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# Synthesis of enantiopure cyclobutane amino acids and amino alcohols

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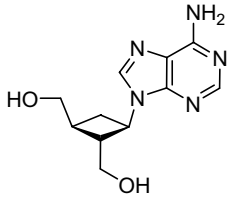
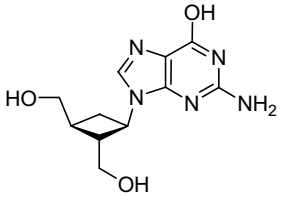
**Abstract**—(−)-(1*R*,3*S*)-3-Amino-2,2-dimethylcyclobutanecarboxylic acid and (+)-(1*R*,3*S*)-3-amino-2,2-dimethylcyclobutylmethanol, which can be used to prepare enantiopure oligopeptides and cyclobutane-based carbocyclic nucleosides, were synthesized from (+)-(1*R*)-α-pinene.


## 1. Introduction

Recent years have seen a great effort devoted to research on amino acids, in which the amino and carboxyl groups (or aminoalkyl and carboxyalkyl groups) are on small rings, such as cyclobutane[1] or cyclopentane.[2] Such molecules can be used to construct conformationally restricted peptides, and can therefore interact with a variety of biological molecules, notably GABA receptors.[3] Furthermore, the corresponding alcohols are embedded in carbocyclic nucleosides such as cyclobut A **1** and cyclobut G **2**, both of which exhibit a broad spectrum of antiviral activities.[4]




**1**




**2**

Although most reported syntheses of compounds of this type give racemic products, stereoselective syntheses such as Adlington et al.'s synthesis of the natural dipeptide antibiotic (1*S*,2*S*)-1-hydroxy-2-[(*S*)-valylamino]cyclobutane-1-acetic acid have begun to appear.[5] In particular, both cyclobut A and cyclobut G have been obtained in their enantiopure forms,[6] while the search for more efficient stereoselective syntheses of these or closely related compounds has resulted in the preparation of a number of enantiopure cyclobutane derivatives that can be used as starting materials. For example, cyclobutanes with two methyls instead of a hydroxymethyl at the 2-position have been prepared from (−)-(*S*)-verbenone and (+)-(1*R*)-nopinone.[7,8] Herein, we report the preparation, from (+)-(1*R*)-α-pinene **4**, of the enantiopure starting compounds **3** and **11**, of opposite configuration to those prepared previously.[7,8]

As a first step towards **3**, commercial enantiopure (+)-(1*R*)-α-pinene was transformed into (+)-pinonic acid **5** [(1*S*,3*S*)-3-acetyl-2,2-dimethylcyclobutylacetic acid] by oxidation with sodium periodate under the catalysis of ruthenium trichloride,[9] and compound **5** was then converted to amido acid **6a** by treatment with hydroxylamine-*O*-sulfonic acid and a Beckmann rearrangement[10] (Scheme 1). To remove the unwanted carbon from the carboxymethyl group, we planned to perform a classical Barbier–Wieland degradation, via methyl ester **6b**, diphenyl alcohol **7**, diphenylvinylcyclobutane derivative **9** and the oxidative cleavage of **9**–**10** (Scheme 1).

Methylation of **6a** in methanol containing *p*-toluenesulfonic acid was uneventful, but when **6b** was refluxed for 15 h with a large excess of phenyllithium in THF, the major product isolated was not **7** but a compound that, following recrystallization from methanol, was

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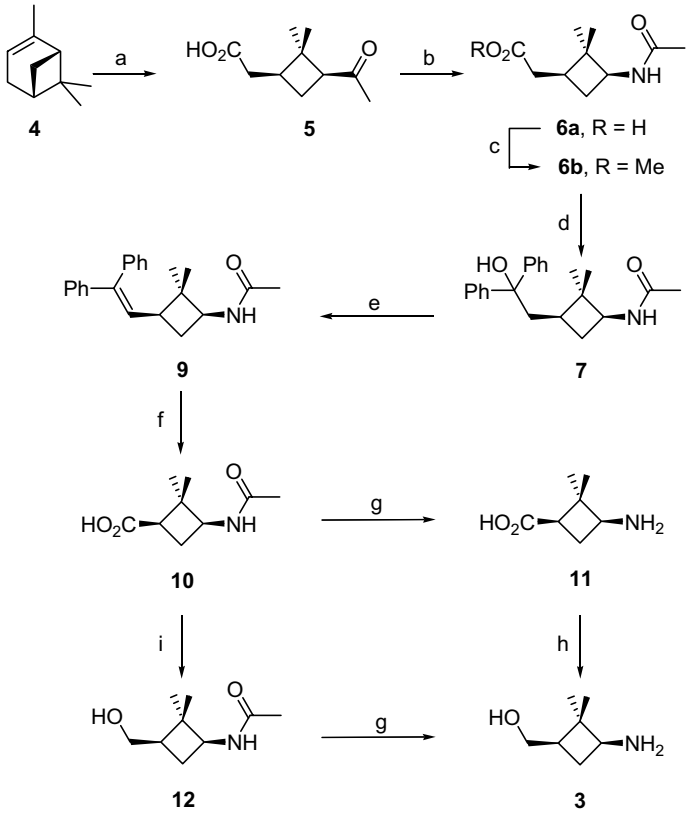


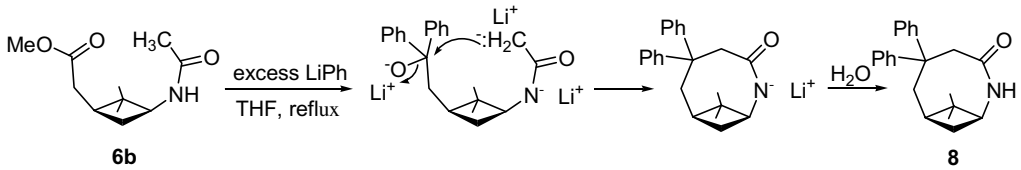

**Scheme 1.** Reagents and conditions: (a) $NaIO_4/RuCl_3$, $CCl_4$–MeCN–$H_2O$, rt; (b) $H_2NOSO_3H$, AcOH, reflux; (c) MeOH/*p*-TsOH, reflux; (d) LiPh, THF, rt; (e) *p*-TsOH, toluene, reflux; (f) oxidizing agent; (g) 2 M HCl, reflux; (h) $LiAlH_4$, THF, reflux; (i) 1, $ClCO_2Et/Et_3N$, THF, 0 °C; 2, $NaBH_4$/MeOH, 10 °C.

identified on the basis of $^1H$, $^{13}C$ and DEPT $^{13}C$ NMR spectra (notably, lack of the methyl group of the acetyl residue and appearance of an extra methylene group) and MS data as (1*S*,3*S*)-2-aza-5,5-diphenyl-8,8-dimethylbicyclo[5.1.1]nonan-3-one **8**. The unusual emergence of this product seems likely to have arisen, following the formation of the alkoxide corresponding to **7**, through the diphenyl carbon being attacked by the carbanion into which the acetyl group will have been transformed in the strongly basic medium (Scheme 2). When **6b** was reacted with phenyllithium at room temperature, compound **7** was, as expected, obtained in good yield (89%).

Unsaturation of **7** by refluxing with *p*-toluenesulfonic acid in toluene proceeded almost quantitatively. However, when oxidative cleavage of the resulting diphenylvinylcyclobutane derivative **9** was attempted by the classical procedure (using $KMnO_4$ in benzene/water in the presence of an aliquat as phase transfer catalyst),[11] only traces of the desired product were obtained. With the same oxidant, a 24% yield was obtained using *cis*-cyclohexyl-18-crown-6 ether as catalyst, with a small quantity of acetic acid acting as an accelerator and dichloromethane as solvent.[8] The best results were achieved with $NaIO_4$ as oxidant and ruthenium oxide as catalyst in a mixture of acetonitrile, carbon tetrachloride and water;[12] this afforded a maximum 44% yield of compound **10** after 1 h.

Refluxing **10** in concentrated hydrochloric acid gave the amino acid as its hydrochloride, while removing the HCl by passage through a basic ion exchange column afforded free amino acid, **11**, in 74% yield from **10**. Enantiomerically pure **11**, a conformationally restricted γ-amino acid, is of interest as a building block for the construction of oligopeptide mimics.[7]

Compound **3** was finally obtained from **11** by reducing the carboxyl group with $LiAlH_4$ in THF. The overall yield in obtaining **3** from **10** (path gh in Scheme 1) was 52%. A better overall yield (63% from **10**) was




**Scheme 2.** Suggested mechanism for the formation of unexpected compound **8**.

achieved by following path ig, which involves the one-pot treatment of **10** with ethyl chloroformate and then $NaBH_4$, to reduce the carboxyl group, followed by hydrolytic deacetylation of hydroxymethyl amide **12** (63% from **10**).

## 2. Conclusion

In conclusion, the previously unreported enantiopure compounds **11** and **3** have been prepared from (+)-(1*R*)-α-pinene. These products are potentially useful starting materials for the synthesis of enantiopure oligopeptides and cyclobutane-based carbocyclic nucleosides.

## 3. Experimental

All chemicals used were of reagent grade and were obtained from the Aldrich Chemical Co. and used without further purification. Mps were measured in a Reichert Kofler Thermopan and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 1640 FTIR spectrophotometer. $^1H$ and $^{13}C$ NMR spectra were recorded in a Bruker AMX-300 spectrometer at 300 and 75 MHz, respectively, using TMS as the internal standard (chemical shifts in $\delta$ values, $J$ in Hz). Microanalysis was performed in a Perkin–Elmer 240B Elemental Analyser at the University of Santiago Microanalysis service. Analyses indicated by the symbols of elements were within ±0.4% of the theoretical values. Flash chromatography was performed on silica gel (Merck 60, 230–240 mesh) and analytical TCL on pre-coated silica gel plates (Merck 60, $F_{254}$, 0.25 mm). EIMS and HRMS spectra were determined on a HP 5988A apparatus and on a Micromass Autospec apparatus, respectively.

### 3.1. (1*S*,3*S*)-(3-Acetyl-2,2-dimethylcyclobutyl)-acetic acid 5

(+)-1*R*-α-Pinene was oxidized to **5** by the method used by Moglioni et al.[9] for its enantiomer. Mp 68–69 °C (hexane), $[\alpha]_D^{25} = +79.5$ (*c* 0.8, $CHCl_3$). {lit. for the enantiomer: mp 65–68 °C (ether), $[\alpha]_D^{25} = -77.8$ (*c* 2.03, MeOH);[9] mp 68–69 °C, $[\alpha]_D^{25} = -77.5$ (*c* 5.0, $CHCl_3$)}.[13] $^1H$ and $^{13}C$ NMR data in agreement with those reported for the enantiomer.[13]

### 3.2. (1*S*,3*S*)-(3-Acetamido-2,2-dimethylcyclobutyl)-acetic acid 6a

The procedure used was the same as described for its enantiomer.[10] Mp 133–134 °C, $[\alpha]_D^{25} = -112.6$ (*c* 1.05, EtOH); [lit. for the enantiomer: $[\alpha]_D^{25} = +111.3$ (*c* 1.0, EtOH)].[10] $^1H$ and $^{13}C$ NMR data in agreement with those reported for the enantiomer.[10]

### 3.3. (1*S*,3*S*)-Methyl (3-acetamido-2,2-dimethylcyclobutyl)acetate 6b

$[\alpha]_D^{25} = -109.3$ (*c* 1.1, EtOH), {lit. for the enantiomer: $[\alpha]_D^{25} = +110.4$ (*c* 1.0, EtOH)}.[10] $^1H$ and $^{13}C$ NMR data in agreement with those reported for the enantiomer.[10]

### 3.4. (1*S*,3*S*)-*N*-[3-(2,2-Diphenyl-2-hydroxyethyl) 2,2-dimethylcyclobutyl]acetamide 7

PhLi (52 mL, 93.6 mmol) was slowly added to a solution of amido ester **6b** (5.0 g, 23.5 mmol) in dry THF (100 mL) and the mixture stirred overnight at room temperature. Water-saturated ether was added, followed by water and the resulting white precipitate filtered out. After removal of the organic solvent, the filtrate was extracted with EtOAc, and this organic phase washed with brine, dried and concentrated under reduced pressure. Chromatography of the resulting oil on a silica gel column with 2:1 EtOAc/$CH_2Cl_2$ as eluent afforded a white solid (7.03 g, yield 89%), an analytical sample of which was obtained by recrystallization from toluene. Mp 140–142 °C. $[\alpha]_D^{25} = -31.4$ (*c* 1.06, $CH_2Cl_2$). IR (*v*): 3321, 2956, 1625, 1539, 1054, 749, 609 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$: 0.92 (3H, s, $CH_3$), 1.04 (3H, s, $CH_3$), 1.20 (1H, q, $J = 10.0$, 4-*H*H), 1.76–1.98 (3H, m, 4-H*H* + 3′-H + $D_2O$ exch., OH), 1.91 (3H, s, $COCH_3$), 2.16 (1H, dd, $J = 13.9$, 9.2, C*H*H), 2,42 (1H, dd, $J = 13.9$, 3.4, CH*H*), 3.86 (1H, dd, $J = 9.8$, 7.6, 1′-H), 5.28 (1H, d, $J = 6.8$, $D_2O$ exch., NH), 7.18–7.41 (10H, m, 2 × Ph). $^{13}C$ NMR ($CDCl_3$) $\delta$: 16.72 ($CH_3$), 23.60 ($CH_3$), 28.52 ($CH_3$), 33.81 ($CH_2$), 35.05 (CH), 42.53 ($CH_2$), 44.52 (C), 51.21 (CH), 126.35 (CH), 126.45 (CH), 127.18 (CH), 127.44 (CH), 128.45 (CH), 128.65 (CH), 147.33 (C), 147.66 (C), 169.95 (CO). EIMS, *m*/*z* (%): 184 (14), 183 (100), 105 (68), 86 (15), 77 (32). Calcd for $C_{22}H_{27}NO_2$ (337.5): C, 78.30; H, 8.06; N, 4.15. Found: C, 78.02; H, 7.89; N, 4.33.

### 3.5. (1*S*,7*S*)-2-Aza-5,5-diphenyl-8,8-dimethylbicyclo-[5.1.1]nonan-3-one 8

PhLi (10.6 mL, 19.6 mmol) was slowly added to a solution of amido ester **6b** (1.05 g, 4.9 mmol) in dry THF (20 mL) and the mixture refluxed for 15 h. Work-up as for compound **7** gave an oil that when chromatographed on a silica gel column using 2:1 EtOAc/$CH_2Cl_2$ as eluent afforded a white solid (0.90 g, yield 58%) that was recrystallized from methanol. Mp 133–134 °C. $[\alpha]_D^{25} = -77.3$ (*c* 1.0, MeOH). $^1H$ NMR (DMSO-$d_6$) $\delta$: 0.84 (3H, s, 8-$CH_3$), 0.88 (3H, s, 8-$CH_3$), 1.42 (1H, q, $J = 10.5$, 9-*H*H), 1.58 (1H, dt, $J = 10.7$, 7.7, 9-H*H*), 1.66–1.76 (1H, m, 7-H), 2.16 and 2.33 (2H, AB part of an ABX system, $J_{AB} = 13.8$, $J_{AX} = 9.0$, $J_{BX} = 3.2$, 6-*HH*), 3.62 (1H, dt, $J = 9.6$, 8.2, 1-H), 3.71 and 3.75 (2H, AB system, $J_{AB} = 15.8$, 4-*HH*), 5.34 (1H, br s, $D_2O$ exch., NH), 7.12 (1H, t, $J = 7.3$, *para*-Ph), 7.14 (1H, t, $J = 7.3$, *para*-Ph′), 7.23 (2H, t, $J = 7.7$, *meta*-Ph), 7.26 (2H, t, $J = 7.7$, *meta*-Ph′), 7.41 (4H, t, $J = 7.1$, *ortho*-(Ph + Ph′)). $^{13}C$ NMR (DMSO-$d_6$) $\delta$: 16.54 ($CH_3$), 28.74 ($CH_3$), 32.48 ($CH_2$), 34.77 (CH), 41.70 ($CH_2$), 44.04 (C), 50.31 (CH), 61.58 ($CH_2$), 76.58 (C), 126.22 and 126.30 (CH), 126.42 (CH), 127.88 and 128.07 (CH), 148.77 and 149.15 (C), 171.57 (CO). EIMS, *m*/*z* (%): 319 ($M^+$, 0.1), 293 (2), 284 (1), 184 (14), 183 (100), 149 (15), 105 (52), 77 (20). HRMS: Calcd for $C_{22}H_{25}NO$, 319.1936. Found: 319.1942.

### 3.6. (1*S*,3*S*)-*N*-[3-(2,2-Diphenylethenyl)-2,2-dimethylcyclobutyl]acetamide 9

A solution of alcohol **7** (7.06 g, 21 mmol) and *p*-toluenesulfonic acid (1.0 mg) in toluene (75 mL) was refluxed for 16 h in a flask with a Dean–Stark trap, cooled to room temperature and extracted several times with toluene. The organic extract was dried over $Na_2SO_4$ and concentrated with chromatography of the residue with 1:3 EtOAc/$CH_2Cl_2$ as eluent to afford **9** as a white solid (6.50 g, yield 98%), an analytical sample of which was obtained by recrystallization from cyclohexane. Mp 125–126 °C. $[\alpha]_D^{25} = -38.7$ (*c* 1.01, $CH_2Cl_2$). IR (*v*): 3298, 2955, 1647, 1559, 1490, 1458, 1443, 1367, 764, 702 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$: 1.03 (3H, s, $CH_3$), 1,04 (3H, s, $CH_3$), 1.65 (1H, q, $J = 10.3$, 4-*H*H), 1.96 (3H, s, $COCH_3$), 2.31 (1H, dt, $J = 10.8$, 7.8, 4-H*H*), 2.49 (1H, dt, $J = 9.9$, 7.8, 3-H), 3.94 (1H, dd, $J = 9.8$, 8.0, 1-H), 5.43 (1H, d, $J = 7.2$, $D_2O$ exch., NH), 5.98 (1H, d, $J = 9.7$, CH=), 7.11–7.39 (10H, m, $2 \times$ Ph). $^{13}C$ NMR ($CDCl_3$) $\delta$: 17.66 ($CH_3$), 23.65 ($CH_3$), 28.85 ($CH_3$), 33.31 ($CH_2$), 39.39 (CH), 46.67 (C), 50.44 (CH), 127.48 (CH), 127.56 (CH), 127.66 (CH), 128.51 (CH), 129.38 (CH), 130.39 (CH), 140.34 (C), 142.98 (C), 143.74 (C), 170.11 (CO). EIMS, *m*/*z* (%): 319 (11), 234 (18), 219 (49), 206 (100), 205 (34), 204 (22), 203 (16), 202 (11), 191 (32), 165 (16), 128 (22), 91 (41). Calcd for $C_{22}H_{25}NO$ (319.4): C, 82.72; H, 7.89; N, 4.38. Found: C, 82.75; H, 7.81; N, 4.20.

### 3.7. (1*R*,3*S*)-3-Acetamido-2,2-dimethylcyclobutanecarboxylic acid 10

A solution of $NaIO_4$ (2.0 g, 9.5 mmol) in water (29 mL) was added to a solution of **9** (1.0 g, 3.13 mmol) in 1:1 MeCN/$CCl_4$ (24 mL), and the mixture was stirred at room temperature for a few minutes. $RuO_2 \cdot H_2O$ (10.42 mg, 0.069 mmol) was added, and stirring continued until TLC monitoring showed a complete reaction (1 h). Water was added, the aqueous phase extracted with EtOAc and the pooled organic phases vacuum-filtered through Celite. The filtrate was washed with $Na_2CO_3$ solution and the aqueous phase acidified with 6 M HCl and extracted repeatedly with EtOAc. Concentration of the pooled organic extract to dryness afforded **10** (0.25 g, yield 44%), an analytical sample of which was obtained by recrystallization from toluene/ethanol. Mp 221–223 °C. $[\alpha]_D^{25} = -195.35$ (*c* 1.02, MeOH), (its enantiomer is described as an oil, $[\alpha]_D^{25} = +38.3$ (*c* 2.14, MeOH) or solid, mp 226–228 °C, $[\alpha]_D^{25} = +198.3$ (*c* 0.54, MeOH)).[8] IR (*v*): 3347, 2962, 1697, 1623, 1557, 1376, 1335, 1254, 1220, 736 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$) $\delta$: 0.80 (3H, s, $CH_3$), 1.16 (3H, s, $CH_3$), 1.79 (3H, s, $COCH_3$), 1.92–2.08 (2H, m, 4-$H_2$), 2.46–2.54 (1H, m, 1-H), 3.86 (1H, q, $J = 8.1$; it turns into a triplet ($J = 8.1$), after $D_2O$ exchange, 3-H), 7.82 (1H, d, $J = 7.8$, $D_2O$ exch., NH), 12.03 (1H, br s, $D_2O$ exch., $CO_2H$). $^{13}C$ RMN (DMSO-$d_6$) $\delta$: 17.15 ($CH_3$), 22.72 ($CH_3$), 25.00 ($CH_2$), 29.25 ($CH_3$), 42.56 (CH), 45.98 (C), 49.38 (CH), 168.00 (CO), 173.87 (CO). EIMS: *m*/*z* (%): 185 ($M^+$, 0.2), 183 (3), 129 (3), 128 (4), 113 (16), 100 (26), 87 (2), 86 (9), 85 (100), 83 (11), 71 (37), 56 (22). Calcd for $C_9H_{15}NO_3$ (185.2): C, 58.36; H, 8.16; N, 7.56. Found: C, 58.09; H, 8.33; N, 7.26.

### 3.8. (1*R*,3*S*)-3-Amino-2,2-dimethylcyclobutanecarboxylic acid 11

A solution of **10** (0.3 g, 1.62 mmol) in 2 M HCl (20 mL) was refluxed for 36 h. Evaporation of the solvent left a residue that was dissolved in water and passed through a column of Dowex 50W, eluting first with water (to neutrality) and then with 1 M $NH_3$ solution (250 mL). Removal of the solvent from the fraction eluted with aqueous $NH_3$ left **11** as a yellow solid (0.17 g, yield 74%), an analytical sample of which was obtained by recrystallization from AcOEt. Mp 255–257 °C. $[\alpha]_D^{25} = -21.5$ (*c* 0.57, MeOH). [No lit. value for its enantiomer was found]. IR (*v*): 3439, 2963, 1635, 1569, 1508, 1415, 1026, 785 $cm^{-1}$. $^1H$ NMR ($D_2O$), $\delta$: 0.90 (3H, s, $CH_3$), 1.10 (3H, s, $CH_3$), 1.96 (1H, dt, $J = 11.6$, 9.5, 4-*H*H), 2.16 (1H, dt, $J = 11.6$, 7.8, 4-H*H*), 2.44 (1H, dd, $J = 9.8$, 7.7, 1-H), 3.26 (1H, t, $J = 8.4$, 3-H). $^{13}C$ NMR ($D_2O$), $\delta$: 16.47 ($CH_3$), 25.74 ($CH_3$), 27.92 ($CH_2$), 42.80 (CH), 46.21 (C), 51.10 (CH), 180.42 (CO). Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.50; H, 9.00; N, 9.99.

### 3.9. (1*S*,3*R*)-*N*-(3-Hydroxymethyl-2,2-dimethylcyclobutyl)acetamide 12

Ethyl chloroformate (0.20 mL) was added dropwise (with temperature monitoring to ensure that the temperature did not exceed −5 °C) to a solution of **10** (0.38 g, 2.05 mmol) and $Et_3N$ (0.28 mL) in dry THF (4 mL) in a salted ice bath. The mixture was stirred for 30 min at this temperature, and the solid formed filtered out and washed with dry THF ($4 \times 5$ mL). The pooled washings and filtrate were placed in an ice bath at 10 °C and treated with a single portion of $NaBH_4$ (0.26 g, 6.8 mmol) followed by 1.22 mL of dry methanol (added dropwise with monitoring to ensure that the temperature did not exceed 10 °C). After 30 min stirring at this temperature, the reaction mixture was treated with water (16 mL) followed by 2 M HCl (3 mL), with stirring in both cases. The THF was removed under reduced pressure, the aqueous phase extracted several times with EtOAc, and the pooled organic extract was dried and concentrated to dryness under reduced pressure. Chromatography of the residue on silica gel with 9:1 $CH_2Cl_2$/MeOH as eluent afforded **12** (0.25 g, yield 73%), an analytical sample of which was obtained by recrystallization from EtOAc. Mp 138–140 °C. $[\alpha]_D^{25} = -97.4$ (*c* 0.51, MeOH), {lit.[8] $[\alpha]_D^{25} = +99.3$ (*c* 0.30, MeOH) for its enantiomer}. IR (*v*): 3274, 2956, 1652, 1557, 1540, 1373, 1020 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$: 0.97 (3H, s, $CH_3$), 1.21 (3H, s, $CH_3$), 1.39 (1H, q, $J = 10.2$, 4-*H*H), 1.89–1.99 (1H, m, 4-H*H*), 1.96 (3H, s, $COCH_3$), 2.30 (1H, dt, $J = 11.0$, 7.9, 3-H), 3.59 and 3.62 (2H, AB part of an ABX system, $J_{AB} = 10.9$, $J_{AX} = 6.4$, $J_{BX} = 7.6$, C$H_2$OH), 4.04 (1H, q, $J = 8.6$, 1-H), 5.50 (1H, br s, $D_2O$ exch., NH). $^{13}C$ NMR ($CDCl_3$) $\delta$: 16.40 ($CH_3$), 23.72 ($CH_3$), 28.75 ($CH_2$), 30.02 ($CH_3$), 41.49 (CH), 43.56 (C), 50.32 (CH), 63.86 ($CH_2$), 171.00 (CO). Calcd for $C_9H_{17}NO_2$

(171.2): C, 63.13; H, 10.01; N, 8.18. Found: C, 63.34; H, 9.82; N, 7.98.

### 3.10. (1*R*,3*S*)-3-Amino-2,2-dimethylcyclobutylmethanol 3

Compound **11** (0.12 g, 0.84 mmol) was added in two portions, under argon, to a suspension of $LiAlH_4$ (0.11 g, 2.89 mmol) in dry THF (3 mL) in an ice bath, and the suspension refluxed for 5 h with stirring and then allowed to cool to room temperature. Water was added, and after stirring for a further 30 min, the mixture was extracted with EtOAc and the pooled organic extract dried over $Na_2SO_4$ and concentrated under reduced pressure. Chromatography of the resulting orange oil on silica gel with 1:1 $CH_2Cl_2$/MeOH as eluent afforded a white solid (75 mg, yield 70%), an analytical sample of which was obtained by sublimation. Mp 74–76 °C. $[\alpha]_D^{25} = +20.6$ (*c* 1.05, MeOH) {its enantiomer is described as a solid, mp 73–75 °C, $[\alpha]_D^{25} = -19.1$ (*c* 0.82, MeOH)}.[8] IR (*v*): 3357, 2930, 1560, 1510, 1418, 760 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$) $\delta$: 1.00 (3H, s, $CH_3$), 1.17 (3H, s, $CH_3$), 1.31 (1H, q, $J = 10.3$, 4-*H*H), 1.41 (1H, br s, $D_2O$ exch., OH), 2.15–2.25 (1H, m, 4-H*H*), 2.22 (1H, dt, $J = 9.7$, 7.7, 1-H), 2.85 (1H, t, $J = 8.2$, 3-H), 3.49 and 3.52 (2H, AB part of an ABX system, $J_{AB} = 10.6$, $J_{AX} = 6.7$, $J_{BX} = 8.2$, thus observed after treating the sample with $D_2O$, C*H*$_2$O). $^{13}C$ NMR (DMSO-$d_6$) $\delta$: 15.27 ($CH_3$), 29.54 ($CH_3$), 31.71 ($CH_2$), 41.05 (CH), 42.30 (C), 54.09 (CH), 62.02 ($CH_2$). EIMS, *m*/*z* (%): 86 (3), 85 (2), 84 (66), 71 (2), 68 (5), 66 (100), 61 (2), 58 (5), 52 (1). Calcd for $C_7H_{15}NO$ (129.2): C, 65.07; H, 11.70; N, 10.84. Found: C, 64.86; H, 11.41; N, 10.52.

### 3.11. Preparation of compound 3 from 12

A mixture of **12** (0.2 g, 1.16 mmol) and 2 M HCl (7 mL) was refluxed for 17 h, the solvent evaporated under reduced pressure and the residual oil dissolved in MeOH and passed through a basic ion exchange resin. The solvent was then removed under reduced pressure, leaving **3** as an oil (0.12 g, yield 86%) that solidified on standing under reduced pressure.

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