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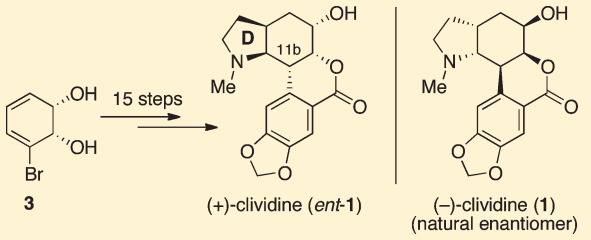
A Chemoenzymatic Total Synthesis of (+)-Clividine

Lorenzo V. White, Brett D. Schwartz, Martin G. Banwell,* and Anthony C. Willis

Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra ACT 0200, Australia

Supporting Information

ABSTRACT: The title compound, *ent*-**1**, the non-natural enantiomeric form of the lycorenine-type alkaloid (−)-clividine (**1**), has been prepared using the enantiomerically pure (ee >99.8%) *cis*-1,2-dihydrocatechol **3** as starting material. A key feature associated with the closing stages of the synthesis involved the diastereoselective addition of a nitrogen-centered radical onto a pendant cyclohexene to establish the cis-fused D-ring and the required stereochemistry at C11b in the final product *ent*-**1**.



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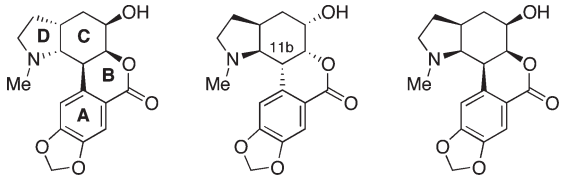
INTRODUCTION

The natural product (−)-clividine was originally isolated from the bush lilly *Clivia miniata* Regel,[1] a species native to South Africa. Extracts of the plant's rhizome have been used in traditional Zulu medicine to ameliorate the effects of fever, as a treatment for snakebites and to relieve pain more generally while extracts of the whole plant have been used to assist with and hasten childbirth. The structure, **1** (Figure 1), of (−)-clividine was assigned by Döpke and Bienert[1] in 1970 using a combination of spectroscopic and chemical correlation studies and thus establishing it as a member of the lycorenine-type class of Amaryllidaceae alkaloid.[2]

In 1973 Irie and co-workers reported[3] a total synthesis of the racemic modification of clividine using a Diels−Alder reaction between a 1-aryl-1,3-butadiene and maleic anhydride to establish the A- and C-rings of the target. Extensive manipulation of the anhydride ring associated with the resulting adduct then allowed for construction of the D-ring. The lactonic B-ring was formed in the final stages of the synthetic sequence using a combination of Friedel−Crafts alkylation chemistry (to install the required one-carbon unit onto the aromatic ring) and an OsO_4-mediated alkene dihydroxylation reaction. Unfortunately, given the racemic nature of the resulting product, no particularly useful comparisons could be made between the natural product and the synthetic material. Since no additional studies related to the synthesis of clividine have been carried out in the intervening period,[4] the development of an enantioselective total synthesis of the (−)- or (+)-forms of this compound seemed warranted. Accordingly, we now report a synthesis of (+)-clividine (*ent*-**1**) from an enantiomerically pure starting material of clearly defined configuration and using, in the closing stages, a novel and diastereoselective cyclization of a nitrogen-centered radical to establish the cis-fused D-ring of the target as well as the required *R*-configuration at C11b.

RESULTS AND DISCUSSION

The opening stages of the present synthesis of (+)-clividine (*ent*-**1**) are shown in Scheme 1 and involve appropriate



1 *ent*-1 2

Figure 1. Structures of compounds **1**, *ent*-**1**, and **2**.

functionalization of the developing C-ring as well as attachment of the fully substituted A-ring and thus following the strategy we employed recently[5] in the synthesis of the structure, **2**, erroneously assigned to the natural product nobilisitine A. So, the enantiomerically pure *cis*-1,2-dihydrocatechol **3**,[6] readily derived from a whole-cell biotransformation of bromobenzene, was converted into the bromohydrin **4** upon treatment with *N*-bromosuccinimide (NBS) in wet tetrahydrofuran (THF).[7] Product **4** was itself transformed into the corresponding acetonide under standard conditions and thus affording compound **5** in 92% yield (from **3**). Reaction of the last compound with NaH followed by a 3-fold excess of the lithium anion derived from acetonitrile then afforded, presumably via the corresponding epoxide, the γ-hydroxynitrile **6** as a single diastereoisomer in 87% yield. The structure of this compound was confirmed by single-crystal X-ray analysis, details of which are provided in the Supporting Information. Subjection of compound **6** to a Barton−McCombie deoxygenation sequence[8] gave, on treatment of the derived xanthate ester **7** (93%) with tri-*n*-butyltin hydride, the nitrile **8** (87%). Subjection of the last compound to Suzuki−Miyaura cross-coupling[9] with the readily obtained arylboronate ester **9**[10] then afforded the required arylated cyclohexane **10** in 95% yield. Once again, the structure of this compound was confirmed by

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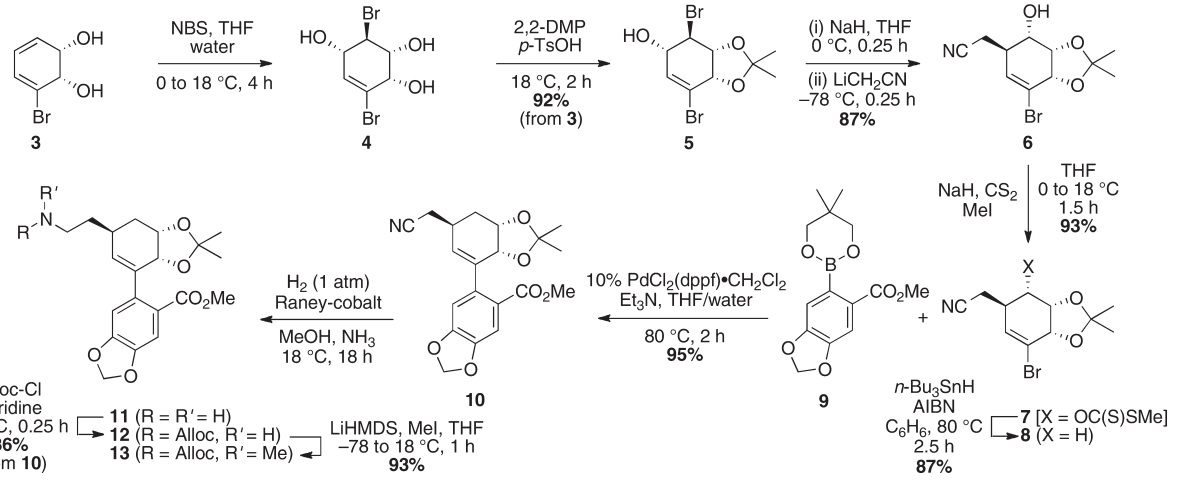
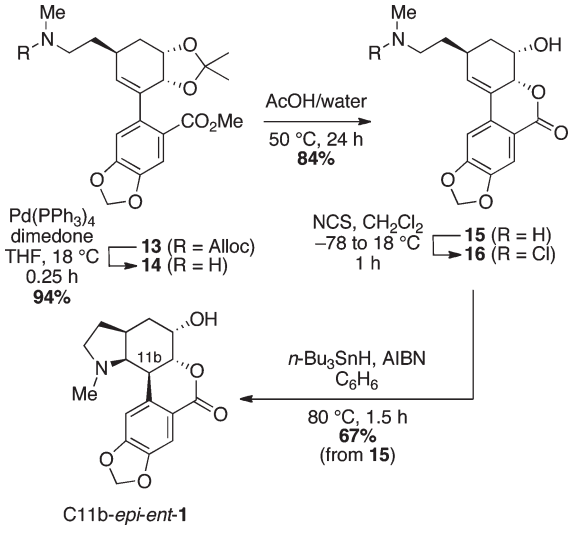
Scheme 1. Synthesis of Compounds 10 and 13, Precursors to (+)-Clividine (*ent*-1) and C11b-*epi*-(+)-Clividine (C11b-*epi*-*ent*-1)



single-crystal X-ray analysis (see Supporting Information for details). In a rather demanding step that required extensive experimentation to establish effective conditions, compound **10** was subjected to chemoselective reduction using hydrogen in the presence of a large excess of Raney-cobalt[11] and thereby affording the requisite primary amine **11** that was immediately protected, using standard conditions, as the corresponding Alloc-derivative **12** (86% from **10**). N-Methylation of compound **12** was readily effected by treating it with lithium hexamethyldisilazide and then methyl iodide, and by such means compound **13** was obtained in 93% yield.

The Alloc-protected secondary amine **13** served as the substrate in what was hoped would be the closing stages of the synthesis of (+)-clividine. Thus, as shown in Scheme 2, compound **13** was subjected to Alloc-deprotection using $Pd(PPh_3)_4$ in the presence of an excess of dimedone[12] and thereby leading to the required secondary amine **14** in 94% yield. In order to ensure the cyclohexenyl double bond was sterically accessible during the foreshadowed nitrogen-centered radical reaction,[13,14] compound **14** was subjected to acetonide hydrolysis and lactonization using aqueous acetic acid and thus delivering lactone **15** (84%), which was immediately N-chlorinated using *N*-chlorosuccinimide (NCS) and thereby giving compound **16** that was used directly in the pivotal nitrogen-centered radical reaction. In the event, treatment of this substrate with tri-*n*-butyltin hydride and azobisisobutyronitrile (AIBN) in refluxing benzene for 1 h afforded a diastereoisomerically pure product in 67% yield. This proved to be the C-11b epimer of (+)-clividine (C11b-*epi*-*ent*-**1**) as determined by single-crystal X-ray analysis of the readily derived oxalic acid salt (see Supporting Information for details).[15] This outcome clearly suggests that the benzylic radical formed after the initial cis-selective cyclization process[16] reacts preferentially at the α-face with tri-*n*-butyltin hydride to generate the observed product. Presumably this preference reflects the greater steric demands imposed by the flanking D-ring over the similarly positioned B-ring in the intermediate benzylic radical.

Scheme 2. Synthesis of C11b-*epi*-(+)-Clividine



Given the stereochemical outcome associated with the conversion **16** → C11b-*epi*-*ent*-**1** and our explanation for this, we reasoned that the *O*-TBDPS-protected form of compound **16** would generate a benzylic radical wherein the steric demands imposed by the bulky OH protecting group would now direct tri-*n*-butyltin hydride to react at the β-face of this intermediate, thus generating the stereochemical array required for the synthesis of (+)-clividine. In order to investigate this possibility, compound **10** was subjected to a tandem acetonide hydrolysis/lactonization sequence (Scheme 3) using acetic acid/water, and the hydroxyl group within the resulting product **17** (84%) was protected, under standard conditions, as the corresponding TBDPS-ether **18** (80%). Raney-cobalt-mediated reduction of the nitrile residue within this last compound resulted in the formation of the anticipated primary amine **19** (82%) which was immediately protected, using standard conditions, as the corresponding allyl carbamate **20** (90%). N-Methylation of compound **20** was achieved by successive treatment of it with LiHMDS and then methyl iodide, and the product **21** (94%) so formed was subjected to Alloc group cleavage under the conditions[1] used previously for the conversion **13** → **14**.

The ensuing secondary amine **22** (89%) was then subjected to N-chlorination using NCS as the halogen-transfer agent. Compound **23** (93%) thus obtained reacted smoothly with tri-*n*-butyltin hydride/AIBN to give the anticipated cyclization product **24**

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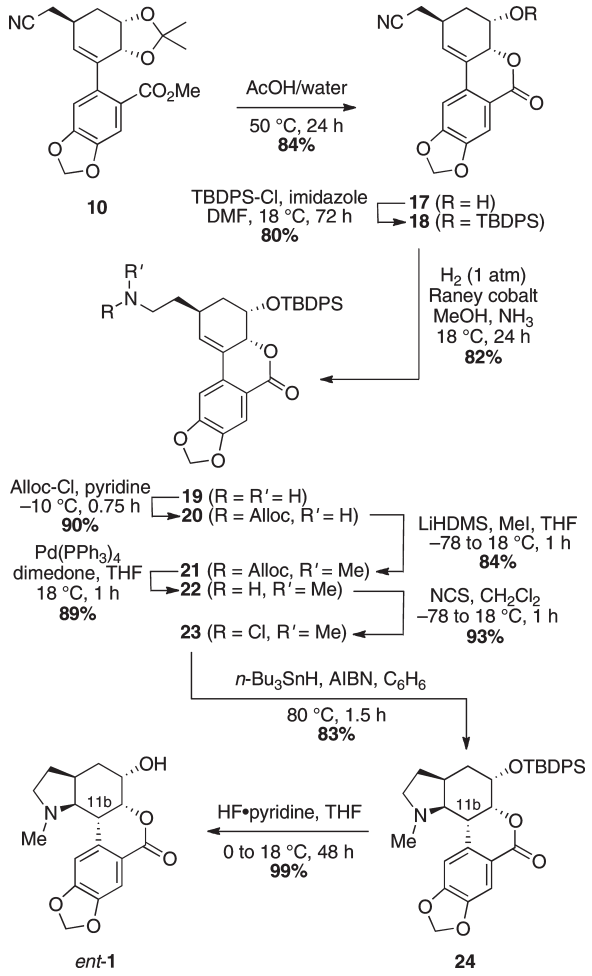
Scheme 3. Completion of the Synthesis of (+)-Clividine



(83%). Treatment of compound **24** with HF·pyridine in THF at 0 → 18 °C then gave (+)-clividine (99%), the structure of which followed from the derived spectral data and a single-crystal X-ray analysis of the readily obtained picrate salt (see Supporting Information for details).[15]

The ^{1}H NMR spectral data obtained on (+)-clividine (*ent*-**1**) compared favorably with those reported by Irie[3] for the synthetically derived racemate (entry 1, Table 1). Various other comparisons (Table 1) of the spectral data reported[1] for the alkaloid (−)-clividine with those acquired on its synthetically derived optical antipode clearly established that they are enantiomers. Because the enantiomer of the starting *cis*-1,2-dihydrocatechol **3** is available[17] the worked described here provides a straightforward means for preparing (−)-clividine (**1**).

EXPERIMENTAL SECTION

General Experimental Procedures. Unless otherwise stated, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 400 and 100 MHz, respectively. Unless otherwise specified, spectra were acquired at 20 °C in deuterochloroform ($CDCl_3$) that had been filtered through basic alumina immediately prior to use. Chemical shifts are recorded as δ values in parts per million (ppm). Infrared spectra (ν_{max}) were analyzed as thin films on KBr plates (for liquids) or as a KBr disk (for solids). Melting points are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included a mixture of phosphomolybdic acid:ceric sulfate:sulfuric acid (concd): water (37.5 g:7.5 g:37.5 g:720 mL). The retardation factor (R_f) values cited here have been rounded at the first decimal point. Flash chromatographic separations were carried out following protocols defined by Still et al.[18] with silica gel 60 (40−63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from commercial companies and were used as supplied. Drying agents and other inorganic salts were purchased from commercial suppliers. THF, dichloromethane, and benzene were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.[19] Spectroscopic grade solvents were used for all analyses. Where necessary, reactions were performed under a nitrogen atmosphere.

Bromohydrin 5. A magnetically stirred solution of diol **3** (5.00 g, 26.2 mmol) in THF/water (80 mL of a 4:1 v/v mixture) maintained under nitrogen at 0 °C was treated with NBS (5.12 g, 28.8 mmol) in small portions over 0.17 h. The ensuing mixture was allowed to warm to 18 °C over 4 h and then treated with $Na_2S_2O_3$ (3.00 g). After a further 0.5 h, NaCl (3.00 g) was added and the aqueous phase extracted with diethyl ether (3 × 50 mL). The combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give an orange oil. This material was immediately dissolved in 2, 2-dimethoxypropane (75 mL) and the resulting solution treated with *p*-toluenesulfonic acid (500 mg, 2.62 mmol) before being stirred at 18 °C for 2 h. After this time, $NaHCO_3$ (100 mL of a saturated aqueous solution) was added to the reaction mixture which was then extracted with ethyl acetate (3 × 50 mL). The combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield an orange oil that was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f = 0.8 in 1:1 v/v ethyl acetate/hexane) afforded *bromohydrin* **5** (7.90 g, 92%) as a white foam, $[\alpha]_D$ +15.6 (*c* 1.5, $CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (m, 1H), 4.68 (d, *J* = 5.1 Hz, 1H), 4.61 (m, 1H), 4.33−4.26 (complex m, 2H), 2.96 (broad s, 1H), 1.53 (s, 3H), 1.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.8, 124.0, 112.1, 78.0, 76.2, 70.6, 48.1, 27.9, 26.4. IR (KBr) ν_{max} 3444, 2986, 2929, 1643, 1453, 1371, 1350, 1216, 1158, 1059, 1009, 967, 861, 791 cm^{-1}. MS (EI, 70 eV) *m*/*z* 315, 313, and 311 [$(M - CH_3\bullet)^+$, 50, 100, and 53%], 255, 253, and 251 (16, 32, and 17), 174 and 172 (15 and 16), 145 (5), 110 (7), 84 (18), 59 (10). HRMS: $(M - CH_3\bullet)^+$ calcd for $C_9H_{12}{}^{79}Br^{81}BrO_3$: 312.8898; found: 312.8899.

Nitrile 6. A magnetically stirred solution of bromohydrin **5** (5.85 g, 17.8 mmol) in THF (60 mL) maintained under a nitrogen atmosphere was cooled to 0 °C and then treated with NaH (0.78 g of a 60% suspension in mineral oil, 19.6 mmol). The ensuing mixture was stirred at 0 °C for 0.25 h before being added, dropwise, to a magnetically stirred solution of acetonitrile (3.73 mL, 71.36 mmol) and *n*-BuLi (32 mL of a 1.6 M solution in THF, 53.52 mmol) in THF (100 mL) maintained at −78 °C. After 0.25 h, the reaction mixture was quenched with NH_4Cl (50 mL of a saturated aqueous solution) and the separated aqueous phase extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with $CuSO_4$ (1 × 50 mL of a 10% w/v solution) and then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a light-yellow oil that was subjected to flash chromatography [(silica, 1:1 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f = 0.4) afforded *nitrile* **6** (4.47 g, 87%) as a gold-colored powder, mp 112.8−114.6 °C, $[\alpha]_D$ −20.3 (*c* 1.5, $CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (d, *J* = 1.4 Hz, 1H), 4.65 (dd, *J* = 5.2 and 1.9 Hz, 1H), 4.49 (dd, *J* = 5.2 and 2.3 Hz, 1H), 3.70 (d, *J* = 8.8 Hz, 1H), 2.81−2.72 (complex m, 2H), 2.62 (dd, *J* = 17.6 and 8.3 Hz, 1H), 2.37 (broad s, 1H), 1.42 (s, 3H), 1.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.9, 125.0, 117.7, 110.9, 78.3, 77.1, 70.1, 37.7, 27.3, 26.5, 19.5. IR

Table 1. Comparison of Data Derived from (+)-Clividine (*ent*-1)[a] with Those Reported for (±)-Clividine[b] and (−)-Clividine (1)[c]

entry	data type	(−)-clividine	(±)-clividine	(+)-clividine
1	^{1}H NMR	NR[d]	δ_H 7.50 (s, 1H), 6.95 (s, 1H), 6.04 (s, 2H), 4.58 (t, J = 3.0 Hz, 1H), 3.98 (dd, J = 8.5 and 3.0 Hz, 1H), 2.16 (s, 3H)	δ_H 7.47 (s, 1H), 6.91 (s, 1H), 6.03 (d, J = 1.3 Hz, 1H), 6.02 (d, J = 1.3 Hz, 1H), 4.56 (t, J = 2.6 Hz, 1H), 3.95 (td, J = 8.7 and 2.6 Hz, 1H), 3.21 (m, 1H), 2.63 (dd, J = 9.3 and 2.2 Hz, 1H), 2.51 (dd, J = 9.3 and 7.4 Hz, 1H), 2.40−2.32 (complex m, 3H), 2.13 (s, 3H), 2.09 (d, J = 4.2 Hz, 1H), 2.07 (d, J = 4.2 Hz, 1H), 1.84 (m, 2H)
2	specific rotation	−75 at 22 °C (c 0.2, $CHCl_3$)	NA[e]	+60.6 at 22 °C (c 1.0, $CDCl_3$)
3	CD (nm)	313 ($\Delta\varepsilon$ = −1.96), 270 ($\Delta\varepsilon$ = −5.52), 246 ($\Delta\varepsilon$ = +1.55)	NA	312 ($\Delta\varepsilon$ = +2.20), 272 ($\Delta\varepsilon$ = +5.73), 249 ($\Delta\varepsilon$ = −1.87)
4	UV/visible (nm)	308 (log ε = 3.74), 267 (log ε = 3.75), 225 (log ε = 4.39) (in MeOH)	NR	308 (log ε = 3.65), 266 (log ε = 3.64), 225 (log ε = 4.26) (in MeOH)
5	IR (cm^{-1})	3595, 1715, 1035, and 940 ($CHCl_3$)	3350 and 1705 (KBr)	3588, 1713, 1041, and 941 ($CHCl_3$)
6	mass spectrum	$M^{+\bullet}$, 317	NR	$M^{+\bullet}$, 317
7	melting point (°C)	195−197	170−172	186−187

[a] Data derived from present work. [b] Data obtained from ref 3. [c] Data obtained from ref 1. [d] NR = not reported. [e] NA = not applicable.

(KBr) ν_{max} 3436, 2990, 2934, 2893, 2245, 2189, 1644, 1423, 1382, 1373, 1274, 1229, 1162, 1107, 1058, 1041 cm^{-1}. MS (EI, 70 eV) m/z 290 and 288 [$(M + H)^+$, both <1%], 274 and 272 (both 80), 260 and 258 (both 10), 214 and 212 (both 28), 202 and 200 (both 22), 186 and 184 (both 24), 133 (100), 82 (33), 59 (59). HRMS: $(M + H)^+$ calcd for $C_{11}H_{14}{}^{81}BrNO_3$: 290.0215; found: 290.0214.

Xanthate 7. A magnetically stirred solution of compound **6** (4.00 g, 13.9 mmol) in THF (80 mL) maintained under nitrogen was cooled to 0 °C and then treated with NaH (0.83 mg of a 60% suspension in mineral oil, 20.8 mmol). The ensuing mixture was warmed to 18 °C over 0.5 h and then cooled again to 0 °C, treated with CS_2 (0.84 mL, 13.9 mmol), warmed to 18 °C over 0.5 h, cooled again to 0 °C, treated with MeI (0.95 mL, 15.3 mmol), and then allowed to warm to 18 °C over a further 0.5 h. The reaction mixture was then quenched with NH_4Cl (50 mL of a half-saturated solution) and the aqueous phase extracted with Et_2O (3 × 40 mL). The combined organic phases were then washed with water (1 × 40 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane →1:4 v/v ethyl acetate/hexane gradient elution). Concentration of the appropriate fractions (R_f = 0.3 in 1:3 v/v ethyl acetate/hexane) afforded *xanthate* **7** (4.89 g, 93%) as a gold-colored foam, $[\alpha]_D$ −105.5 (c 2.0, $CDCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.08 (d, J = 2.0 Hz, 1H), 5.91 (dd, J = 10.2 and 2.1 Hz, 1H), 4.70 (dd, J = 5.0 and 2.4 Hz, 1H), 4.67 (dd, J = 5.0 and 2.1 Hz, 1H), 3.28 (m, 1H), 2.62 (dd, J = 16.8 and 4.8 Hz, 1H), 2.62 (s, 3H), 2.45 (dd J = 16.8 and 7.8 Hz, 1H), 1.46 (s, 3H), 1.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 216.0, 127.9, 125.6, 116.9, 111.5, 78.7, 78.0, 73.9, 35.1, 27.4, 26.7, 19.5 (one signal obscured or overlapping). IR (KBr) ν_{max} 2987, 2932, 2249, 1718, 1643, 1483, 1423, 1382, 1372, 1191, 1106, 1068, 980, 870 cm^{-1}. HRMS: $(M + Na)^+$ calcd for $C_{13}H_{16}BrNO_3S_2$: 399.9653; found: 399.9653.

Bromide 8. A magnetically stirred solution of xanthate **7** (4.89 g, 12.9 mmol) in benzene (80 mL) was heated to reflux while being maintained under an atmosphere of nitrogen then treated with AIBN (0.21 g, 1.29 mmol) and *n*-Bu_3SnH (3.83 mL, 14.2 mmol). The ensuing mixture was heated at reflux for a further 2 h, additional *n*-Bu_3SnH (0.90 mL, 3.23 mmol) was added, and heating was continued for a further 0.5 h. The cooled reaction mixture was treated NH_4Cl (50 mL of a saturated aqueous solution) and the separated aqueous phase extracted with Et_2O (3 × 40 mL). The combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield a yellow oil that was dissolved in acetonitrile (50 mL). The resulting solution was washed with pentane (3 × 30 mL) and then concentrated under reduced pressure, and the light-yellow oil thus obtained was subjected to flash chromatography (silica, dichloromethane elution). Concentration of the appropriate fractions (R_f = 0.25 in 1:2 v/v ethyl acetate/hexane) afforded *bromide* ***8*** (3.06 g, 87%) as a golden foam, $[\alpha]_D$ +29.1 (c 3.0, $CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (m, 1H), 4.51−4.46 (complex m, 2H), 2.82 (m, 1H), 2.46 (dd, J = 16.3 and 6.0 Hz, 1H), 2.40 (dd, J = 16.3 and 6.3 Hz, 1H), 2.31 (m, 1H), 1.64 (m, 1H), 1.40 (s, 3H), 1.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.8, 125.9, 117.4, 109.8, 76.1, 73.3, 30.5, 30.3, 27.4, 26.4, 22.9. IR (KBr) ν_{max} 2986, 2933, 2247, 1644, 1455, 1435, 1381, 1370, 1350, 1314, 1227, 1155, 1073, 1043 cm^{-1}. MS (EI, 70 eV) m/z 273 and 271 ($M^{+\bullet}$, both <1%), 258 and 256 (98 and 100), 216 and 214 (20 and 22), 198 and 196 (61 and 63), 171 and 169 (both 55), 117 (21), 94 (18), 77 (35), 65 (32). HRMS: $M^{+\bullet}$ calcd for $C_{11}H_{14}{}^{79}BrNO_2$: 271.0208; found: 271.0210.

Acetonide 10. A magnetically stirred solution of bromide **8** (5.42 g, 19.91 mmol) in degassed THF/water (200 mL of a 9:1 v/v mixture) was treated with boronate ester **9**[20] (8.16 g, 27.9 mmol), Et_3N (28 mL, 199.1 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (1.63 g, 2.00 mmol) and then heated at reflux under an atmosphere of nitrogen for 2 h. The cooled reaction mixture was diluted with ethyl acetate (50 mL) and washed with H_2O (2 × 150 mL) and brine (1 × 100 mL). The combined aqueous phases were extracted with ethyl acetate (2 × 50 mL), and the combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield a brown powder that was subjected to flash chromatography (silica, 1:2 → 1:1 v/v ethyl acetate/hexane gradient elution]. Concentration of the appropriate fractions (R_f = 0.5 in 1:1 v/v ethyl acetate/hexane) afforded *acetonide* ***10*** (7.03 g, 95%) as a golden foam, $[\alpha]_D$ +15.8 (c 1.0, $CDCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (s, 1H), 6.70 (s, 1H), 6.03 (d, J = 1.4 Hz, 1H), 6.01 (d, J = 1.4 Hz, 1H), 5.5 (app. t, J = 1.6 Hz, 1H), 4.82 (dd, J = 6.0 and1.6 Hz, 1H), 4.61 (m, 1H), 3.79 (s, 3H), 2.85 (m, 1H), 2.45 (dd, J = 16.7 and 6.7 Hz, 1H),

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2.39 (dd, J = 16.7 and 7.1 Hz, 1H), 2.31 (dm, J = 13.8 Hz, 1H), 1.75 (ddd, J = 13.9, 11.1, and 2.3 Hz, 1H), 1.46 (s, 3H), 1.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.2, 150.6, 147.0, 141.8, 138.5, 127.3, 121.9, 118.1, 111.7, 110.2, 108.6, 101.9, 74.4, 72.6, 51.9, 31.8, 27.9, 27.5, 25.9, 23.3. IR (KBr) ν_{max} 2986, 2916, 2246, 1717, 1613, 1504, 1484, 1436, 1370, 1247, 1156, 1125, 1072, 1036 cm^{-1}. MS (EI, 70 eV) m/z 371 ($M^{+\bullet}$, 16%), 356 (8), 313 (13), 282 (29), 264 (53), 254 (26), 241 (100), 213 (42), 69 (37). HRMS $M^{+\bullet}$ calcd for $C_{20}H_{21}NO_6$: 371.1369; found: 371.1372.

Carbamate 12. A magnetically stirred mixture of nitrile **10** (1.00 g, 2.69 mmol) and Raney-cobalt (2.00 g, 200% w/w) in MeOH (50 mL, saturated with ammonia) was maintained under a hydrogen atmosphere at 18 °C for 18 h. The reaction mixture was then filtered through Celite and the residual Raney-cobalt washed with MeOH (3 × 20 mL). The combined filtrates were concentrated under reduced pressure to afford a brown oil that was dissolved in pyridine (20 mL). The resulting solution was cooled to −10 °C and then treated, dropwise over 0.5 h and while being maintained under nitrogen, with a solution of allyl chloroformate (0.29 mL, 2.69 mmol) in dichloromethane (15 mL). After a further 0.25 h, the reaction mixture was treated with $NaHCO_3$ (50 mL of a saturated aqueous solution) and the separated aqueous phase extracted with dichloromethane (3 × 30 mL). The combined organic phases were concentrated under reduced pressure at 25 °C to give a yellow oil that was subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f = 0.5) afforded *carbamate* ***12*** (1.06 g, 86%) as clear, colorless oil, $[\alpha]_D$ −9.4 (c 1.0, $CDCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (s, 1H), 6.70 (s, 1H), 6.01 (d, J = 1.2 Hz, 1H), 5.99 (d, J = 1.2 Hz, 1H), 5.85 (m, 1H), 5.47 (s, 1H), 5.23 (d, J = 17.3 Hz, 1H), 5.16 (d, J = 10.4 Hz, 1H), 4.92 (m, 1H), 4.77 (dd, J = 4.9 and 1.4 Hz, 1H), 4.56 (m, 1H), 4.50 (d, J = 5.2 Hz, 2H), 3.77 (s, 3H), 3.26 (m, 2H), 2.52 (m, 1H), 2.15 (dt, J = 13.9 and 4.0 Hz, 1H), 1.63 (m, 3H), 1.45 (s, 3H), 1.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.5, 156.2, 150.5, 146.7, 139.5, 138.9, 132.9, 131.1, 121.7, 117.4, 111.8, 110.1, 108.3, 101.8, 74.8, 73.1, 65.3, 51.7, 38.3, 35.0, 31.3, 27.6, 27.6, 26.1. IR (KBr) ν_{max} 3351, 2984, 2934, 1720, 1613, 1529, 1504, 1484, 1436, 1369, 1245, 1188, 1159, 1126, 1070, 1038 cm^{-1}. HRMS: $(M + Na)^+$ calcd for $C_{24}H_{29}NO_8$: 482.1791; found: 482.1794.

N*-Methylcarbamate 13.** A magnetically stirred solution of carbamate **12** (4.54 g, 9.9 mmol) in THF (85 mL) maintained under nitrogen was cooled to −78 °C and then treated, dropwise, with LiHMDS (15 mL of a 1 M solution in THF, 14.81 mmol). The ensuing mixture was stirred at 18 °C for 0.5 h and then treated with methyl iodide (1.23 mL, 19.7 mmol). After a further 0.5 h, the reaction mixture was quenched with NH_4Cl (150 mL of a saturated aqueous solution) and the separated aqueous phase extracted with dichloromethane (3 × 60 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield a yellow oil that was subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f = 0.5) afforded *N-methylcarbamate* ***13 (4.42 g, 93%) as a clear, colorless oil, $[\alpha]_D$ +12.4 (c 3.0, $CDCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (s, 1H), 6.72 (s, 1H), 6.00 (app. d, J = 11.3 Hz, 2H), 5.91 (m, 1H), 5.50 (d, J = 10.0 Hz, 1H), 5.27 (d, J = 17.1 Hz, 1H), 5.16 (t, J = 10.2 Hz, 1H), 4.78 (m, 1H), 4.56 (m, 3H), 3.77 (s, 3H), 3.35 (m, 2H), 2.90 (s, 3H), 2.44 (m, 1H), 2.18 (d, J = 13.1 Hz, 1H), 1.60 (m, 3H), 1.45 (s, 3H), 1.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.5, 156.0, 150.5, 146.7, 139.5, 139.1, 133.2, 131.3, 131.2, 121.9, 117.2, 117.1, 111.9, 110.1, 108.3, 101.8, 74.8, 73.2, 65.9, 51.7, 46.8, 46.3, 34.6, 34.0, 33.5, 33.0, 32.1, 27.8, 27.5, 26.0 (additional signals due to the presence of carabmate rotamers). IR (KBr) ν_{max} 2985, 2933, 1704, 1648, 1613, 1503, 1484, 1435, 1402, 1369, 1244, 1203, 1162, 1125, 1070, 1037 cm^{-1}. MS (EI, 70 eV) m/z 473 ($M^{+\bullet}$, <1%), 415 (3), 383 (5), 342 (6), 308 (10), 298 (13), 282 (38), 238 (23), 128 (100), 84 (58). HRMS: $M^{+\bullet}$ calcd for $C_{25}H_{31}NO_8$: 473.2050; found: 473.2043.

N*-Methylamine 14.** Dimedone (6.55 g, 46.7 mmol) was dissolved in magnetically stirred and degassed THF (50 mL), being maintained at 18 °C under nitrogen, and the solution thus obtained was treated with *N*-methylcarbamate **13** (2.21 g, 4.67 mmol) and then $Pd(PPh_3)_4$ (1.08 g, 0.93 mmol). The ensuing mixture was stirred at 18 °C for 0.25 h, diluted with dichloromethane (150 mL), and washed with $NaHCO_3$ (3 × 150 mL of a saturated aqueous solution). The separated organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give an orange oil that was subjected to flash chromatography (silica, 1:9 v/v ammonia saturated methanol/dichloromethane elution). Concentration of the appropriate fractions (R_f = 0.3) then gave *amine* ***14 (1.70 g, (94%) as a light-yellow oil, $[\alpha]_D$ +19.8 (c 2.0, $CDCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (s, 1H), 6.72 (s, 1H), 6.01 (m, 1H), 5.98 (m, 1H), 5.49 (s, 1H), 4.77 (dd, J = 6.2 and 1.4 Hz, 1H), 4.55 (m, 1H), 3.77 (s, 3H), 2.69 (t, J = 7.6 Hz, 2H), 2.60−2.48 (complex m, 2H), 2.44 (s, 3H), 2.16 (dt, J = 14.3 and 4.9 Hz, 1H), 1.65−1.56 (complex m, 3H), 1.45 (s, 3H), 1.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.5, 150.4, 146.7, 139.4, 138.8, 131.6, 122.0, 111.8, 110.0, 108.3, 101.8, 74.8, 73.2, 51.7, 49.1, 36.1, 35.0, 31.9, 28.2, 27.6, 26.0. IR (KBr) ν_{max} 2984, 2931, 2794, 1718, 1613, 1504, 1484, 1436, 1369, 1245, 1190, 1126, 1070, 1036, 930, 882 cm^{-1}. MS (EI, 70 eV) m/z 389 ($M^{+\bullet}$, 4%), 374 (24), 314 (23), 270 (30), 238 (100), 225 (11), 149 (15), 57 (28). HRMS: $M^{+\bullet}$ calcd for $C_{21}H_{27}NO_6$: 389.1838; found: 389.1837.

Lactone 15. A magnetically stirred solution of compound **14** (0.68 g, 1.73 mmol) in acetic acid/water (30 mL of a 4:1 v/v mixture) was maintained at 50 °C for 18 h, allowed to cool to 18 °C, quenched with $NaHCO_3$ (50 mL of a saturated aqueous solution), and extracted with dichloromethane (4 × 50 mL). The combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield a yellow oil that was triturated with dichloromethane (10 mL) to yield *lactone* ***15*** (0.46 g, 84%) as a white, crystalline solid, mp 214.3−216.1 °C, $[\alpha]_D$ +41.4 (c 1.5, CD_3OD). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.38 (s, 1H), 7.22 (s, 1H), 6.36 (s, 1H), 6.09 (app. d, J = 4.9 Hz, 2H), 5.16 (m, 1H), 4.37 (m, 1H), 3.30 (m, 1H), 3.10 (m, 1H), 2.80 (m, 1H), 2.73 (s, 3H), 2.16 (dt, J = 13.5 and 4.6 Hz, 1H), 1.88 (m, 1H), 1.77 (m, 1H), 1.55 (dd, J = 12.3 and 1.7 Hz, 1H) (signal due to OH and NH protons not observed). ^{13}C NMR (CD_3OD, 100 MHz) δ 166.3, 154.8, 149.9, 135.3, 130.2, 127.7, 118.2, 109.1, 103.9, 103.5, 78.4, 66.3, 48.1, 34.1, 33.8, 32.8, 30.9. IR (KBr) ν_{max} 3386, 2922, 2790, 1703, 1615, 1502, 1481, 1393, 1350, 1303, 1276, 1247, 1190, 1139, 1079, 1034, 930, 856 cm^{-1}. HRMS: $(M + H)^+$ calcd for $C_{17}H_{19}NO_5$: 318.1341; found: 318.1341.

C11b-*epi*-(+)-Clividine (C11b-*epi*-*ent*-1). A magnetically stirred solution of amine **15** (95 mg, 0.30 mmol) in dichloromethane (5 mL) maintained under nitrogen was cooled to −78 °C and then treated, dropwise, with a solution of NCS (40 mg, 0.3 mmol) in dichloromethane (5 mL). The ensuing mixture was allowed to warm to 18 °C and then concentrated under reduced pressure to yield a white paste that was dissolved in ethyl acetate/hexane (10 mL of 1:4 v/v mixture). The resulting solution was passed through a pad of TLC-grade silica that was then washed with ethyl acetate/hexane (50 mL of a 1:1 v/v mixture). The combined filtrates were concentrated under reduced pressure, and the light-yellow oil thus obtained, and containing the *N*-chloroamine **16**, was dissolved in degassed benzene (25 mL) maintained under nitrogen and containing AIBN (5 mg, 0.025 mmol). The resulting solution was heated at reflux and then treated, dropwise, with *n*-Bu_3SnH (88 μL, 0.33 mmol). After addition was complete, the reaction mixture was heated at reflux for 1 h, treated with additional *n*-Bu_3SnH (20 μL, 0.08 mmol), and heated for a further 0.5 h. The cooled reaction mixture was then concentrated under reduced pressure and the resulting yellow oil subjected to flash chromatography (silica, 1:19 v/v ammonia saturated methanol/dichloromethane elution). Concentration of the appropriate fractions (R_f = 0.5 in 1:9 v/v ammonia saturated methanol/dichloromethane) afforded *C11b*-epi-(+)-*clividine* (*C11b*-epi-ent-***1***)

(63 mg, 62% from **15**) as a white powder, mp 91.8−92.6 °C, $[\alpha]_D$ +110.2 (*c* 0.5, $CDCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.51 (s, 1H), 6.97 (s, 1H), 6.03 (d, *J* = 1.2 Hz, 1H), 6.01 (d, *J* = 1.2 Hz, 1H), 4.83 (dd, *J* = 12.5 and 2.3 Hz, 1H), 4.23 (dd, *J* = 5.5 and 2.7 Hz, 1H), 3.80 (dd, *J* = 12.5 and 1.8 Hz, 1H), 3.18 (app. t, *J* = 2.7 Hz, 1H), 3.15 (dt, *J* = 12.7 and 5.5 Hz, 1H), 2.48 (m, 1H), 2.32 (m, 1H), 1.97 (s, 3H), 1.91−1.77 (complex m, 4H), 1.37 (ddd, *J* = 13.2, 9.1, and 4.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.4, 152.2, 146.7, 137.9, 118.0, 109.7, 105.2, 101.9, 77.9, 68.3, 63.9, 54.9, 42.3, 36.3, 33.7, 33.2, 27.9. IR (KBr) ν_{max} 3421, 2931, 2788, 1707, 1618, 1503, 1483, 1445, 1388, 1274, 1244, 1132, 1085, 1038, 883, 730 cm^{-1}. MS (EI, 70 eV) *m*/*z* 317 ($M^{+\bullet}$, 81%), 300 (4), 228 (10), 162 (9), 126 (14), 96 (100), 82 (83). HRMS: $M^{+\bullet}$ calcd for $C_{17}H_{19}NO_5$: 317.1263; found: 317.1257.

Alcohol 17. A magnetically stirred solution of acetonide **10** (0.99 g, 2.68 mmol) in acetic acid/water (50 mL of a 4:1 v/v mixture) was heated at 50 °C for 18 h, allowed to cool to 18 °C, and quenched with $NaHCO_3$ (50 mL of a saturated aqueous solution). The mixture thus obtained was extracted with dichloromethane (4 × 50 mL), and the combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a light-yellow oil. Trituration of this material with dichloromethane (10 mL) then gave *alcohol* ***17*** (0.67 g, 84%) as a white, crystalline solid mp 153.4−154.9 °C, $[\alpha]_D$ +41.5 (*c* 1.0, CD_4OD). ^1H NMR (DMSO-d_6, 400 MHz) δ 7.34 (s, 1H), 7.29 (s, 1H), 6.39 (s, 1H), 6.16 (d, *J* = 1.1 Hz, 1H), 6.15 (d, *J* = 1.1 Hz, 1H), 5.33 (d, *J* = 4.0 Hz, 1H), 5.15 (dd, *J* = 5.9 and 3.6 Hz, 1H), 4.24 (m, 1H), 3.16 (d, *J* = 8.0 Hz, 1H), 2.75 (dd, *J* = 16.9 and 5.7 Hz, 1H), 2.69 (dd, *J* = 16.9 and 6.4 Hz, 1H), 2.06 (m, 1H), 1.53 (app. t, *J* = 12.3 Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 163.5, 152.8, 148.1, 133.1, 127.8, 127.1, 119.3, 117.0, 107.7, 102.5(2), 102.5(1), 76.5, 64.0, 32.8, 29.3, 22.3. IR (KBr) ν_{max} 3118, 2923, 2852, 2246, 1725, 1716, 1612, 1499, 1481, 1399, 1307, 1281, 1243, 1094, 1079, 1030, 926, 860 cm^{-1}. MS (EI, 70 eV) *m*/*z* 299 ($M^{+\bullet}$, 100%), 281 (30), 272 (20), 259 (70), 254 (54), 241 (58), 215 (36), 213 (42), 115 (17), 57 (22). HRMS: $M^{+\bullet}$ calcd for $C_{16}H_{13}NO_5$: 299.0794; found: 299.0801.

Ether 18. A magnetically stirred solution of alcohol **17** (0.89 g, 2.97 mmol) in DMF (30 mL) maintained under nitrogen at 18 °C was treated with imidazole (1.01 g, 14.9 mmol) and *tert*-butyldiphenylchlorosilane (2.32 mL, 8.92 mmol). After 72 h, the reaction mixture was quenched with $NaHCO_3$ (30 mL of a half-saturated aqueous solution), and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield a yellow oil that was subjected to flash chromatography (silica, 1:3 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f = 0.8 in 1:2 v/v ethyl acetate/hexane) afforded *ether* ***18*** (1.27 g, 80%) as a white foam, $[\alpha]_D$ +1.0 (*c* 1.0, $CDCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.76−7.72 (complex m, 4H), 7.49 (s, 1H), 7.45−7.32 (complex m, 6H), 7.03 (s, 1H), 6.23 (m, 1H), 6.07 (s, 2H), 4.98 (dd, *J* = 3.5 and 2.6 Hz, 1H), 4.49 (t, *J* = 3.5 Hz, 1H), 3.18 (m, 1H), 2.48 (dd, *J* = 16.8 and 7.1 Hz, 1H), 2.37 (dd, *J* = 7.1 and 16.3 Hz, 1H), 1.89 (m, 1H), 1.39 (m, 1H), 1.05 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.9, 152.8, 148.7, 136.2, 136.0, 133.8, 132.9, 132.3, 129.9, 129.7, 128.8, 127.7, 127.5, 124.9, 118.0, 117.7, 109.0, 102.2, 102.1, 76.5, 67.1, 33.6, 30.1, 27.0, 23.4, 19.5. IR (KBr) ν_{max} 2930, 2857, 2248, 1713, 1616, 1504, 1480, 1427, 1393, 1349, 1302, 1277, 1243, 1187, 1111, 1037, 911, 737, 703 cm^{-1}. HRMS: $(M + Na)^+$ calcd for $C_{32}H_{31}NO_5Si$: 560.1869; found: 560.1869.

Amine 19. A magnetically stirred solution of nitrile **18** (1.25 g, 2.32 mmol) and Raney-cobalt (2.50 g, 200% w/w) in MeOH (75 mL of ammonia saturated material) was maintained under an atmosphere of hydrogen at 18 °C for 18 h and then filtered through a pad of Celite, and the Raney-cobalt thus retained was washed with MeOH (3 × 20 mL). The combined filtrates were concentrated under reduced pressure to afford a brown oil that was subjected to flash chromatography (silica, 1:19 v/v ammonia saturated methanol/dichloromethane elution). Concentration of the appropriate fractions (R_f = 0.4 in 1:9 v/v ammonia saturated methanol/dichloromethane) afforded *amine* ***19*** (1.04 g, 82%) as a clear foam, $[\alpha]_D$ +11.2 (*c* 1.0, $CDCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.76−7.74 (complex m, 4H), 7.49 (s, 1H), 7.44−7.32 (complex m, 6H), 6.99 (s, 1H), 6.24 (s, 1H), 6.05 (s, 2H), 4.96 (m, 1H), 4.45 (t, *J* = 3.8 Hz, 1H), 2.85 (m, 1H), 2.68 (m, 2H), 1.79 (m, 1H), 1.62 (m, 1H), 1.40 (m, 1H), 1.25 (m, 2H), 1.17 (dd, *J* = 10.1 and 2.7 Hz, 1H), 1.05 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.4, 152.6, 148.0, 136.3, 136.0, 134.4, 133.5, 133.3, 130.3, 129.7, 129.6, 127.6, 127.4, 125.5, 117.5, 109.0, 102.0, 101.9, 77.2, 67.4, 39.5, 39.4, 33.7, 30.2, 27.0, 19.5. IR (KBr) ν_{max} 3369, 2929, 2856, 1712, 1617, 1504, 1479, 1427, 1392, 1350, 1272, 1242, 1189, 1111, 1037, 931 cm^{-1}. HRMS: $(M + H)^+$ calcd for $C_{32}H_{35}NO_5Si$: 542.2363; found: 542.2363.

Carbamate 20. A magnetically stirred solution of amine **19** (1.03 g, 1.89 mmol) in pyridine (15 mL) maintained under nitrogen was cooled to −10 °C and then treated, dropwise over 0.5. h, with a solution of allyl chloroformate (0.22 mL, 2.08 mmol) in dichloromethane (10 mL). After a further 0.25 h, the reaction mixture was treated with $NaHCO_3$ (40 mL of a saturated aqueous solution) and then extracted with dichloromethane (3 × 20 mL). The combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure at 25 °C to give a yellow foam that was subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane elution]. Concentration of the appropriate fractions (R_f = 0.6) afforded *carbamate* ***20*** (1.07 g, 90%) as a white foam, $[\alpha]_D$ +85.7 (*c* 1.0, $CDCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.75 (m, 4H), 7.49 (s, 1H), 7.46−7.32 (complex m, 6H), 6.98 (s, 1H), 6.23 (s, 1H), 6.05 (s, 2H), 5.92 (m, 1H), 5.31 (dm, *J* = 17.3 Hz, 1H), 5.22 (dm, *J* = 10.4 Hz, 1H), 4.96 (m, 1H), 4.61 (m, 1H), 4.56 (d, *J* = 5.1 Hz, 2H), 4.47 (t, *J* = 3.9 Hz, 1H), 3.22 (m, 1H), 3.09 (m, 1H), 2.82 (m, 1H), 1.78−1.70 (complex m, 2H), 1.54−1.37 (complex m, 1H), 1.28−1.16 (complex m, 1H), 1.04 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.4, 156.1, 152.7, 148.1, 136.3, 136.0, 134.4, 133.3, 133.2, 132.8, 129.8, 129.6, 129.4, 127.6, 127.4, 125.9, 117.7, 117.6, 109.0, 102.0, 101.9(5), 77.06, 67.3, 65.6, 38.3, 35.4, 33.5, 30.0, 27.0, 19.4. IR (KBr) ν_{max} 3368, 2930, 2856, 1710, 1617, 1504, 1479, 1427, 1392, 1359, 1273, 1243, 1112, 1037, 933 cm^{-1}. MS (EI, 70 eV) *m*/*z* 625 ($M^{+\bullet}$, 3%), 568 (9), 511 (23), 510 (60), 251 (12), 199 (100), 149 (39), 60 (55), 57 (95). HRMS: $M^{+\bullet}$ calcd for $C_{36}H_{39}NO_7Si$: 625.2496; found: 625.2515.

N*-Methylcarbamate 21.** A magnetically stirred solution of carbamate **20** (1.10 g, 1.68 mmol) in THF (20 mL) maintained under nitrogen was cooled to −78 °C and then treated, dropwise, with LiHMDS (2.25 mL of a 1 M solution in THF, 2.25 mmol). The ensuing mixture was stirred at −78 °C for 0.5 h, treated with methyl iodide (0.21 mL, 3.36 mmol) before being warmed to 18 °C, allowed to stand at this temperature for 0.5 h, and then quenched with NH_4Cl (30 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (2 × 40 mL), and the combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield a yellow oil that was subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane ether elution). Concentration of the appropriate fractions (R_f = 0.6) afforded N-*methylcarbamate* ***21 (0.90 g, 84%) as a white foam, $[\alpha]_D$ +78.6 (*c* 1.0, $CDCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.76−7.73 (complex m, 4H), 7.48 (broadened s, 1H), 7.45−7.30 (complex m, 6H), 6.99 (broadened s, 1H), 6.28 (m, 1H), 6.05 (s, 2H), 5.92 (m, 1H), 5.28 (m, 1H), 5.19 (dm, *J* = 10.7 Hz, 1H), 4.96 (m, 1H), 4.57 (m, 2H), 4.44 (m, 1H), 3.45−3.30 (complex m, 1H), 3.25−3.10 (complex m, 1H), 2.91 (s, 3H), 2.80 (m, 1H), 1.72−1.85 (complex m, 1H), 1.64 (m, 1H), 1.54 (m, 1H), 1.24 (m, 1H), 1.04 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.4, 156.0, 150.5, 146.7, 139.4, 139.1, 133.2, 131.1, 121.9, 117.2, 111.8, 110.1, 108.2, 101.8, 74.8, 73.2, 65.9, 51.7, 46.8, 46.3, 34.6, 34.0, 33.5, 32.9, 32.1, 27.8, 27.5, 26.0 (signals due to various carbons obscured or overlapping). IR (KBr) ν_{max} 2930, 2857, 1704, 1617, 1504, 1479, 1427, 1394, 1361, 1300, 1273, 1242, 1202, 1111, 1060, 1036 cm^{-1}. MS (EI, 70 eV) *m*/*z* 639 ($M^{+\bullet}$, 8%), 583 (45),

582 (100), 555 (13), 523 (30), 524 (48), 510 (20), 498 (17), 467 (40), 437 (18). HRMS: $M^{+\bullet}$ calcd for $C_{37}H_{41}NO_7Si$: 639.2652; found: 639.2667.

N*-Methylamine 22.** A magnetically stirred solution of dimedone (1.96 mg, 14 mmol) in degassed THF (20 mL) maintained under nitrogen at 18 °C was treated with *N*-methylcarbamate **21** (0.89 g, 1.39 mmol) and $Pd(PPh_3)_4$ (0.16 g, 0.14 mmol). The ensuing mixture was stirred for 1 h at this temperature, diluted with dichloromethane (30 mL), and washed with $NaHCO_3$ (3 × 50 mL of a saturated aqueous solution). The separated organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure and the orange oil thus obtained subjected to flash chromatography (silica, 1:19 v/v ammonia saturated methanol/dichloromethane elution). Concentration of the appropriate fractions (R_f = 0.4 in 1:9 v/v ammonia saturated methanol/dichloromethane) afforded N-*methylamine* ***22 (0.69 g, 89%) as a light-yellow foam, $[\alpha]_D$ +8.4 (*c* 3.0, $CDCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77−7.74 (complex m, 4H), 7.49 (s, 1H), 7.44−7.32 (complex m, 6H), 6.99 (s, 1H), 6.25 (s, 1H), 6.04 (s, 2H), 4.95 (m, 1H), 4.45 (t, *J* = 3.8 Hz, 1H), 2.84 (broadened s, 1H), 2.56 (t, *J* = 7.6 Hz, 2H), 2.45 (s, 3H), 1.79 (m, 2H), 1.73−1.64 (complex m, 1H), 1.50−1.41 (complex m, 1H), 1.19 (m, 1H), 1.04 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.4, 152.6, 148.0, 136.3, 136.0, 134.4, 133.5, 133.2, 130.1, 129.7, 129.6, 127.6, 127.4, 125.6, 117.6, 108.9, 102.0, 101.9, 77.1, 67.4, 49.2, 36.4, 35.3, 33.7, 30.6, 27.0, 19.4. IR (KBr) ν_{max} 3326, 3070, 2930, 2856, 2794, 2249, 1713, 1617, 1504, 1479, 1427, 1392, 1361, 1350, 1273, 1242, 1189, 1111, 1037 cm^{-1}. MS (EI, 70 eV) *m*/*z* 555 ($M^{+\bullet}$, 83%), 498 (100), 467 (57), 277 (38), 238 (33), 199 (70), 96 (30), 83 (81). HRMS: $M^{+\bullet}$ calcd for $C_{33}H_{37}NO_5Si$: 555.2441; found: 555.2441.

N*-Chloroamine 23.** A magnetically stirred solution of *N*-methylamine **22** (0.34 g, 0.61 mmol) in dichloromethane (10 mL) maintained under nitrogen was cooled to −78 °C and then treated, dropwise, with a solution of NCS (90 mg, 0.67 mmol) in dichloromethane (5 mL). The ensuing mixture was allowed to warm to 18 °C over 1 h and then concentrated under reduced pressure to yield a white paste that was redissolved in ethyl acetate/hexane (10 mL of 1:4 v/v mixture). The solution thus obtained was passed through a pad of TLC-grade silica that was washed with ethyl acetate/hexane (200 mL of a 1:4 v/v mixture). Concentration of the combined filtrates yielded N-*chloroamine* ***23 (334 mg, 93%) as a white foam, $[\alpha]_D$ +7.6 (*c* 2.0, $CDCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, *J* = 6.2 Hz, 4H), 7.49 (s, 1H), 7.40−7.33 (complex m, 6H), 7.01 (s, 1H), 6.29 (s, 1H), 6.04 (s, 2H), 4.96 (m, 1H), 4.45 (t, J = 3.8 Hz, 1H), 2.95 (s, 3H), 2.84 (t, *J* = 7.5 Hz, 2H), 1.89−1.81 (complex m, 2H), 1.59 (m, 1H), 1.27−1.17 (complex m, 2H), 1.06 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.4, 152.6, 148.0, 136.3, 136.0, 134.3, 133.4, 133.2, 129.9, 129.6, 129.5, 127.5, 127.4, 125.7, 117.5, 108.9, 102.0, 101.9, 77.0, 67.3, 63.3, 53.1, 33.7, 33.6, 30.3, 27.0, 19.4. IR (KBr) ν_{max} 2929, 2856, 1713, 1617, 1504, 1478, 1427, 1392, 1361, 1273, 1241, 1187, 1111, 1037 cm^{-1}. HRMS: $(M + H)^+$ calcd for $C_{33}H_{36}{}^{35}ClNO_5Si$: 590.2130; found: 590.2131.

Pyrrolidine 24. A magnetically stirred solution of *N*-chloroamine **23** (0.33 g, 0.57 mmol) and AIBN (10 mg, 0.06 mmol) in benzene (40 mL) maintained under nitrogen was heated at reflux and then treated, dropwise, with *n*-Bu_3SnH (0.17 mL, 0.63 mmol). Heating of the ensuing mixture was continued for 1 h, and then it was treated with additional *n*-Bu_3SnH (38 μL, 0.14 mmol). After being heated for a further 0.5 h, the reaction mixture was cooled and then concentrated under reduced pressure and the resulting yellow oil subjected to flash chromatography (silica, 1:19 v/v ammonia saturated methanol/dichloromethane elution]. Concentration of the appropriate fractions (R_f = 0.85) afforded *pyrrolidine* ***24*** (0.26 g, 83%) as a white foam, $[\alpha]_D$ −17.6 (*c* 2.0, $CDCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69−7.67 (complex m, 4H), 7.52 (s, 1H), 7.45−7.33 (complex m, 6H), 6.81 (s, 1H), 6.02 (d, *J* = 1.3 Hz, 1H), 6.01 (d, *J* = 1.3 Hz, 1H), 4.39 (m, 1H), 3.93 (m, 1H), 3.05 (t, *J* = 7.9 Hz, 1H), 2.48 (dm, *J* = 7.4 Hz, 1H), 2.40 (dm, *J* = 7.5 Hz, 1H), 2.25 (m, 3H), 2.08 (s, 3H), 1.71 (dd, *J* = 7.8 and 5.0 Hz, 1H), 1.54 (m, 1H), 1.45−1.38 (complex m, 1H), 1.05 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.3, 151.6, 147.2, 140.3, 135.8, 135.7, 133.8, 133.7, 129.7, 127.6, 118.4, 109.8, 107.5, 101.7, 80.1, 68.1, 67.1, 55.9, 45.0, 43.1, 36.4, 29.9, 29.1, 26.8, 19.1 (two signals obscured or overlapping). IR (KBr) ν_{max} 3071, 2931, 2788, 2249, 1716, 1617, 1504, 1478, 1427, 1387, 1285, 1257, 1111, 1035 cm^{-1}. MS (EI, 70 eV) *m*/*z* 555 ($M^{+\bullet}$, 15%), 498 (24), 96 (17), 86 (70), 84 (100), 83 (72). HRMS: $M^{+\bullet}$ calcd for $C_{33}H_{37}NO_5Si$: 555.2441; found: 555.2443.

ent*-Clividine (*ent*-1).** A magnetically stirred solution of pyrrolidine **24** (78 mg, 0.14 mmol) in THF (5 mL) maintained under nitrogen was cooled to 0 °C and then treated with HF·pyridine (200 μL) [CAUTION!] and the ensuing mixture allowed to warm to 18 °C, kept at this temperature for 48 h, treated with $NaHCO_3$ (10 mL of a saturated aqueous solution), and extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield a brown oil that was subjected to flash chromatography (silica, 1:19 v/v ammonia saturated methanol/dichloromethane elution). Concentration of the appropriate fractions (R_f = 0.7) afforded ent-*clividine* (ent-1***) (44 mg, 99%) as a white crystalline solid, mp 185.4−186.9 °C, $[\alpha]_D$ +60.6 (*c* 1.0, $CDCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) see Table 1. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.8, 151.9, 147.3, 140.4, 117.8, 109.6, 108.0, 101.8, 80.0, 67.1, 66.2, 56.0, 45.2, 43.0, 36.6, 30.1, 29.5. IR (KBr) ν_{max} 3368, 2932, 2772, 1709, 1618, 1502, 1479, 1447, 1385, 1289, 1256, 1237, 1111, 1076, 1027, 934, 751 cm^{-1}. MS (EI, 70 eV) *m*/*z* 317 ($M^{+\bullet}$, 25%), 96 (38), 83 (100), 82 (32). HRMS: $M^{+\bullet}$ calcd for $C_{17}H_{19}NO_5$: 317.1263; found: $M^{+\bullet}$, 317.1264.

■ ASSOCIATED CONTENT

Supporting Information. Data derived from the single-crystal X-ray analyses of, as well as CIF files for, the oxalate salt of compound C11b-*epi*-*ent*-**1**, the picrate salt of compound *ent*-**1**, and compounds **6**, **10**, and **15**; ^{1}H and ^{13}C NMR spectra of compounds *ent*-**1**, C11b-*epi*-*ent*-**1**, **5**−**8**, **10**, **12**−**15**, and **17**−**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: mgb@rsc.anu.edu.au

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