation/ring expansion regio- and stereoselectively to form optically active butyrolactones[2] which were converted to butenolides and used in the synthesis of (+)-tetrahydrocerulenin,[3] (+)-cerulenin,[4] optically active spiroketals,[5] and a template for nucleoside analogues.[6]

Cyclobutanones are also subject to carbocyclic ring expansions[7] by reaction with a variety of reagents including diazomethane, sulfur-stabilized carbanions, and samarium iodide/diiodomethane[8] as well as two-step procedures involving methylenation/epoxidation. Carbocyclic ring expansion of the optically active cyclobutanone used as a template for nucleoside analogues[6] should provide cyclopentanones convertible to carbocyclic nucleoside analogues, provided the ring expansion proceeds with the desired regiochemistry. Carbocyclic nucleoside analogues are of substantial current interest as antiviral compounds, since many display potent biological activity, and possess substantially greater metabolic stability than their carbohydrate-derived analogues.[9]

The recent discovery of oxetanocin A (**1**), a natural product containing an unusual four-membered oxetane ring substituting the ribose of adenosine and possessing potent anti-HIV properties, has further expanded the scope in the search for therapeutic nucleoside derivatives.[10] Cyclobut-A (**2**), the carbocyclic analogue of oxetanocin, was first synthesized in 1989 by Honjo,[11] and its remarkable antiviral activity[12] has prompted numerous subsequent syntheses of both the parent and related compounds.[13] The observation of differing activities between opposite enantiomers[14] highlights the need for asymmetric syntheses, and several nonracemic approaches have succeeded in providing material of high optical purity. In some early studies, chiral resolutions were performed to deliver nonracemic intermediates.[15] Jung et al. utilized an enzymatic desymmetrization[16] of a *meso*-cyclobutene as the enantioselecive step in their formation of nonracemic cyclobut-A. In another notable approach, Ichikawa employed a chiral titanium complex as the catalyst in an asymmetric [2 + 2] cyclization to provide a functionalized cyclobutane intermediate in >98% ee, which was readily converted to the final product.[17]



Oxetanocin A (**1**) Cyclobut-A (**2**) Cyclobut-G (**3**)

A series of studies examining the reactivity of an appropriately substituted optically active cyclobutanone in the context of the synthesis of (−)-cyclobut-A are described below.

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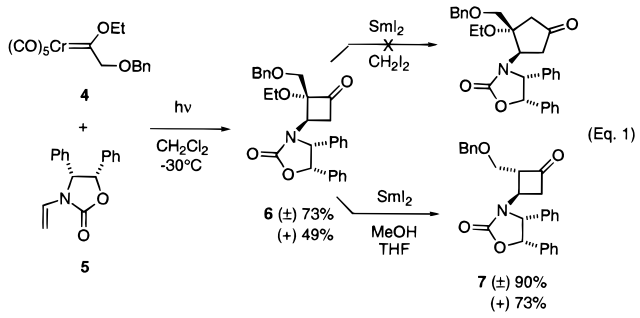
Table 1.

substrate	conditions	yield, %	ratio **a**/**b**
8	BH_3·THF	82	4/1
	9-BBN	63	1/1
	c-Hex_2BH	84	15/1
	catecholborane/Rh^I	79	7/1
10	BH_3·THF (3 equiv)	85	5/1
	9-BBN	75	1/1

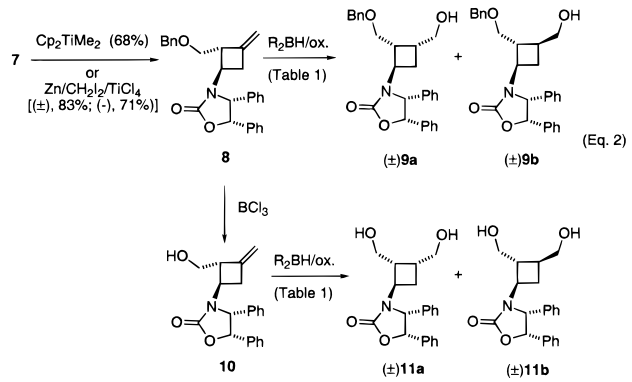
Results and Discussion

The requisite optically active cyclobutanone precursor to carbocyclic nucleoside analogues was synthesized, using a previously developed procedure,[6] by the photolysis of chromium carbene complex **4** with optically active ene-carbamate **5** (eq 1). Attempted ring expansion to the cyclopentanone using SmI_2/CH_2I_2[8] in THF resulted instead in α-deoxygenation of the cyclobutanone. Optimization of this deoxygenation provided **7** in excellent yield with high selectivity (eq 1). This reductive cleavage of α-heteroatom-substituted carbonyl compounds is a well-known process for SmI_2, and is thought to proceed via the enolate or enol.[18] In the case of cyclobutanone **6**, protonation of the reduction intermediate gave the more stable *trans*-disubstituted cyclobutanone **7**. Since this cyclobutanone has many of the structural features found in cyclobut-A (**2**), its reaction chemistry was examined in the context of the synthesis of **2**.

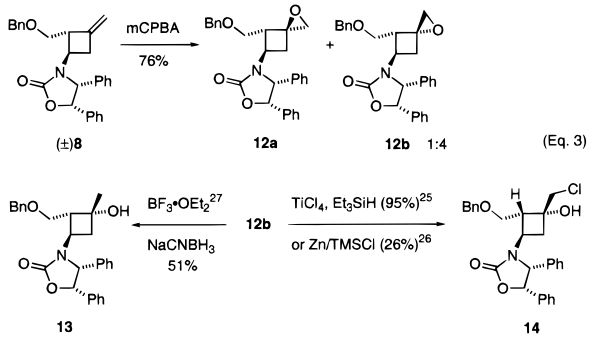


Direct introduction of a hydroxymethyl group surrogate using basic methylenation reagents $Ph_3P{=}CHOMe$,[19] [TMSCHOMe]Li,[20] or [t-BuN=CHN(Me)CHTMS]Li[21] resulted in consumption of the starting material and production of free oxazolidinone, but failed to provide any of the desired compounds. It is likely that base-induced *β*-elimination of the oxazolidinone occurred, and the resulting cyclobutenone decomposed, as has previously been observed for related compounds.[1c] As a consequence, a two-step hydroxymethylation of **7** was next examined.

Methylenation of **7** was successful with both the Petasis reagent, Cp_2TiMe_2,[22] and the Takai reagent, Zn/$CH_2I_2/TiCl_4$,[23] although the latter was preferred for its higher yields. Hydroboration/oxidation of methylenecyclobutane **8** under a variety of conditions always led to the undesired *cis*-dialkyl product **9a** as the major product, with only minor (50% maximum) amounts of the desired trans compound **9b** (Table 1, eq 2). Attempts to direct the hydroboration[24] to the opposite face of **8** utilizing the adjacent hydroxymethyl group also failed (Table 1, eq 2).



In contrast to hydroboration, epoxidation of **8** with mCPBA occurred predominantly from the bottom face giving a 4:1 mixture of isomers. Epoxide ring opening, even under Lewis-acidic conditions, produced the tertiary alcohol rather than the desired primary alcohol.



Both Swern and Dess−Martin oxidation of alcohols **9a**, **9b** followed by epimerization with NaOMe gave the more stable *trans*-aldehyde in good yield and as a >17:1 mixture of *β* to α-epimers (eq 4). Attempts to produce this aldehyde directly from methylenecyclobutane **8** using Wacker oxidation chemistry[28] met with limited success (eq 5). Although some aldehyde was formed, the major products arose from ring expansion of the product from Wacker hydroxylation at the more substituted olefin terminus (eq 4).[29] This ring expansion is under current study.

The most efficient route to **9b** was a sequence of hydroboration/oxidation (Swern)/epimerization (NaOMe)/reduction ($NaBH_4$), carried out sequentially with minimal purification of the intermediates. In this way, (−)-**9b** was obtained in 67% overall yield from (−)-**8**. With optically active precursors to cyclobut-A and 3′-*epi*-cyclobut-A in hand, elaboration of the nucleoside base was addressed.

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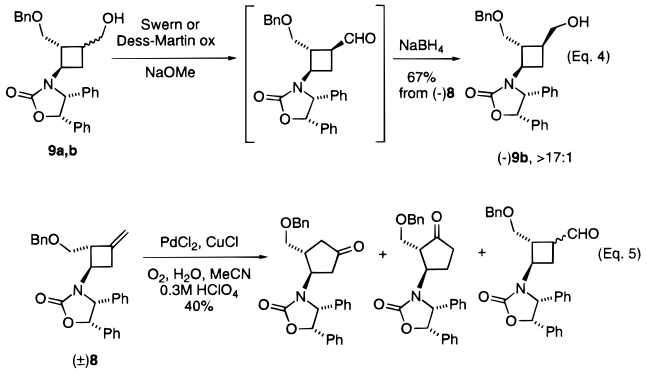
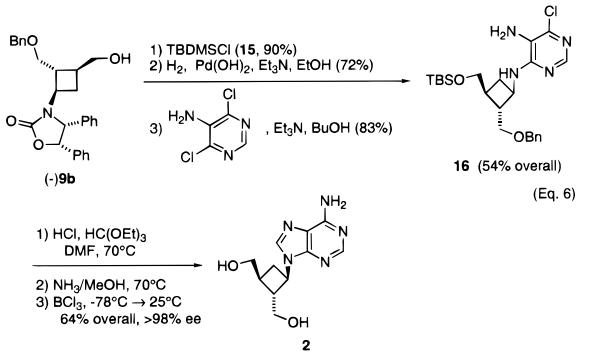


Hydrogenolytic cleavage of the oxazolidinone [$Pd(OH)_2$/H_2] to generate the free amine is normally straightforward. However, with these substrates it proved more efficient to silylate the free hydroxyl group prior to hydrogenolysis. Treatment of the resulting free amine with 5-amino-4,6-dichloropyrimidine introduced the core of the adenine, giving **16** in good yield. Elaboration of **16** to cyclobut-A by conventional methodology,[30] followed by removal of the protecting groups with BCl_3 gave cyclobut-A in 64% yield for the three steps (eq 6). This material had physical properties identical to those reported[15b,17] for authentic material, and was found to be optically pure (>98% ee) by chiral HPLC analysis (Chiralcel OD) of its bis-TBS derivative.



( )-3′-*epi*-Cyclobut-A was synthesized from (±)-**9a** by the same sequence of steps, albeit in lower overall yield (±**9a** → *epi*-**19**; 34%: *epi*-**19** → *epi*-**2**; 49%) because efforts to optimize the process were minimal. The characterization of this material was in agreement with previously reported data.[31]

In summary, the above studies reveal a number of unusual reactions of four-membered ring compounds, as well as some unexpected stereoselectivities, and resulted in the synthesis of (−)-cyclobut-A and (±)-3′-*epi*-cyclobut-A.

Experimental Section

General Methods. THF was distilled from sodium−benzophenone ketyl, CH_2Cl_2, DMF, and Et_3N were distilled from CaH_2, and n-BuOH was distilled from Na. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded in $CDCl_3$ except where noted, and chemical shifts are given in ppm relative to Me_4Si (0 ppm, ^1H), $CDCl_3$ (77.0 ppm, ^{13}C). Column chromatography was performed with ICN 32−63 nm, 60 Å silica gel using flash column techniques. Elemental analyses were performed by M−H−W Laboratories, Phoenix, AZ. All reactions were performed under an atmosphere of Ar unless otherwise noted.

Cyclobutanone 6. A solution of carbene complex **4** (4.19 g, 11.2 mmol) and (4*R*,5*S*)-oxazolidinone **5** (5.77 g, 21.7 mmol) in CH_2Cl_2 (110 mL, degassed) in a Pyrex pressure tube was placed under CO (∼80 psi), cooled to −35 °C, and irradiated with a 400 W Hg-vapor lamp for 6 days. Concentration of the crude reaction mixture followed by removal of $Cr(CO)_6$ by sublimation gave 9.2 g of a light green solid. Purification by flash chromatography (80% Hex/CH_2Cl_2 to 25% EtOAc/Hex gradient elution) provided 3.28 g of recovered oxazolidinone **5** (12.4 mmol, 57%) as a white solid and slightly impure cyclobutanone **6** (2.57 g, 5.45 mmol, 49% of ∼95% pure material) as a yellow gum, which was used without further purification: ^1H NMR δ 7.38−7.50 (m, 5 H), 6.97−7.10 (m, 6 H), 6.74−6.80 (m, 2 H), 6.54 (bs, 2 H), 5.59 (d, J = 7.5 Hz, 1 H), 5.03 (d, J = 7.5 z, 1 H), 4.81 (t, J = 10.2 Hz, 1 H), 4.70 (d, J = 11.1 Hz, 1 H), 4.55 (d, J = 11.1 Hz, 1 H), 4.06 (d, J = 9.0 Hz, 1 H), 3.87 (d, J = 9.0 Hz, 1 H), 3.75 (m, 2 H), 2.71 (dd, J = 9.6, 18.0 Hz, 1 H), 2.45 (dd, J = 10.6, 18.0 Hz, 1 H), 1.23 (t, J = 7.0 Hz, 3 H); ^{13}C NMR δ 206.4, 158.5, 137.2, 135.5, 133.6, 128.7, 128.3, 128.1, 128.0, 127.9, 127.7, 126.7, 125.9, 97.7, 80.3, 74.4, 69.0, 64.8, 61.6, 48.0, 46.1, 15.6; IR (film) 1791, 1752 cm^{-1}; $[\alpha]^{24}_D$ 42.4 (*c* 1.0, $CHCl_3$).

Racemic cyclobutanone **6** was formed similarly, but using carbene complex **4** (3.64 g, 9.71 mmol) and oxazolidinone **5** (5.302 g, 20.0 mmol) in CH_2Cl_2 (35 mL, degassed) to provide recovered oxazolidinone **5** (2.95 g, 11.1 mmol, 56%) and cyclobutanone **6** (3.36 g, 7.13 mmol, 73%) as a white solid: mp 170−172 °C. Anal. Calcd for $C_{29}H_{29}NO_5$: C, 73.87; H, 6.20; N, 2.97. Found: C, 73.66; H, 6.12; N, 2.97.

Cyclobutanone 7. A freshly prepared solution of SmI_2 (0.17 M in THF, 32 mL, 5.3 mmol) was added slowly (5 min) to a 0 °C suspension of **6** (1.00 g, 2.12 mmol) and MeOH (3.5 mL) in THF (7.0 mL, degassed). The mixture was stirred for 5 min and allowed to warm to room temperature, over which time the blue color disappeared. More SmI_2 (1.0 mL, 0.17 mmol) was added until the blue remained for a few seconds, at which point the reaction mixture was quenched with H_2O (2 mL) and concentrated. The crude mixture was diluted with 1 N HCl (15 mL) and H_2O (30 mL) and extracted with EtOAc (2 × 40 mL) and CH_2Cl_2 (15 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (15 mL), washed with brine (15 mL), dried (Na_2SO_4), and concentrated to give 1.06 g of crude material. Flash chromatography (25% EtOAc/Hex) provided 0.82 g of **7** as a clear gum (1.92 mmol, 90%): ^1H NMR δ 7.22−7.33 (m, 4H), 7.07−7.18 (m, 7H), 6.98−7.04 (m, 2H), 6.89−6.95 (m, 2H), 5.91 (d, J = 8.0 Hz, 1H), 5.08 (d, J = 8.0 Hz, 1H), 4.34 (d, J = 12.0 Hz, 1H), 4.28 (d, J = 12.0 Hz, 1H), 4.18 (dt, J = 6.9, 8.4 Hz, 1H), 4.09 (m, 1H), 3.68 (dd, J = 3.2, 10.0 Hz, 1H), 3.47 (ddd, J = 3.2, 7.2, 17.6 Hz, 1H), 3.30 (dd, J = 3.7, 10.0 Hz, 1H), 3.04 (ddd, J = 2.1, 8.4, 17.6 Hz, 1H); ^{13}C NMR δ 204.8, 157.5, 137.8, 134.6, 134.1, 128.7, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 125.8, 79.7, 73.2, 66.5, 65.8, 64.7, 49.7, 42.9; IR (film) 1789, 1746 cm^{-1}; mp 98−100 °C.

Nonracemic **7** was prepared as above by adding SmI_2 (120 mL, 0.15 M in THF, 18 mmol) to (+)-**6** (3.14 g, 6.66 mmol) in MeOH (11 mL) and THF (25 mL) to provide 90% pure (+)-**7** as a white solid (2.00 g, ∼4.68 mmol, ∼70%), which could be taken on without further purification. Recrystallization (EtOAc/Hex) affords analytically pure material as a white solid (1.10 g, 2.56 mmol, 39%): mp 111−112 °C. Anal. Calcd for $C_{27}H_{25}NO_4$: C, 75.86; H, 5.89; N, 3.28. Found: C, 76.06; H, 5.79; N, 3.32. $[\alpha]^{24}_D$ 3.1 (*c* 0.70, $CHCl_3$).

Methylenecyclobutane 8. Following the general procedure of Takai,[23] neat CH_2I_2 (0.75 mL, 9.3 mmol) was added dropwise to a suspension of activated Zn (1.10 g, 16.9 mmol) in THF (17.5 mL). The mixture was stirred for 30 min and cooled to 0 °C, and $TiCl_4$ (1.0 M in CH_2Cl_2, 2.10 mL, 2.10 mmol) was added dropwise. After the addition, the cooling bath was removed, and the resulting slurry was stirred for 30 min. A solution of cyclobutanone **7** (0.801 g) in THF (4 mL) was added dropwise and allowed to react for 30 min. The reaction

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mixture was quenched with 1 N HCl (20 mL) and water (10 mL) and extracted with Et_2O (2 × 40 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated to give a green foam. Purification by flash chromatography (20% EtOAc/Hex) provided methylenecyclobutane **8** as an off-white solid (0.663 g, 1.56 mmol, 83%): ^{1}H NMR δ 7.23−7.40 (m, 5H), 7.00−7.15 (m, 5H), 6.92−6.99 (m, 3H), 6.84−6.91 (m, 2H), 5.79 (d, J = 8.0 Hz, 1H), 5.07 (d, J = 8.0 Hz, 1H), 4.89 (q, J = 2.4 Hz, 1H), 4.79 (dd, J = 1.7, 2.4 Hz, 1H), 4.47 (s, 2H), 4.06 (q, J = 8.2 Hz, 1H), 3.50−3.66 (m, 3H), 2.53−2.74 (m, 2H); ^{13}C NMR δ 157.6, 143.0, 138.4, 135.6, 134.3, 128.3, 128.2, 127.8, 127.7, 127.5, 126.0, 105.9, 79.9, 73.2, 70.5, 64.5, 49.7, 48.7, 35.8; IR (film) 1751 cm^{-1}; mp 90−91 °C.

Nonracemic **8** was prepared as above using CH_2I_2 (1.00 mL), Zn (1.45 g, 22.3 mmol), $TiCl_4$ (1.0 M in CH_2Cl_2, 2.70 mL, 2.70 mmol), and cyclobutanone **7** (1.05 g, 2.45 mmol) to give (−)-**8** (0.720 g, 1.69 mmol, 69%) as a white solid: mp 60−61 °C. Anal. Calcd for $C_{28}H_{27}NO_3$: C, 79.03; H, 6.40; N, 3.29. Found: C, 79.16; H, 6.55; N, 3.32. $[\alpha]^{24}_D$ −3.0 (*c* 0.71, $CHCl_3$).

Alternatively, a solution of Cp_2TiMe_2[22] (0.40 M in THF, 4.7 mL, 1.9 mmol) was added to **7** (0.200 g, 0.47 mmol), and the resultant solution was heated in a sealed tube to 75 °C for 4 h. The crude mixture was adsorbed onto florisil and purified by flash chromatography (10% to 15% EtOAc/Hex gradient elution) to provide **8** as a yellow film (0.135 g, 0.32 mmol, 68%).

Hydroboration of 8. (a) With BH_3·THF: A solution of BH_3·THF (1.0 M in THF, 0.11 mL, 0.11 mmol) was added dropwise to a 0 °C solution of **8** (31 mg, 0.072 mmol) in THF (0.40 mL), and the resultant solution was stirred at 0 °C for 1 h. 1 N NaOH (0.15 mL) and 30% H_2O_2 (0.05 mL) were added and allowed to react for 1.5 h. The mixture was diluted with saturated aqueous sodium potassium tartrate (5 mL) and H_2O (2 mL) and extracted with CH_2Cl_2 (2 × 7 mL). The combined organic layer was washed with brine (5 mL), dried (Na_2SO_4), and concentrated to give 33.5 mg of a white foam. Purification by flash chromatography (60% EtOAc/Hex) afforded 26 mg of a 4:1 mixture (^{1}H NMR) of **9a**:**b** as a white foam (0.059 mmol, 82%).

(b) With $[Rh(COD)Cl]_2$·4PPh_3/catecholborane: A solution of $[Rh(COD)Cl]_2$ (2.9 mg, 0.0059 mmol) and PPh_3 (6.2 mg, 0.024 mmol) in THF (0.50 mL) was stirred for 20 min, with care being taken to exclude oxygen. A solution of **8** (50.2 mg, 0.118 mmol) in THF (0.40 mL) was added, and the resultant solution was cooled to 0 °C. Catecholborane (0.037 mL, 0.30 mmol) was added, the cooling bath was removed, and the reaction mixture was stirred for 3 h. Workup as above (0.35 mL 1 N NaOH, 0.11 mL 30% H_2O_2) provided a 7.3:1 ratio (^{1}H NMR) of **9a**:**b** (41.4 mg, 0.0933 mmol, 79%).

(c) With 9-BBN: A solution of 9-BBN (0.5 M in THF, 0.10 mL, 0.050 mmol) was added to a solution of **8** (19.7 mg, 0.0463 mmol) in THF (0.20 mL) and was allowed to react for 15 h. Workup as above (0.15 mL 1 N NaOH, 0.06 mL 30% H_2O_2) gave a 1:1 mixture of **9a**:**b** (^{1}H NMR) (13.0 mg, 0.0293 mmol, 63%).

(d) With $cHex_2BH$: BH_3·DMS (0.105 mL, 1.11 mmol) was added to a 0 °C solution of cyclohexene (0.23 mL, 2.3 mmol) in CH_2Cl_2 (1.5 mL), and stirred for 3 h. A solution of **8** (0.355 g, 0.835 mmol) in CH_2Cl_2 (1.5 mL) was added, and the resultant solution was stirred for 18 h, allowing it to warm slowly. Workup as above (4.5 mL of 1 N NaOH, 0.51 mL of 30% H_2O_2) afforded a ∼15:1 mixture (^{1}H NMR) of **9a**:**b** (0.311 g, 0.702 mmol, 84%). **9a**: ^{1}H NMR δ 7.21−7.38 (m, 5H), 7.04−7.11 (m, 6H), 6.94−7.00 (m, 2H), 6.83−6.89 (m, 2H), 5.81 (d, J = 8.0 Hz, 1H), 5.00 (d, J = 8.0 Hz, 1H), 4.39 (s, 2H), 4.06 (q, J = 9.0 Hz, 1H), 3.49−3.70 (m, 4H), 3.19−3.31 (m, 2H), 2.44 (m, 1H), 2.21 (dt, J = 9.8, 11.6 Hz, 1H), 1.75 (ddd, J = 2.9, 9.0, 11.6 Hz, 1H); ^{13}C NMR δ 157.4, 137.2, 135.6, 134.3, 128.4, 128.2, 128.1, 127.8, 127.7, 127.4, 125.9, 79.7, 73.4, 68.6, 64.7, 62.1, 49.3, 41.6, 33.3, 26.4; IR (film) 3452, 1748 cm^{-1}; mp 145−147 °C. Anal. Calcd for $C_{28}H_{29}NO_4$: C, 75.82; H, 6.59; N, 3.16. Found: C, 75.99; H, 6.36; N, 3.19. **9b**: ^{1}H NMR δ 7.24−7.38 (m, 5H), 7.00−7.11 (m, 6H), 6.91−7.00 (m, 2H), 6.80−6.88 (m, 2H), 5.80 (d, J = 8.0 Hz, 1H), 5.01 (d, J = 8.0 Hz, 1H), 4.51 (d, J = 11.8 Hz, 1H), 4.46 (d, J = 11.8, Hz, 1H), 3.83 (dt, J = 7.9, 9.1 Hz, 1H), 3.69 (dd, J = 4.4, 9.0 Hz, 1H), 3.52 (dd, J = 3.3, 10.5 Hz, 1H), 3.31 (t, J = 9.1 Hz, 2H), 2.99 (bs, 1H), 2.64 (dq, J = 4.4, 8.5 Hz, 1H), 1.88 (m, 2H), 1.56 (m, 1H); ^{13}C NMR δ 157.5, 137.5, 135.5, 134.1, 128.3, 128.2, 127.7, 127.3, 125.9, 79.8, 73.3, 71.6, 65.9, 64.1, 47.9, 46.8, 36.2, 27.1; IR (film) 3445, 1748 cm^{-1}; mp 118−119 °C; Anal.calcd for $C_{28}H_{29}NO_4$: C, 75.82; H, 6.59; N, 3.16. Found: C, 75.64; H, 6.43; N, 3.08. $[\alpha]^{24}_D$ −8.8 (*c* 0.60, $CHCl_3$).

Alternatively, **9b** was obtained more selectively via an oxidation−epimerization−reduction sequence using a mixture of **9a**/**b**. Hydroboration of **8** (0.626 g, 1.47 mmol) with BH_3·THF (3.0 mL) as described above provided 0.63 g of a 4:1 mixture (^{1}H NMR) of crude **9a**:**b** as a white solid, which was used without purification. Swern oxidation was performed by adding $(COCl)_2$ (0.250 mL, 2.90 mmol) to a −78 °C solution of DMSO (0.300 mL, 4.23 mmol) in CH_2Cl_2 (7.0 mL), followed by stirring for 10 min. A solution of crude **9a**/**b** in CH_2Cl_2 (2.5 mL) was then added dropwise and allowed to react for 20 min. To the reaction mixture was added Et_3N (0.79 mL, 5.7 mmol). The resultant solution was stirred for 2 min at −78 °C, allowed to warm over 20 min, quenched with saturated aqueous $NaHCO_3$ (20 mL), and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), concentrated, and purified by flash chromatography (30 to 50% EtOAc/Hex gradient elution) to provide 0.488 g of a 4:1 mixture (^{1}H NMR) of diastereomeric aldehydes as a yellow foam. Major: ^{1}H NMR δ 9.76 (d, J = 2.2 Hz, 1H), 6.84−7.35 (m, 15H), 5.84 (d, J = 8.0 Hz, 1H), 4.98 (d, J = 8.0 Hz, 1H), 4.26 (d, J = 11.6 Hz, 1H), 4.14 (d, J = 11.6 Hz, 1H), 4.03 (q, J = 8.8 Hz, 1H), 3.59 (m, 1H), 3.42 (dd, J = 3.6, 10.2 Hz, 1H), 3.19 (dd, J = 5.8, 10.2 Hz, 1H), 3.11 (m, 1H), 2.42 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 157.2, 137.7, 135.2, 134.2, 128.3, 128.2, 127.7, 127.5, 127.4, 125.8, 79.5, 73.0, 67.7, 65.4, 48.9, 44.6, 42.1, 23.8. Minor: ^{1}H NMR δ 9.62 (d, J = 2.2 Hz, 1H), 7.23−7.36 (m, 5H), 7.03−7.10 (m, 6H), 6.93−6.99 (m, 2H), 6.84−6.89 (m, 2H), 5.80 (d, J = 8.1 Hz, 1H), 5.04 (d, J = 8.1 Hz, 1H), 4.44 (d, J = 11.8 Hz, 1H), 4.39 (d, J = 11.8 Hz, 1H), 4.08 (q, J = 8.6 Hz, 1H), 3.55 (dd, J = 4.3, 9.8 Hz, 1H), 3.43 (dd, J = 5.5, 9.8 Hz, 1H), 3.17 (m, 1H), 2.75 (m, 1H), 2.17 (dt, J = 9.8, 11.2 Hz, 1H), 2.02 (dt, J = 8.1, 11.2 Hz, 1H); ^{13}C NMR δ 201.0, 157.4, 138.1, 135.4, 134.1, 128.3, 128.2, 128.1, 127.7, 127.5, 127.4, 125.9, 79.8, 73.0, 69.9, 64.3, 47.3, 43.4, 41.7, 25.0; IR (film) 1747, 1721 cm^{-1}.

The mixture of aldehydes was dissolved in a 0.1 M solution of NaOMe in MeOH (10 mL) and stirred for 13 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to afford 0.49 g of a white foam, which was dissolved in EtOH (7.0 mL) and treated with $NaBH_4$ (41.7 mg, 1.10 mmol). After stirring for 2.5 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give 0.474 g of white solid. Purification by trituration with Et_2O provided a >17:1 mixture (^{1}H NMR) of **9b**:**a** as a white solid (0.424 g, 0.956 mmol, 67% from **8**).

Methylenecyclobutane 10. A solution of BCl_3 (1.0 M in CH_2Cl_2, 2.8 mL, 2.8 mmol) was added dropwise to a −78 °C solution of **8** (0.150 g, 0.353 mmol) in CH_2Cl_2 (2.5 mL), and the mixture was stirred for 3 h. The reaction was quenched with MeOH (5 mL) and allowed to warm. The crude mixture was concentrated, diluted with saturated aqueous $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2 (3 × 8 mL). The combined organic layer was washed with brine (5 mL), dried (Na_2SO_4), and concentrated to give 0.135 g of a gummy brown solid. Purification by flash chromatography (50% EtOAc/Hex) provided **10** as a light yellow solid (92.3 mg, 0.275 mmol, 78%): ^{1}H NMR δ 7.05−7.15 (m, 6H), 6.96−7.03 (m, 2H), 6.81−6.89 (m, 2H), 5.91 (d, J = 7.9 Hz, 1H), 5.14 (d, J = 7.9 Hz, 1H), 4.80−4.88 (m, 2H), 3.94 (dd, J = 2.6, 9.3 Hz, 1H), 3.73−3.87 (m, 2H), 3.67 (ddd, J = 2.6, 8.6, 11.3 Hz, 1H), 3.41−3.52 (m, 1H), 2.63−2.76 (m, 1H), 2.42 (dddd, J = 2.0, 4.1, 8.1, 15.0 Hz, 1H); ^{13}C NMR δ 158.7, 141.6, 134.5, 133.7, 128.4, 127.9, 127.8, 127.1, 125.9, 106.7, 80.2, 64.9, 63.1, 54.2, 50.3, 34.9; IR (film)

3424, 1736 cm^{-1}; mp 110−112 °C; HRMS *m*/*z* (M + H) calcd 336.1600, obsd 336.1600.

Hydroboration of 10. (a) With BH_3·THF: A solution of BH_3·THF (1.0 M in THF, 0.059 mL, 0.059 mmol) was added dropwise to a −78 °C solution of **10** (19 mg, 0.057 mmol) in THF (0.50 mL), and the resultant solution was stirred for 12 h, allowing it to warm slowly. The reaction mixture was heated to 55 °C for 1 h and allowed to cool. NaOH (1 N) (0.24 mL) and 30% H_2O_2 (0.04 mL) were added and allowed to react for 45 min. The mixture was diluted with saturated aqueous sodium potassium tartrate (2 mL) and saturated aqueous $NaHCO_3$ (4 mL) and extracted with CH_2Cl_2 (3 × 7 mL). The combined organic layer was washed with brine (5 mL), dried (Na_2SO_4), and concentrated to give 20 mg of a 7:1 mixture of **11a**:**b** (^{1}H NMR) as a clear film. Purification by flash chromatography (35 to 50% EtOAc/Hex to 15% MeOH/CH_2Cl_2 gradient elution) afforded 15 mg of **11a** as a clear film (0.043 mmol, 75%).

(b) With 9-BBN: A solution of 9-BBN in THF (0.5 *M*, 0.30 mL, 0.15 mmol) was added to a solution of **10** (20.3 mg, 0.0606 mmol) in THF (0.30 mL) and allowed to react for 14 h. Workup as above (0.45 mL 1 N NaOH, 0.08 mL 30% H_2O_2) gave a 33.7 mg of a 1:1 mixture of **11a**:**b** as judged by crude ^{1}H NMR.

Debenzylation of 9a. A solution of BCl_3 (1.0 M in CH_2Cl_2, 1.3 mL, 1.3 mmol) was added dropwise to a −78 °C solution of **9a** (60.8 mg, 0.137 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was allowed to warm over 30 min following the addition and then quenched with MeOH (2 mL) and concentrated. MeOH (2 mL) was added and concentrated twice more, and the residue was then dissolved in a solution of NH_3 in MeOH (2 mL, satd at 0 °C) and concentrated again. The resulting film was purified by flash chromatography (2% MeOH/CH_2Cl_2) to afford an 11:1 mixture (^{1}H NMR) of **11a**:**b** as a white solid (33.3 mg, 0.0942 mmol, 69%). **11a**: ^{1}H NMR δ 7.05−7.13 (m, 6H), 6.94−7.00 (m, 2H), 6.82−6.88 (m, 2H), 5.86 (d, J = 7.9 Hz, 1H), 5.10 (d, J = 7.9 Hz, 1H), 4.12 (q, J = 9.2 Hz, 1H), 3.60−3.80 (m, 4H), 3.00 (m, 1H), 2.45 (m, 1H), 2.03 (dt, J = 9.7, 11.6 Hz, 1H), 1.60 (ddd, J = 2.0, 9.2, 11.6 Hz, 1H); ^{13}C NMR δ 158.1, 135.4, 134.0, 128.3, 127.9, 127.8, 127.2, 126.0, 80.2, 64.2, 62.2, 60.9, 49.3, 44.6, 33.0, 26.3; IR (film) 3382, 1732 cm^{-1}; mp 154−155 °C; HRMS *m*/*z* (M + H) calcd 354.1705, obsd 354.1706.

Debenzylation of 9b. A solution of BCl_3 (1 M in CH_2Cl_2, 1.0 mL, 1.0 mmol) was added dropwise to a −78 °C solution of **9b** (49.4 mg, 0.111 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was allowed to warm over 30 min following the addition and then quenched with MeOH (2 mL) and concentrated. MeOH (2 mL) was added and concentrated twice more, and the residue was then dissolved in a solution of NH_3 in MeOH (2 mL, satd at 0 °C) and concentrated again. The resulting film was purified by flash chromatography (3% MeOH/CH_2Cl_2) to afford **11b** as a white solid (24.0 mg, 0.063 mmol, 61%): ^{1}H NMR δ 7.05−7.15 (m, 6H), 6.95−7.02 (m, 2H), 6.82−6.89 (m, 2H), 5.87 (d, J = 7.0 Hz, 1H), 5.10 (d, J = 7.0 Hz, 1H), 3.69−3.80 (m, 2H), 3.63 (dd, J = 3.0, 10.5 Hz, 1H), 3.55 (dd, J = 6.9, 10.5 Hz, 1H), 3.43 (dd, J = 6.7, 10.0 Hz, 1H), 2.54−2.92 (m, 3H), 1.84 (quin, J = 6.8 Hz, 2H), 1.66 (m, 1H); ^{13}C NMR δ 158.2, 135.1, 134.0, 128.4, 128.0, 127.9, 127.3, 126.0, 80.2, 65.0, 64.5, 49.2, 48.7, 35.1, 26.6; IR (film) 3379, 1732 cm^{-1}; mp 160−161 °C; HRMS *m*/*z* (M + H) calcd 354.1705, obsd 354.1715.

Epoxides 12a/b. A suspension of **8** (60.3 mg, 0.142 mmol), $NaHCO_3$ (68.3 mg, 0.813 mmol), and mCPBA (50%, 120 mg, 0.35 mmol) in CH_2Cl_2 (1 mL) at 0 °C was stirred for 10 h, allowing it to warm to room temperature. The mixture was diluted with saturated aqueous $NaHCO_3$ (7 mL) and extracted with CH_2Cl_2 (3 × 8 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated to give 91 mg of a clear gum. Purification by flash chromatography (20% EtOAc/Hex) and crystallization (Et_2O/Hex) afforded **12a** (10.0 mg, 0.0226 mmol, 16%) and **12b** (37.7 mg, 0.854 mmol, 60%) as white solids. **12a**: ^{1}H NMR δ 7.26−7.38 (m, 5H), 7.05−7.12 (m, 6H), 6.95−7.00 (m, 2H), 6.86−6.92 (m, 2H), 5.84 (d, J = 8.0 Hz, 1H), 5.07 (d, J = 8.0 Hz, 1H), 4.42 (s, 2H), 4.08 (q, J = 8.2 Hz, 1H), 3.48 (d, J = 4.7 Hz, 2H), 3.38 (m, 1H), 2.80 (d, J = 4.9 Hz, 1H), 2.60 (d, J = 4.9 Hz, 1H), 2.49 (dd, J = 9.0, 12.5 Hz, 1H), 2.22 (ddd, J = 0.9, 8.2, 12.5 Hz, 1H); ^{13}C NMR δ 157.6, 138.1, 135.2, 134.1, 128.4, 128.3, 127.9, 127.7, 127.6, 127.4, 126.0, 80.0, 73.2, 67.6, 64.5, 56.8, 49.6, 48.0, 43.5, 33.8; IR (film) 1752 cm^{-1}; mp 117−118 °C. **12b**: ^{1}H NMR δ 7.23−7.36 (m, 5H), 7.05−7.11 (m, 6H), 6.95−7.00 (m, 2H), 6.86−6.92 (m, 2H), 5.84 (d, J = 8.1 Hz, 1H), 5.06 (d, J = 8.1 Hz, 1H), 4.39 (s, 2H), 4.11 (dt, J = 7.8, 9.1 Hz, 1H), 3.56 (q, J = 6.1 Hz, 1H), 3.40 (dd, J = 1.0, 6.1 Hz, 2H), 2.74 (ddd, J = 1.0, 7.8, 13.4 Hz, 1H), 2.67 (d, J = 4.8 Hz, 1H), 2.64 (d, J = 4.8 Hz, 1H), 2.31 (ddd, J = 1.2, 9.1, 13.4 Hz, 1H); ^{13}C NMR δ 157.4, 138.2, 135.0, 134.2, 128.3, 128.2, 127.8, 127.6, 127.5, 127.3, 125.8, 79.7, 73.0, 67.5, 65.3, 59.0, 49.6, 47.8, 46.0, 34.0; IR (film) 1751 cm^{-1}; mp 99−101 °C. Anal. Calcd for $C_{28}H_{27}NO_4$: C, 76.17; H, 6.16; N, 3.17. Found: C, 76.00; H, 6.13; N, 3.14.

Cyclobutanol 13. To a solution of **12b** (38 mg, 0.085 mmol) and $NaCNBH_3$ (10 mg, 0.16 mmol) in THF (0.80 mL) containing bromocresol green indicator was added BF_3·OEt_2 (0.01 mL) until the solution became yellow. The solution was stirred for 2 h, when more BF_3·OEt_2 (0.01 mL) was added. After stirring an additional 3 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (7 mL) and extracted with CH_2Cl_2 (3 × 7 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concentrated to give 56 mg of a pale gum. Flash chromatography (25 to 50% EtOAc/Hex gradient elution) provided **13** as a clear film (19 mg, 0.043 mmol, 51%): ^{1}H NMR δ 7.20−7.36 (m, 5H), 7.05−7.11 (m, 6H), 6.97−7.01 (m, 2H), 6.85−6.89 (m, 2H), 5.82 (d, J = 8.1 Hz, 1H), 4.96 (d, J = 8.1 Hz, 1H), 4.42 (d, J = 11.7 Hz, 1H), 4.34 (d, J = 11.7 Hz, 1H), 4.01 (q, J = 8.6 Hz, 1H), 3.66 (dd, J = 4.1, 9.8 Hz, 1H), 3.57 (dd, J = 6.7, 9.8 Hz, 1H), 2.96 (m, 2H), 2.18 (dd, J = 8.6, 12.1 Hz, 1H), 2.05 (dd, J = 8.6, 12.1 Hz, 1H), 1.35 (s, 3H); ^{13}C NMR δ 157.4, 137.8, 135.2, 134.4, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 126.0, 79.6, 73.3, 71.3, 68.5, 65.5, 49.0, 46.7, 39.2, 29.3; IR (film) 3444, 1749 cm^{-1}; mp 117−118 °C. Anal. Calcd for $C_{28}H_{29}NO_4$: C, 75.82; H, 6.59; N, 3.16. Found: C, 76.00; H, 6.56; N, 3.14.

Cyclobutanol 14. A solution of $TiCl_4$ (1.0 M in CH_2Cl_2, 0.110 mL, 0.110 mmol) was added dropwise to a −78 °C solution of **12b** (40.1 mg, 0.091 mmol) and Et_3SiH (0.023 mL, 0.14 mmol) in CH_2Cl_2 (0.80 mL). After stirring for 1 h, the reaction mixture was quenched with 1 N HCl (7 mL) and extracted with CH_2Cl_2 (3 × 7 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated to give 45 mg of a clear film. Purification by flash chromatography (25% EtOAc/Hex) afforded **14** as a clear film (41.2 mg, 0.086 mmol, 95%): ^{1}H NMR δ 7.17−7.36 (m, 5H), 7.04−7.14 (m, 6H), 6.95−7.01 (m, 2H), 6.84−6.92 (m, 2H), 5.83 (d, J = 7.9 Hz, 1H), 4.98 (d, J = 7.9 Hz, 1H), 4.38 (d, J = 11.7 Hz, 1H), 4.30 (d, J = 11.7 Hz, 1H), 4.04 (q, J = 8.6 Hz, 1H), 3.44−3.68 (m, 5H), 3.16 (m, 1H), 2.41 (dd, J = 8.6, 12.4 Hz, 1H), 2.06 (dd, J = 9.0, 12.4 Hz, 1H); ^{13}C NMR δ 157.4, 137.5, 135.2, 134.3, 129.7, 128.5, 128.5, 128.4, 127.9, 127.8, 127.7, 127.6, 125.9, 79.6, 73.4, 72.6, 68.4, 65.8, 52.7, 46.4, 46.1, 36.5; IR (film) 3418, 1746 cm^{-1}; mp 129−131 °C. Anal. Calcd for $C_{28}H_{28}ClNO_4$: C, 70.36; H, 5.90; N, 2.93. Found: C, 70.27; H, 6.02; N, 2.92.

$PdCl_2$-Catalyzed Ring Expansion of 8. A suspension of racemic **8** (17.3 mg, 0.0407 mmol), $PdCl_2$ (1.4 mg, 0.0079 mmol), CuCl (4.4 mg, 0.044 mmol), and 70% aqueous $HClO_4$ (0.008 mL, 0.1 mmol) in 7:1 MeCN:water (0.41 mL) was stirred under O_2 (1 atm) at room temperature for 19 h and then heated to 60 °C for 22 h. The mixture was diluted with aq NH_4Cl/NH_4OH (pH 10, 7 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was washed with brine (5 mL), dried (Na_2SO_4), and concentrated to give 16.2 mg of a clear film. Purification by flash chromatography provided impure α-(benzyloxymethyl)-β-(diphenyloxazolidinonyl)cyclopentanone (3.8 mg, 0.0086 mmol, ∼21%) and impure β-(benzyloxymethyl)-β-(diphenyloxazolidinonyl)cyclopentanone (3.5 mg, 0.0079 mmol, ∼19%), each contaminated with ∼4% of the desired cyclobutyl aldehyde.

α-(Benzyloxymethyl)-β-(diphenyloxazolidinonyl)cyclopentanone: ^{1}H NMR δ 6.84−7.34 (m, 15H), 5.59 (d, J = 8.2 Hz, 1H),

5.03 (d, J = 8.2 Hz, 1H), 4.32−4.45 (m, 3H), 4.36 (d, J = 11.3 Hz, 1H), 4.36 (d, J = 11.3 Hz, 1H), 3.74 (d, J = 4.5 Hz, 2H), 2.92 (m, 1H), 2.27−2.39 (m, 1H), 2.01−2.16 (m, 2H), 1.54−1.69 (m, 1H); ^{13}C NMR δ 213.2, 158.1, 137.8, 135.7, 134.3, 128.6, 128.5, 128.3, 128.2, 128.0, 127.8, 127.6, 127.5, 126.0, 80.0, 73.7, 67.8, 63.7, 56.0, 51.4, 37.5, 25.4.

β-(Benzyloxymethyl)-β-(diphenyloxazolidinonyl)cyclopentanone: ^{1}H NMR δ 6.83−7.37 (m, 15H), 5.59 (d, J = 8.1 Hz, 1H), 5.00 (d, J = 8.1 Hz, 1H), 4.51 (d, J = 11.3 Hz, 1H), 4.45 (d, J = 11.3 Hz, 1H), 4.33−4.44 (m, 1H), 3.61 (d, J = 4.9 Hz, 2H), 2.87 (m, 1H), 2.53 (dd, J = 8.7, 18.9 Hz, 1H), 2.38 (dd, J = 7.5, 18.9 Hz, 1H), 1.93−2.16 (m, 2H).

Silyl Ether 15. To a solution of alcohol **9b** (0.411 g, 0.926 mmol) and imidazole (94.6 mg, 1.39 mmol) in DMF (5 mL) was added TBDMSCl (0.174 g, 1.16 mmol). After stirring for 45 min, the reaction mixture was diluted with Et_2O (40 mL), washed with H_2O (2 × 20 mL), and washed with brine (20 mL). The organic layer was dried (Na_2SO_4) and concentrated to provide 0.515 g of a white solid. Purification by flash chromatography (15% EtOAc/Hex) afforded silyl ether **15** as a white solid (0.465 g, 0.834 mmol, 90%): ^{1}H NMR δ 7.26−7.37 (m, 5H), 7.00−7.09 (m, 6H), 6.91−6.97 (m, 2H), 6.82−6.87 (m, 2H), 5.74 (d, J = 8.0 Hz, 1H), 5.04 (d, J = 8.0 Hz, 1H), 4.49 (d, J = 12.0 Hz, 1H), 4.45 (d, J = 12.0 Hz, 1H), 4.05 (q, J = 9.3 Hz, 1H), 3.54 (d, J = 5.1 Hz, 2H), 3.49 (dd, J = 4.8, 10.3 Hz, 1H), 3.41 (dd, J = 4.9, 10.3 Hz, 1H), 2.69 (m, 1H), 1.80−1.98 (m, 2H), 1.57 (m, 1H), 0.84 (s, 9H), −0.04 (s, 3H), −0.05 (s, 3H); ^{13}C NMR δ 157.6, 138.6, 136.0, 134.4, 128.2, 128.0, 127.7, 127.6, 127.4, 127.3, 126.0, 80.0, 73.0, 71.4, 64.8, 63.8, 48.3, 43.4, 33.6, 27.2, 25.9, 18.2, −5.5; IR (film) 1752 cm^{-1}; mp 98−99 °C. Anal. Calcd for $C_{34}H_{43}NO_4$: C, 73.21; H, 7.77; N, 2.51. Found: C, 73.45; H, 7.79; N, 2.49. $[\alpha]^{24}_D$ 2.7 (c 1.0, $CHCl_3$).

Pyrimidine 16. A mixture of silyl ether **15** (0.460 g, 0.825 mmol), Et_3N (1.15 mL, 8.25 mmol), and 20% $Pd(OH)_2/C$ (0.405 g) in EtOH (8.2 mL) was stirred under H_2 (35 psi) for 25 h, filtered through Celite, and concentrated to give 0.40 g of clear oil. Purification by flash chromatography (30% EtOAc/Hex to 10% MeOH/CH_2Cl_2, 1% Et_3N gradient elution) provided 0.198 g of impure free amine as a clear oil, which was used without further purification: ^{1}H NMR δ 7.23−7.37 (m, 5H), 4.50 (s, 2H), 3.43−3.61 (m, 4H), 3.07 (q, J = 7.8 Hz, 1H), 2.25 (dt, J = 7.8 10.8 Hz, 1H), 1.92−2.03 (m, 1H), 1.79−1.92 (m, 1H), 1.70 (bs, 2H), 1.35 (dt, J = 9.1, 10.4 Hz, 1H), 0.89 (s, 9H), 0.03 (s, 6H); ^{13}C NMR δ 138.7, 128.2, 127.4, 72.9, 72.1, 65.8, 49.7, 48.3, 33.0, 32.7, 25.9, 18.3, −5.4.

A solution of the crude oil, Et_3N (0.33 mL, 2.4 mmol), and 5-amino-4,6-dichloropyrimidine (0.194 g, 1.18 mmol) in n-BuOH (4.0 mL) was heated in a sealed vial to 110 °C for 23 h. Concentration and flash chromatographic purification (20% EtOAc/Hex) of the reaction mixture yielded the desired product **16** as a yellow gum (0.226 g, 0.487 mmol, 59%): ^{1}H NMR δ 8.04 (s, 1H), 7.22−7.38 (m, 5H), 4.96 (d, J = 6.9 Hz, 1H), 4.53 (d, J = 12.1 Hz, 1H), 4.49 (d, J = 12.1 Hz, 1H), 4.30 (quin, J = 9.0 Hz, 1H), 3.53−3.66 (m, 4H), 3.32 (bs, 2H), 2.46 (dt, J = 7.9 10.7 Hz, 1H), 2.33 (ddt, J = 5.9, 6.2, 8.3 Hz, 1H), 2.09 (m, 1H), 1.62 (q, J = 9.9 Hz, 1H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR δ 154.5, 149.7, 138.5, 128.3, 127.5, 127.4, 121.5, 73.1, 71.9, 65.1, 46.7, 46.4, 34.0, 30.5, 26.0, 18.3, −5.3; IR (film) 3352, 3246, 1643, 1576 cm^{-1}. Anal. Calcd for $C_{23}H_{35}N_4O_2Si$: C, 59.65; H, 7.62; N, 12.10. Found: C, 60.00; H, 7.63; N, 12.24. $[\alpha]^{24}_D$ −46.0 (c 1.0, $CHCl_3$).

Cyclobut-A 2. Following the general procedure of Parratt,[30] concentrated aq HCl (0.04 mL) was added to a solution of pyrimidine **16** (44.4 mg, 0.0959 mmol) in EtOH (1 mL), which was then concentrated to a gummy foam. Following the addition of $HC(OEt)_3$ (0.11 mL, 0.66 mmol) and DMF (0.25 mL), the resultant solution was heated to 70 °C for 3 h, transferred to a pressure tube, concentrated, and redissolved in a solution of NH_3 in MeOH (1.5 mL, satd at 0 °C). After heating to 70 °C in the sealed tube for 24 h, the mixture was concentrated, dried by coevaporation with PhMe, and diluted with $CHCl_3$ (0.90 mL). The brown mixture was cooled to −78 °C, and a solution of BCl_3 in CH_2Cl_2 (1.0 M, 1.35 mL, 1.35 mmol) was added. The mixture was allowed to warm over 30 min following the addition, at which point MeOH (1 mL) was added and the solution was concentrated. This addition/evaporation process was repeated twice more, and followed by the addition of a solution of NH_3 in MeOH (2 mL, satd at 0 °C) and concentration to provide a brown solid. Purification by flash chromatography (15% MeOH/CH_2Cl_2) provided a clear film which was triturated (5% MeOH/CH_2Cl_2) to remove any inorganic impurities. Concentration of the triturating solvent gave 16.1 mg of a tan solid, which was triturated with Et_2O to afford **2** as a tan film (15.3 mg, 0.0614 mmol, 64%): ^{1}H NMR (DMSO) δ 8.23 (s, 1H), 8.12 (s, 1H), 7.19 (bs, 2H), 4.76 (t, J = 5.1 Hz, 1H), 4.56−4.67 (m, 2H), 3.48−3.55 (m, 4H), 2.77 (m, 1H), 2.43 (dt, J = 8.0, 10.2 Hz, 1H), 2.22 (q, J = 9.8 Hz, 1H), 2.08 (m, 1H); ^{13}C NMR (DMSO) δ 156.0, 152.2, 149.4, 139.6, 119.1, 63.6, 61.6, 47.7, 47.4, 33.2, 29.2; IR (film) 3329, 3196, 1648, 1601, 1572 cm^{-1}; mp 155−156 °C (lit. 149−151 °C).[15b] Anal. Calcd for $C_{11}H_{15}N_5O_2$: C, 53.00; H, 6.07; N, 28.10. Found: C, 52.87; H, 6.09; N, 28.28. $[\alpha]^{24}_D$ −39.7 (c 1.0, pyridine) [lit. −45.7 (c 1.0, pyridine)[17]].

3′-*epi*-15. To a solution of alcohol **9a** (0.126 g, 0.283 mmol) and imidazole (29.8 mg, 0.438 mmol) in DMF (1 mL) was added TBDMSCl (53.6 mg, 0.356 mmol). The solution was stirred for 2.5 h, diluted with Et_2O (15 mL), and washed with water (2 × 8 mL) and brine (5 mL). The organic layer was dried (Na_2SO_4) and concentrated to give a 0.16 g of white solid. Purification by flash chromatography (15% EtOAc/Hex) afforded a ∼9:1 ratio of epimers (^{1}H NMR) of 3′-*epi*-**15** as a white solid (0.140 g, 0.251 mmol, 89%): ^{1}H NMR δ 7.24−7.36 (m, 5H), 7.01−7.07 (m, 6H), 6.90−6.96 (m, 2H), 6.84−6.89 (m, 2H), 5.71 (d, J = 8.0 Hz, 1H), 5.07 (d, J = 8.0 Hz, 1H), 4.49 (d, J = 11.7 Hz, 1H), 4.42 (d, J = 11.7 Hz, 1H), 4.23 (q, J = 9.1 Hz, 1H), 3.53−3.68 (m, 4H), 3.11 (m, 1H), 2.24 (m, 1H), 1.92 (m, 1H), 1.78 (m, 1H), 0.81 (s, 9H), −0.04 (s, 6H); ^{13}C NMR δ 157.8, 138.5, 136.0, 134.5, 128.3, 128.1, 128.0, 127.7, 127.6, 127.5, 127.4, 126.0, 79.9, 73.2, 69.9, 64.0, 62.5, 51.0, 41.8, 32.7, 27.3, 25.8, 18.0, −5.6, −5.7; IR (film) 1752 (CO) cm^{-1}; mp 104−105 °C. Anal. Calcd for $C_{34}H_{43}NO_4Si$: C, 73.21; H, 7.77; N, 2.51. Found: C, 73.34; H, 7.59; N, 2.56.

3′-*epi*-16. A suspension of 3′-*epi*-**15** (0.216 g, 0.388 mmol), Et_3N (0.16 mL, 1.1 mmol), and 20% $Pd(OH)_2/C$ (0.156 mg) was stirred under H_2 (35 psi) for 21 h. The mixture was filtered through Celite and evaporated to give 0.19 g of a clear oil. Purification by flash chromatography (30% EtOAc/Hex to 5% MeOH/CH_2Cl_2, 1% Et_3N gradient elution) provided 94.2 mg of the free amine as a clear oil, which was used without further purification: ^{1}H NMR δ 7.24−7.37 (m, 5H), 4.49 (s, 2H), 3.53−3.69 (m, 4H), 3.31 (m, 1H), 2.52 (bs, 2H), 2.32−2.41 (m, 2H), 2.07 (m, 1H), 1.72 (dt, J = 8.6, 11.0 Hz, 1H), 0.87 (s, 9H), 0.01 (s, 6H); ^{13}C NMR δ 138.6, 128.3, 127.6, 127.5, 73.1, 70.2, 63.2, 50.4, 48.1, 32.2, 32.0, 25.9, 18.1, −5.5.

A solution of the crude oil, Et_3N (0.16 mL, 1.1 mmol), and 5-amino-4,6-dichloropyrimidine (92.5 mg, 0.564 mmol) in n-BuOH (2.5 mL) was heated in a sealed vial to 120 °C for 44 h. Concentration and flash chromatographic purification (20% EtOAc/Hex) of the reaction mixture yielded the desired product 3′-*epi*-**16** as a white foam which was crystallized (Et_2O/Hex) to give a white solid (74.4 mg, 0.161 mmol, 41%): ^{1}H NMR δ 8.02 (s, 1H), 7.22−7.32 (m, 5H), 5.12 (d, J = 6.6 Hz, 1H), 4.45−4.55 (m, 3H), 3.71−3.82 (m, 3H), 3.61−3.71 (m, 1H) 3.40 (bs, 2H), 2.64 (m, 1H), 2.46 (quin, J = 8.1 Hz, 1H), 2.29 (t, J = 2.2, 9.1 Hz, 1H), 1.88 (dt, J = 9.1, 11.3 Hz, 1H), 0.90 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR δ 154.4, 149.7, 143.0, 138.3, 128.3, 127.6, 121.5, 73.3, 70.1, 63.0, 48.9, 45.6, 33.0, 30.9, 25.9, 18.2, −5.4, −5.5; IR (film) 3352, 3246, 1576 cm^{-1}; mp 112−113 °C; HRMS m/z (M + H) calcd 463.2296, obsd 463.2280.

5′-*O*-Benzyl-3′-*epi*-2. Concentrated aq HCl (0.04 mL) was added to a solution of 3′-*epi*-**16** (44.3 mg, 0.0956 mmol) in EtOH (0.5 mL) and concentrated. The residue was dissolved in DMF (0.30 mL), and $HC(OEt)_3$ (0.11 mL) was added. The solution was heated to 80 °C in a sealed vial for 3.5 h, transferred to a pressure tube, and concentrated. The resultant residue was dissolved in a solution of NH_3 in MeOH (0.75 mL, satd at 0 °C) and heated to 60 °C for 20 h. Evaporation of the reaction mixture gave 42 mg of a brown film, which was purified by flash chromatography (3% to 6% MeOH/CH_2Cl_2 gradient

elution) to yield 5′-*O*-benzyl-3′-*epi*-**2** as a white solid (17.9 mg, 0.0527 mmol, 55%): ^{1}H NMR δ 8.34 (s, 1H), 7.86 (s, 1H), 7.27−7.38 (m, 5H), 5.88 (bs, 2H), 5.01 (m, 1H), 4.56 (s, 2H), 3.80−3.90 (m, 2H), 3.69−3.80 (m, 2H), 3.44 (m, 2H), 2.78 (m, 2H), 2.43 (t, J = 8.1 Hz, 1H); ^{13}C NMR δ 155.5, 152.7, 150.2, 139.2, 137.1, 128.5, 128.1, 127.9, 120.1, 73.6, 68.0, 62.0, 49.7, 44.0, 33.8, 28.8; IR (film) 3322, 3169, 1652, 1599, 1574 cm^{-1}; mp 145−147 °C.

3′-*epi*-Cyclobut-A. A solution of BCl_3 (1.0 M in CH_2Cl_2, 0.84 mL, 0.84 mmol) was added to a −78 °C suspension of 5′-*O*-benzyl-3′-*epi*-**2** (28.6 mg, 0.0843 mmol) in $CHCl_3$ (0.85 mL). After the addition, the cooling bath was removed and the mixture was stirred for 30 min. The reaction was quenched with MeOH (0.5 mL) and evaporated. This process was repeated twice and followed by the addition of a solution of NH_3 in MeOH (0.5 mL, satd at 0 °C) and concentration to afford a brown solid. Flash chromatography (15% MeOH/CH_2Cl_2) followed by trituration (5% MeOH/CH_2Cl_2) and evaporation to remove insoluble material provided 18.6 mg of ∼90% pure 3′-*epi*-**2** as a white foam (0.0746 mmol, 89%). Recrystallization (EtOH/EtOAc) provided analytically pure material (8.2 mg, 0.033 mmol, 39%): ^{1}H NMR (DMSO) δ 8.29 (s, 1H), 8.12 (s, 1H), 7.19 (bs, 2H), 4.82 (q, J = 8.6 Hz, 1H), 4.76 (t, J = 4.9 Hz, 1H), 4.60 (t, J = 4.9 Hz, 1H), 3.52−3.75 (m, 4H), 3.19 (m, 1H), 2.62 (q, J = 9.5 Hz, 1H), 2.50 (m, 1H), 2.26 (t, J = 9.8 Hz, 1H); ^{13}C NMR (DMSO) δ 156.0, 152.1, 149.4, 139.8, 119.2, 60.6, 59.8, 50.0, 45.8, 32.5, 28.7; IR (film) 3330, 3180, 1652, 1601, 1571 cm^{-1}; mp 187−188 °C (lit. 190−191);[31] HRMS m/z (M + H) calcd 250.1304, obsd 250.1305.

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