Organic & Biomolecular Chemistry

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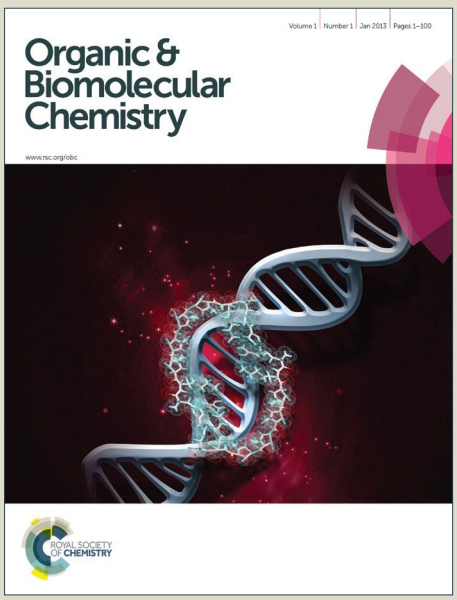

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ARTICLE

Synthesis of substituted tetrahydroisoquinolines by lithiation then electrophilic quench

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Substituted *N*-*tert*-butoxycarbonyl (Boc)-1,2,3,4-tetrahydroisoquinolines were prepared and treated with *n*-butyllithium in THF at –50 °C to test the scope of the metallation and electrophilic quench. The lithiation was optimised by using in situ ReactIR spectroscopy and the rate of rotation of the carbamate was determined. The 1-lithiated intermediates could be trapped with a variety of electrophiles to give good yields of 1-substituted tetrahydroisoquinoline products. Treatment with acid or reduction with $LiAlH_4$ allows conversion to the *N*–H or *N*–Me compound. The chemistry was applied to the efficient total syntheses of the alkaloids (±)-crispine A and (±)-dysoxyline.

Introduction

The tetrahydroisoquinoline ring structure is present in a large number of natural and biologically active products. Derivatives with a substituent in the 1-position are particularly common and are typically prepared by Pictet–Spengler or Bischler–Napieralksi reactions.[1] Other methods include addition to iminium ions or reduction of isoquinoline rings.[2] An alternative approach to such compounds makes use of the ability to deprotonate at the 1-position of the tetrahydroisoquinoline ring. This method has potential to provide access to a large range of differently substituted derivatives. Various *N*-substituents on the tetrahydroisoquinoline can be used to aid the metallation.[3] We have reported that an efficient and relatively mild method is to use the *N*-Boc derivative with deprotonation by using *n*-BuLi.[4,5] However we have so far reported only a few examples with the parent compound *N*-Boc-tetrahydroisoquinoline **1** and with the 6,7-dimethoxy derivative **2** (Fig. 1).[4] Here we demonstrate that the chemistry is amenable to other substituted tetrahydroisoquinolines and to a variety of different electrophiles, leading to its application to the syntheses of the alkaloids (±)-crispine A and (±)-dysoxyline.

In our earlier work we showed that the Boc group in *N*-Boc-tetrahydroisoquinoline rotates slowly at –78 °C.[4] As the lithiation at the 1-position is directed by complexation of the base (*n*-butyllithium) with the carbonyl of the Boc group,[6] better yields can be obtained at –50 °C since the Boc rotation is faster. We wanted to test whether the same phenomenon also occurs with other derivatives and whether the lithiation–substitution chemistry is amenable to different substituted tetrahydroisoquinolines. The lithiations of a selection of *N*-Boc-tetrahydroisoquinoline compounds (**2**–**5**) and applications of this chemistry to the preparation of some natural products are described in this article.

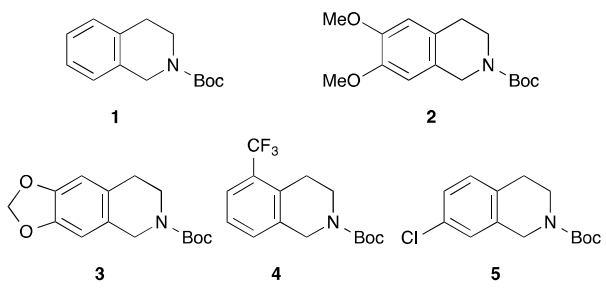

Fig. 1 Structures of some *N*-Boc-tetrahydroisoquinolines.

Results and discussion

We selected to prepare the tetrahydroisoquinolines **2**–**5** (Fig. 1). These compounds provide a range of electron-donating (alkoxy) and electron-withdrawing (chloro and trifluoromethyl) groups on the tetrahydroisoquinolines used for the lithiation chemistry. For syntheses of compounds **2**–**5**, see the Supplementary Information.

The lithiation of tetrahydroisoquinoline **3** was monitored by *in situ* ReactIR spectroscopy. With 1.2 equivalents of *n*-BuLi in THF at –78 °C the lithiation was slow. However, by conducting the reaction at –50 °C a rapid lithiation took place (Figure 2). This result indicates that the rotation of the Boc group is slow at –78 °C, but fast at –50 °C, in line with previous work.[4,7] The *n*-BuLi coordinates to the carbonyl oxygen atom of the Boc group (sometimes referred to as a 'complex induced proximity effect'),[6] so for benzylic lithiation to occur in high yield the Boc group must rotate under the conditions of the reaction.

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†Electronic Supplementary Information (ESI) available: Preparation of **2**–**5**, ReactIR and NMR spectra. See DOI: 10.1039/x0xx00000x

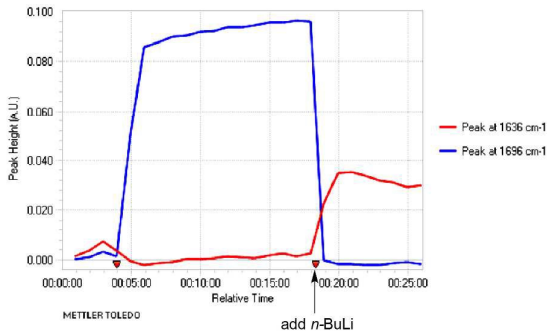
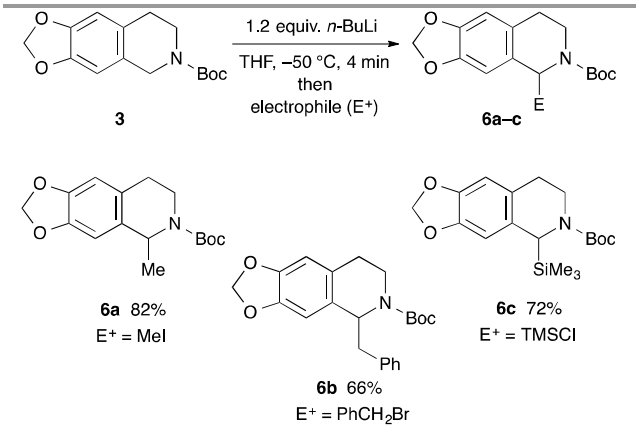


Fig. 2 *In situ* IR plot of the lithiation of **3** with *n*-BuLi in THF at –50 °C with time in h:min:sec. $\nu_{C=O}$ **3** 1696 cm^{-1}, *n*-BuLi added at time 18 min, $\nu_{C=O}$ lithiated **3** 1636 cm^{-1}.



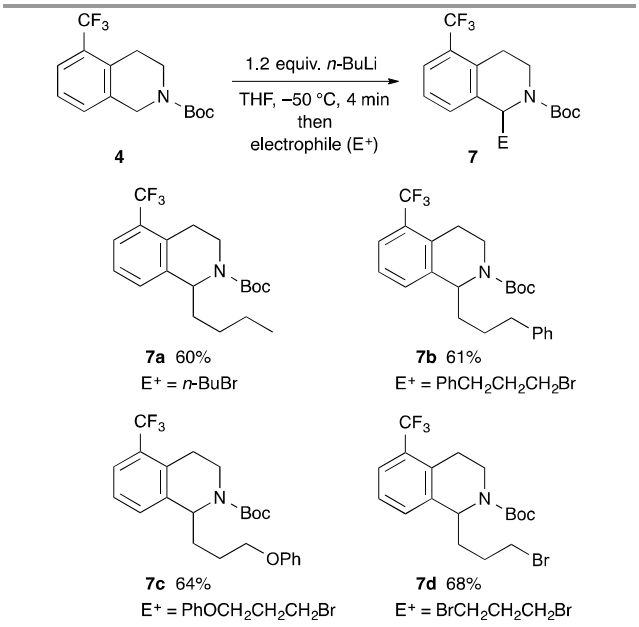
Scheme 1 Lithiation–substitution of the tetrahydroisoquinoline **3**.

By using the optimised lithiation conditions (THF, –50 °C, 4 min), followed by electrophilic quench and purification by column chromatography, the substituted products **6a–c** were obtained with reasonable to good yields (Scheme 1). Lithiation occurs only in the benzylic position, as judged by ^{1}H NMR spectroscopy. We did not observe any other substitution products.

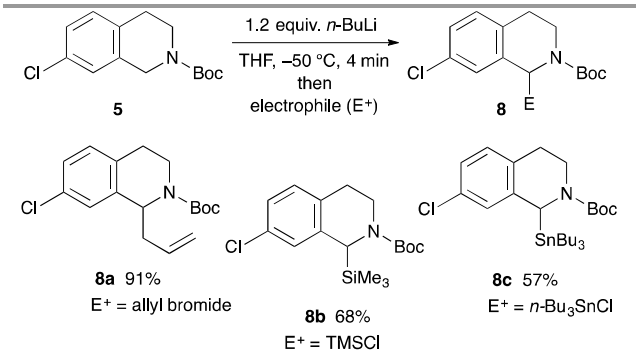
To expand the range of substrates beyond the parent or electron-rich tetrahydroisoquinolines (compounds **1–3**), we prepared the tetrahydroisoquinolines **4** and **5** (see the Supplementary Information). We found that these compounds behaved in a similar way and lithiation could be achieved at –50 °C over the course of only a few minutes. Some examples of the substitution products that were obtained in this chemistry are shown in Schemes 2 and 3. The chemistry was successful for a variety of electrophiles including alkyl and allyl bromides, and trialkyltin or silyl chlorides. After column chromatography reasonable to good yields of the 1-substituted products **7a–d** and **8a–c** were obtained. The lithiation–substitution was selective for the 1-position, indicating that the Boc group is a better directing group for lithiation than CF_3 or chlorine.

As mentioned above, in the lithiation step the *n*-BuLi coordinates to the carbonyl oxygen atom,[6] so the rate of lithiation will depend on the rate of rotation of the Boc group. We had previously determined an approximate value for the barrier to rotation, $\Delta G^{\ddagger} \approx 60.8$ kJmol^{-1} at 5.5 °C of the parent compound **1**.[4] We therefore decided to determine the kinetics for rotation of the Boc group for the tetrahydroisoquinoline **4** for comparison. Variable temperature NMR spectroscopy in D_8-THF was carried out and coalescence of the benzylic CH_2 signals occurred at about 5 °C (for selected spectra, see Fig. 3). Line shape analysis (see SI) revealed activation parameters $\Delta H^{\ddagger} \approx 81$ kJmol^{-1} and $\Delta S^{\ddagger} \approx 77$ JK^{-1}mol^{-1}. These values lead to a similar overall barrier to rotation ($\Delta G^{\ddagger} \approx 60$ kJmol^{-1} at 5 °C) for the Boc group in both compounds **4** and **1**. From this we can determine, for rotation of the Boc group in **4**, the half-life $t_{1/2} \approx$ 2 min at –50 °C. Therefore the lithiation requires only a few minutes at this temperature for complete reaction.

By using 1.2 equivalents of the electrophile 1,3-dibromopropane, the 1-substituted product **7d** was formed without any appreciable formation of the product from double electrophilic substitution. The product **7d** was treated with trifluoroacetic acid (TFA) (Scheme 4). This resulted in the removal of the Boc group and concomitant cyclization to give the product **9** in high yield.



Scheme 2 Lithiation–substitution of the tetrahydroisoquinoline **4**.



Scheme 3 Lithiation–substitution of the tetrahydroisoquinoline **5**.

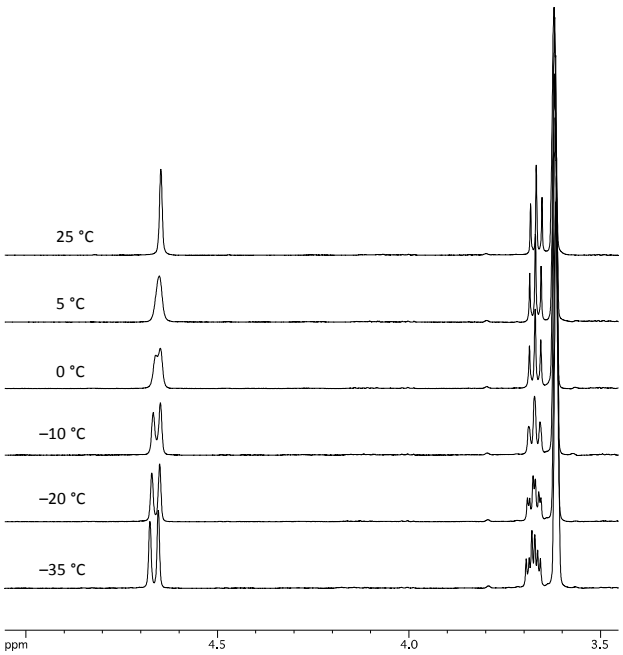
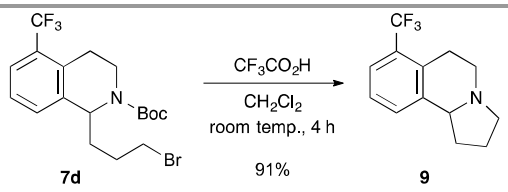
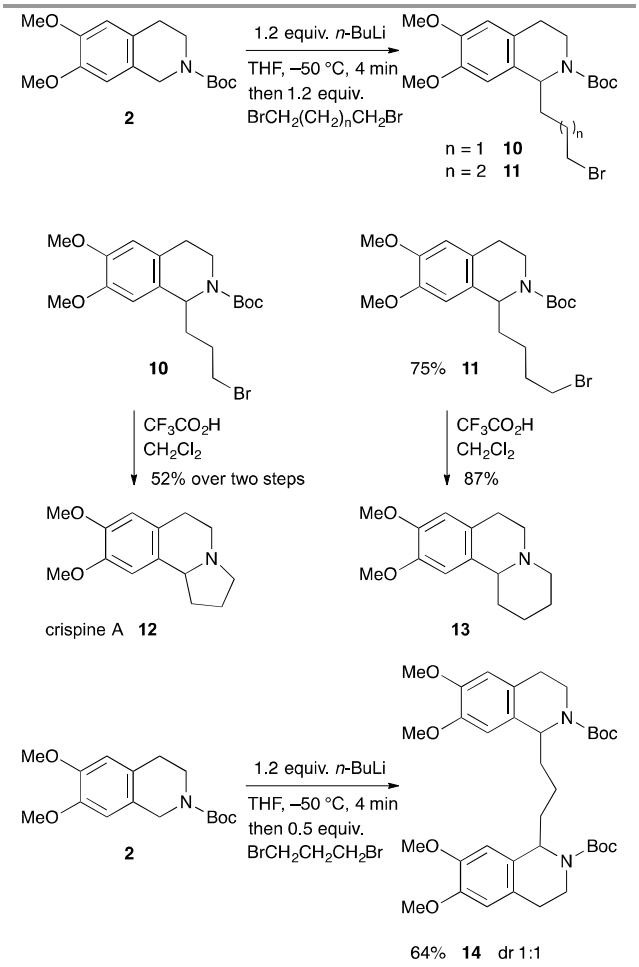


Fig. 3 Variable temperature NMR spectroscopy of tetrahydroisoquinoline **4** in D_8-THF showing selected spectra only the region from 5.00–3.50 ppm.



Scheme 4 Removal of Boc group from the tetrahydroisoquinoline **7d**.

We were interested to test dibromoalkane electrophiles further and selected to use the tetrahydroisoquinoline substrate **2** for this work. Lithiation of compound **2** with *n*-BuLi in THF at –50 °C for 4 min followed by addition of more than one equivalent of 1,3-dibromopropane or 1,4-dibromobutane gave the expected 1-substituted products **10** and **11** (Scheme 5). By using 0.5 equivalents of 1,3-dibromopropane we were able to prepare the 1,1'-disubstituted product **14** as a separable mixture of diastereoisomers. Related bis-tetrahydroisoquinolinium salts have recently been found to be high affinity ligands for SK channels.[8]

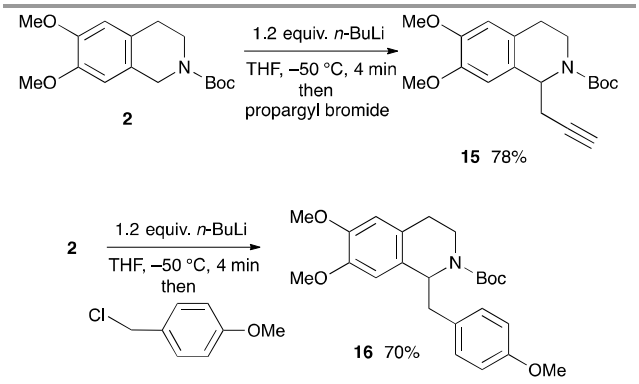


Scheme 5 Use of dibromoalkane electrophiles and synthesis of (±)-crispine A.

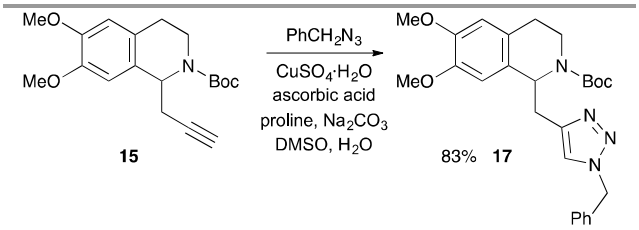
Treatment of the crude product **10** with trifluoroacetic acid gave the natural product (±)-crispine A, **12**, in 52% yield over the two steps. This chemistry therefore provides a short and efficient synthesis of this compound (just three steps from commercial 6,7-dimethoxytetrahydroisoquinoline).[9] In the same way as the formation of crispine A, hydrolysis of the Boc group from compound **11** was carried out to provide the homologous product **13** in high yield (Scheme 5).[10]

To expand the range of electrophiles that have been shown to be successful in these alkylation reactions, we treated the tetrahydroisoquinoline **2** with *n*-BuLi in THF at –50 °C for 4 min followed by addition of propargyl bromide or 4-methoxybenzyl chloride (Scheme 6). The products **15** and **16** were isolated with good yields.

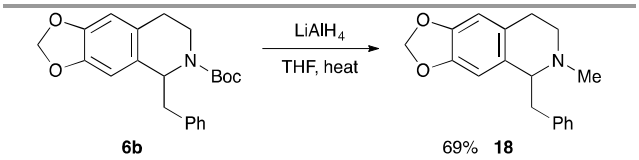
We have demonstrated that the Boc group can be removed from several of these products (**7d**, **10**, **11**) by using TFA. Other transformations of the substituted products are possible. For example, treating the product **15** with benzyl azide and a copper catalyst gave the expected triazole **17** (Scheme 7).[11] Reduction of the Boc group in the tetrahydroisoquinoline **6b** with $LiAlH_4$ gave the *N*-methyl derivative **18** (Scheme 8).



Scheme 6 Lithiation–substitution of the tetrahydroisoquinoline **2**.

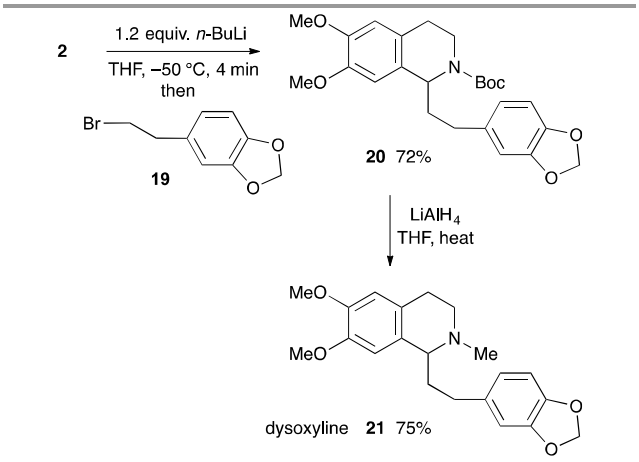


Scheme 7 Further transformation of the product **16**.



Scheme 8 Reduction of the tetrahydroisoquinoline **6b**.

Finally, we prepared the natural product (±)-dysoxyline using this chemistry.[12] The tetrahydroisoquinoline **2** was deprotonated under the standard conditions and then treated with the bromide **19** (Scheme 9). We were pleased that this gave a good yield of the 1-substituted product **20** despite the potential for β-elimination. Reduction of this product with $LiAlH_4$ gave (±)-dysoxyline **21**. Hence this chemistry allows an efficient way to prepare simple tetrahydroisoquinoline alkaloids.



Scheme 9 Synthesis of (±)-dysoxyline.

Conclusions

We have found that the lithiation of *N*-Boc-tetrahydroisoquinolines can be extended to a selection of different substituted derivatives by using the conditions found previously for the parent compound (**1**) and this requires only a few minutes at –50 °C with *n*-butyllithium. The intermediate organolithium can be trapped with a wide selection of different electrophiles to give good yields of a variety of 1-substituted tetrahydroisoquinoline products. The chemistry was applied to the short syntheses of the alkaloids crispine A and dysoxyline.

Acknowledgements

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Experimental

***tert*-Butyl 7,8-Dihydro-5-Methyl-[1,3]dioxolo[4,5-g]isoquinoline-6(5H)-carboxylate 6a**

n-BuLi (0.17 mL, 0.43 mmol, 2.5 M in hexane) was added to tetrahydroisoquinoline **3** (100 mg, 0.36 mmol) in THF (1.5 mL) at –50 °C. After 4 min, iodomethane (0.08 mL, 1.26 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (92:8), to give the carbamate **6a** (85 mg, 82%) as plates; m.p. 81-82 °C; R_f 0.39 [petrol–EtOAc (90:10)]; ν_{max} (neat)/cm^{-1} 2970, 2875, 1670, 1485; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 6.58–6.57 (2H, m, 2 x CH), 5.80 (2H, s, CH_2), 5.18–4.96 (1H, br m, CH), 4.27–3.91 (1H, br m, CH), 3.67–2.60 (3H, br m, 3 x CH), 1.50 (9H, s, *t*-Bu), 1.40 (3H, d, *J* 7, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 154.9 & 154.4, 146.1, 146.0, 127.3, 127.1, 108.4, 106.7, 100.7, 79.6, 50.5 & 49.8, 38.0 & 36.6, 29.6, 29.0 & 28.0, 22.0; HRMS (ES) Found: MNa^+, 314.1360. $C_{16}H_{22}NO_4Na$ requires MNa^+, 314.1368; LRMS *m/z* (ES) 314 (100%).

***tert*-Butyl 5-Benzyl-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline-6(5H)-carboxylate 6b**

n-BuLi (0.17 mL, 0.43 mmol, 2.5 M in hexane) was added to tetrahydroisoquinoline **3** (100 mg, 0.36 mmol) in THF (1.5 mL) at –50 °C. After 4 min, benzyl bromide (0.15 mL, 1.26 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (93:7), to give the carbamate **6b** (87 mg, 66%) as an oil;

R_f 0.41 [petrol–EtOAc (90:10)]; ν_{max} (neat)/cm^{-1} 2975, 2925, 1680, 1485; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36–7.20 (3H, m, 3 x CH), 7.15–7.04 (2H, m, 2 x CH), 6.61–6.54 (2H, m, 2 x CH), 5.94–5.90 (2H, m, CH_2), 5.27 (0.35H, t, *J* 7, CH), 5.13–5.10 (0.65H, m, CH), 4.20–4.12 (0.65H, m, CH), 3.81–3.72 (0.35H, m, CH), 3.34–3.23 (1H, m, CH), 3.06–2.95 (2H, m, CH), 2.91-2.81 (0.65H, m, CH), 2.74–2.67 (0.35H, m, CH), 2.63–2.57 (0.65H, m, CH), 2.52–2.46 (0.35H, m, CH), 1.26 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ= 154.5 & 154.3, 146.3 & 146.1, 145.8 & 145.7, 138.5 & 138.1, 130.1 & 130.0, 129.7 & 129.6, 129.0 & 128.8, 128.3, 128.1, 127.8 & 127.7, 126.4 & 126.2, 108.6 & 108.2, 107.6 & 107.2, 100.8 & 100.7, 79.6 & 79.4, 56.8 & 55.7, 43.0 & 42.7, 39.3 & 37.0, 29.7 & 28.6, 28.5 & 28.4; HRMS (ES) Found: MNa^+, 390.1674. $C_{22}H_{26}NO_4Na$ requires MNa^+ 390.1618, LRMS *m/z* (ES) 390 (100%).

***tert*-Butyl 7,8-Dihydro-5-(trimethylsilyl)-[1,3]dioxolo[4,5-g]isoquinoline-6(5H)-carboxylate 6c**

n-BuLi (0.17 mL, 0.43 mmol, 2.5 M in hexane) was added to tetrahydroisoquinoline **3** (100 mg, 0.36 mmol) in THF (1.5 mL) at –50 °C. After 4 min, Me_3SiCl (0.16 mL, 1.2 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (92:8), to give the carbamate **6c** (90 mg, 72%) as an oil; R_f 0.36 [petrol–EtOAc (90:10)]; ν_{max} (neat)/cm^{-1} 2965, 2930, 1680, 1480, 836, ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 6.60 (0.5H, s, CH), 6.57 (0.5H, s, CH), 6.46 (0.5H, s, CH), 6.45 (0.5H, s, CH), 5.92–5.89 (2H, m, CH), 4.83 (0.5H, br, CH), 4.67 (0.5H, br, CH), 4.18 (0.5H, dt, *J* 12, 5, CH), 3.93 (0.5H, dt, *J* 12, 5, CH), 3.25 (0.5H, ddd, *J* 12, 9, 5, CH), 3.11–3.05 (0.5H, m, CH), 2.90–2.78 (1H, m, CH), 2.65–2.55 (1H, m, CH), 1.50 (4.5H, s, *t*-Bu), 1.49 (4.5H, s, *t*-Bu), 0.06 (4.5H, s, $SiMe_3$), 0.05 (4.5H, s, $SiMe_3$); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ= 154.4, 145.9 & 144.8, 145.1 & 144.9, 130.3 & 129.7, 125.7 & 125.6, 108.9 & 108.6, 105.4 & 105.1, 100.7 & 100.6, 79.7 & 79.2, 49.9 & 49.0, 41.0 & 39.8, 28.9 & 28.55, 28.5, –1.4 & –1.6; HRMS (ES) Found: MNa^+, 372.1603. $C_{18}H_{28}NO_4SiNa$ requires MNa^+ 372.1607; LRMS *m/z* (ES) 372 (100%).

***tert*-Butyl 1-Butyl-5-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate 7a**

n-BuLi (0.19 mL, 0.49 mmol, 2.5 M in hexane) was added to tetrahydroisoquinoline **4** (100 mg, 0.33 mmol) in THF (1.5 mL) at –50 °C. After 4 min, *n*-butyl bromide (0.12 mL, 1.16 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), to give the carbamate **7a** (70 mg, 60%) as an oil; R_f 0.36 [petrol–EtOAc (90:10)]; ν_{max} (neat)/cm^{-1} 2965, 2930, 1690, 1425; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.52–7.51 (1H, m, CH), 7.29–7.28 (2H, m, 2 x CH), 5.21–5.18 (0.5H, br m, CH), 5.07–5.05 (0.5H, br m, CH), 4.25–4.22 (0.5H, br m, CH), 4.00–3.97 (0.5H, br m, CH), 3.36–3.15 (1H, br m, CH), 3.05–2.93 (2H, br m, 2 x CH), 1.89–1.66 (2H, br m, CH), 1.50 (9H, s, *t*-Bu), 1.45–1.29 (4H, m, 4 x CH), 0.94–0.89 (3H, m, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 154.8, 140.3 & 140.1, 133.3 & 133.0, 131.2 & 130.9, 128.3 (q, *J* 28.5 Hz), 125.6, 124.1, 121.7 (CF_3, q, *J* 269), 80.0 & 79.7, 54.9 & 54.1, 37.7 & 36.9, 36.5 & 35.9, 29.7 & 28.7, 28.4, 25.2 & 25.1, 22.5, 14.0; HRMS (ES) Found: MNa^+, 380.1795. $C_{19}H_{26}NO_2F_3Na$, requires MNa^+ 380.1813; LRMS *m/z* (ES) 380 (100%).

***tert*-Butyl 5-(Trifluoromethyl)-3,4-dihydro-1-(3-phenylpropyl)isoquinoline-2(1H)-carboxylate 7b**

n-BuLi (0.19 mL, 0.49 mmol, 2.5 M in hexane) was added to tetrahydroisoquinoline **4** (100 mg, 0.33 mmol) in THF (1.5 mL) at –50 °C. After 4 min, $Br(CH_2)_3Ph$ (0.17 mL, 1.16 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (99:1), to give the carbamate **7b** (84 mg, 61%) as an oil; R_f 0.25 [petrol–EtOAc (90:10)]; ν_{max} (neat)/cm^{-1} 2970, 2930, 1690, 1420; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.53–7.52 (1H, m, CH), 7.30–7.19 (7H, m, 7 x CH), 5.30–5.25 (0.5H, m, CH), 5.09–5.00 (0.5H, m, CH), 4.30–4.16 (0.5H, m, CH), 4.00–3.97 (0.5H, m, CH), 3.26–3.16 (1H. m, CH), 3.05–2.92 (2H, m, 2 x CH), 2.75–2.67 (2H, m, 2 x CH), 1.90–1.72 (4H, m, 4 x CH), 1.51 (4.5H, s, *t*-Bu), 1.49 (4.5H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 154.8 & 154.6, 142.2 & 141.8, 140.1 & 139.8, 133.3 & 133.0, 131.2, 130.9, 128.3, 125.8, 124.3 (CF_3, q, *J* 270), 124.2, 80.1 & 79.8, 54.9 & 53.8, 37.6, 36.4, 36.0, 35.4, 28.4, 27.9, 25.2 & 25.1; HRMS (ES) Found: MNa^+, 442.1961. $C_{24}H_{28}NO_2F_3Na$ requires MNa^+ 442.1970; LRMS *m/z* (ES) 442 (100%).

***tert*-Butyl 5-(Trifluoromethyl)-3,4-dihydro-1-(3-phenoxypropyl)isoquinoline-2(1H)-carboxylate 7c**

n-BuLi (0.19 mL, 0.49 mmol, 2.5 M in hexane) was added to tetrahydroisoquinoline **4** (100 mg, 0.33 mmol) in THF (1.5 mL) at –50 °C. After 4 min, $Br(CH_2)_3OPh$ (0.17 mL, 1.16 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (99:1), to give the carbamate **7c** (90 mg, 64%) as an oil; R_f 0.22 [petrol–EtOAc (90:10)]; ν_{max} (neat)/cm^{-1} 2970, 1685, 1420; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52–7.45 (1H, m, CH), 7.37–7.25 (4H, m, 4 x CH), 6.96–6.90 (3H, m, 3 x CH), 5.30–5.27 (0.5H, m, CH), 5.15–5.12 (0.5H, m, CH), 4.30–4.25 (0.5H, m, CH), 4.10–4.02 (2.5H, m, CH), 3.37–3.20 (1H, m, CH), 3.08–2.98 (2H, m, 2 x CH), 2.03–1.90 (4H, m, 4 x CH), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 159.0, 154.9 & 154.5, 140.2 & 139.7, 133.3 & 133.0 (C), 131.2 & 130.9, 129.4, 128.6 (q, *J* 31), 125.8, 124.3, 121.0 (CF_3, q, *J* 274), 120.7 & 120.6, 114.5, 80.2 & 79.9, 67.2, 54.6 & 53.7, 37.6 & 36.0, 33.5 & 33.1, 29.7 & 28.4, 26.2, 25.2 & 25.0; HRMS (ES) Found: MNa^+, 458.1918. $C_{24}H_{29}NO_3F_3Na$ requires MNa^+, 458.1919; LRMS *m/z* (ES) 458 (100%).

tert-Butyl 1-(3-Bromopropyl)-5-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate 7d

n-BuLi (0.31 mL, 0.78 mmol, 2.5 M in hexane) was added to tetrahydroisoquinoline **4** (200 mg, 0.66 mmol) in THF (3 mL) at –50 °C. After 4 min, $Br(CH_2)_3Br$ (0.08 mL, 0.79 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (99:1), to give the carbamate **7d** (180 mg, 68%) as an oil; R_f 0.4 [petrol–EtOAc (80:20)]; ν_{max} (neat)/cm^{-1} 2975, 2925, 1690, 1420; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.55–7.53 (1H, m, CH), 7.35–7.30 (2H, m, 2 x CH), 5.26–5.23 (0.5H, m, CH), 5.10–5.08 (0.5H, m, CH), 4.33–4.27 (0.5H, m, CH), 4.08–4.06 (0.5H, m, CH), 3.68–3.51 (2H, m, 2 x CH), 3.31–3.15 (1H, m, CH), 3.00–2.97 (2H, m, 2 x CH), 2.05–1.95 (4H, m, 4 x CH), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 154.9 & 154.2, 139.7, 139.2, 133.6 & 132.6, 131.3 & 130.8, 125.9 & 125.8, 124.4, 124.3 (q, *J* 280), 80.5 & 80.0, 54.1 & 52.9, 37.6 & 35.9, 35.2 & 34.7, 33.5 & 33.0, 29.8 & 29.2, 28.4, 25.6 & 25.0; HRMS (ES) Found: MNa^+, 444.0754. $C_{18}H_{23}NO_2F_3{}^{79}BrNa$ requires MNa^+ 444.0762; LRMS *m/z* (ES) 446 (97%), 444 (100%).

tert-Butyl 1-Allyl-7-chloro-3,4-dihydroisoquinoline-2(1H)-carboxylate 8a

n-BuLi (0.17 mL, 0.44 mmol, 2.5 M in hexane) was added to tetrahydroisoquinoline **5** (100 mg, 0.37 mmol) in THF (1.5 mL) at –50 °C. After 4 min, allyl bromide (0.13 mL, 1.3 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), to give the carbamate **8a** (100 mg, 91%) as plates m.p. 94–96 °C; R_f 0.6 [petrol–EtOAc (95:5)]; ν_{max} (neat)/cm^{-1} 2975, 2930, 1690, 1420; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.15–7.14 (2H, m, 2 x CH), 7.08–7.06 (1H, m, CH), 5.85–5.80 (1H, m, CH), 5.26–5.24 (0.4H, m, CH), 5.10–5.06 (2.6H, m, CH), 4.25–4.22 (0.6H, m, CH), 4.01–3.96 (0.4H, m, CH), 3.30–3.13 (1H, m, CH), 2.93–2.85 (1H, m, CH), 2.73–2.70 (1H, m, CH), 2.56–2.52 (2H, m, 2 x CH), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 154.7 & 154.5, 139.1 & 138.9, 134.6, 132.9 & 132.7, 131.5, 130.4 & 130.0, 127.1, 126.8 & 126.7, 117.7 & 117.3, 80.1 & 79.7, 54.2 & 53.3, 41.3 & 41.0, 38.2 & 36.5, 28.4, 28.2 & 28.0; HRMS (ES) Found: MNa^+, 330.1223. $C_{17}H_{22}{}^{35}ClNO_2$ requires MNa^+ 330.1237; LRMS *m/z* (ES) 332 (33%), 330 (100%).

tert-Butyl 7-Chloro-3,4-dihydro-1-(trimethylsilyl)isoquinoline-2(1H)-carboxylate 8b

n-BuLi (0.17 mL, 0.44 mmol, 2.5 M in hexane) was added to tetrahydroisoquinoline **5** (100 mg, 0.37 mmol) in THF (1.5 mL) at –50 °C. After 4 min, Me_3SiCl (0.13 mL, 1.0 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), to give the carbamate **8b** (85 mg, 68%) as plates, m.p. 115–116 °C; R_f 0.36 [petrol–EtOAc (95:5)]; ν_{max} (neat)/cm^{-1} 2980, 2930, 1700, 1420, 935; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.05–7.03 (2H, m, 2 x CH), 6.96–6.95 (1H, m, CH), 4.95 (0.5H, s, CH), 4.78 (0.5H, s, CH), 4.30–4.20 (0.5H, m, CH), 4.00 (0.5H, dt, 12.5, 5, CH), 3.25 (0.5H, ddd, *J* 12.5, 9, 5, CH), 3.10–3.05 (0.5H, m, CH), 2.95–2.82 (1H, m, CH), 2.72–2.65 (1H, m, CH), 1.50 (4.5H, s, *t*-Bu), 1.48 (4.5H, s, *t*-Bu), 0.09–0.06 (9H, m, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 154.4 & 154.3, 139.2 & 138.7, 131.4 & 131.3, 131.2 & 131.1, 130.8 & 130.4, 129.9 & 128.8, 125.0 & 124.6, 79.9 & 79.4, 49.7 & 48.9, 40.8 & 39.5, 28.5 & 28.4, 28.3 & 28.0, -1.4 & -1.7; HRMS (ES) Found: MNa^+, 362.1329. $C_{17}H_{26}NO_2NaSi^{35}Cl$ requires M^+ 362.1319; LRMS *m/z* (ES) 364 (33%), 362 (100).

tert-Butyl 1-(Tributylstannyl)-7-chloro-3,4-dihydroisoquinoline-2(1H)-carboxylate 8c

n-BuLi (0.17 mL, 0.44 mmol, 2.5 M in hexane) was added to tetrahydroisoquinoline **5** (100 mg, 0.37 mmol) in THF (1.5 mL) at –50 °C. After 4 min, *n*-Bu_3SnCl (0.36 mL, 1.3 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), to give the carbamate **8b** (120 mg, 57%) as an oil; R_f 0.6 [petrol–EtOAc (95:5)]; ν_{max} (neat)/cm^{-1} 2955, 2925, 2855, 1700, 1150; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.00–6.95 (2H, m, 2 x CH), 6.85–6.80 (1H, m, CH), 5.34–5.17 (1H, m, CH), 4.35–4.25 (0.5H, m, CH), 3.85 (0.5H, dt, *J* 12, 6, CH), 3.31 (0.5H, ddd, *J* 12, 8, 4, CH), 3.01–2.85 (1.5H, m, CH), 2.75–2.65 (1H, m, CH), 1.60 (4.5H, s, *t*-Bu), 1.59 (4.5H, s, *t*-Bu), 1.45–1.20 [12H, m, $Sn(CH_2CH_2CH_2CH_3)_3$], 0.95–0.78 [15H, m, $Sn(CH_2CH_2CH_2CH_3)_3$]; ^{13}C NMR (100 MHz, $CDCl_3$, rotamers and C=O could not be observed) δ = 131.8, 130.1 & 129.5, 130.0, 129.9 & 129.8, 123.9 & 123.7, 123.4, 79.4, 49.6 & 49.3, 41.7 & 40.6, 29.0, 28.9 & 28.8, 28.6 & 28.5, 27.4 & 27.3, 13.5, 10.6 & 10.4; HRMS (ES) Found: MH^+, 558.2134. $C_{26}H_{45}NO_2{}^{35}Cl^{120}Sn$, requires MH^+; 558.2161; LRMS *m/z* (ES) 560 (33%), 558 (100%).

7-(Trifluoromethyl)-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinoline 9

Trifluoroacetic acid (0.28 mL, 3.66 mmol) was added to the tetrahydroisoquinoline **7d** (400 mg, 0.95 mmol) in CH_2Cl_2 (5 mL) at room temperature. After 4 h, the solvent was removed under reduced pressure. Aqueous NaOH (30 mL, 1 M) was added and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined extracts were dried ($MgSO_4$), evaporated, and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (92:8), to give the amine **9** (210 mg, 91%) as a solid; m.p. 76–78 °C; R_f 0.5 [petrol–EtOAc (80:20)]; ν_{max} (neat)/cm^{-1} 2920, 2850, 1470, 1375; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.52–7.50 (1H, m, CH), 7.29–7.23 (2H, m, 2 x CH), 3.27–3.04 (4H, m, 4 x CH), 2.69–2.54 (2H, m, 2 x H), 2.45–2.37 (1H, m, CH), 2.01–1.71 (4H, m 4 x CH); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ= 140.5, 133.0, 129.6, 128.1, (q, *J* 25), 125.7, 124.5 (CF_3, q, *J* 276), 123.9 (q, *J* 7), 63.5,

53.5, 47.9, 30.6, 25.4, 22.1; HRMS (ES) Found: MH^+, 242.1147. $C_{13}H_{15}NF_3$ requires MH^+ 242.1157; LRMS *m/z* (ES) 242 (100%).

tert-Butyl 1-(4-Bromobutyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate 11

n-BuLi (1.24 mL, 2.86 mmol, 2.5 M in hexane) was added to tetrahydroisoquinoline **2** (700 mg, 2.38 mmol) in THF (10 mL) at –50 °C. After 4 min, $Br(CH_2)_4Br$ (0.34 mL, 2.86 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), to give the carbamate **11** (760 mg, 75%) as an oil; R_f 0.21 [petrol–EtOAc (80:20)]; ν_{max} (neat)/cm^{-1} 2965, 2935, 1680, 1515, 1415; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 6.61–6.60 (2H, m, 2 x CH), 5.12–5.08 (0.5H, m, CH), 4.98–4.95 (0.5H, m, CH), 4.27–4.23 (0.5H, m, CH), 4.01–3.98 (0.5, m, CH), 3.88 (6H, br s, 2 x CH_3), 3.48–3.42 (2H, m, 2 x CH), 3.27–3.22 (0.5H, m, CH), 3.15–3.08 (0.5H, m, CH), 3.00–2.79 (1H, m, CH), 2.65–2.61 (1H, m, CH), 2.06–1.54 (6H, m, 6 x CH), 1.51 (9H, br s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 154.8, 147.8, 147.4, 130.2 & 129.8, 126.5 & 126.0, 111.6, 110.2 & 109.9, 79.9 & 79.5, 56.1, 55.9, 54.2 & 53.4, 38.3 & 36.5, 36.2 & 35.7, 33.6, 32.5, 28.4, 27.9, 25.4 & 25.1; HRMS (ES) Found: MNa^+, 450.1247. $C_{20}H_{30}NO_4{}^{79}BrNa$ requires MNa^+ 450.1256; LRMS *m/z* (ES) 452 (97%), 450 (100%).

Crispine A 12

n-BuLi (1.63 mL, 4.1 mmol, 2.5 M in hexane) was added to tetrahydroisoquinoline **2** (1.0 g, 3.4 mmol) in THF (14 mL) at –50 °C. After 4 min, dibromopropane (0.41 mL, 4.1 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated to give the crude product **10**. Trifluoroacetic acid (0.37 mL, 4.9 mmol) was added to this crude product **10** in CH_2Cl_2 (15 mL) and the mixture was stirred at room temperature. After 4 h, the solvent was evaporated and aqueous NaOH (30 mL, 1 M) was added. The mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined extracts were dried ($MgSO_4$), evaporated, and purified by column chromatography on silica, eluting with petrol–EtOAc (92:8), to give (±)-crispine A (410 mg, 52%) as an oil; R_f 0.18 [petrol–EtOAc (80:20)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.63 (1H, s, CH), 6.58 (1H, s, CH), 4.12–4.05 (1H, m, CH), 3.86 (6H, s, 2 x CH_3), 3.21–3.17 (2H, m, 2 x CH), 3.12–3.05 (2H, m, 2 x CH), 2.97–2.96 (2H, m, 2 x CH), 2.56–2.48 (1H, m, CH), 2.07–1.99 (2H, m, 2 x CH), 1.93–1.83 (1H, m, CH). Data as reported.[9]

9,10-Dimethoxy-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinoline 13

Trifluoroacetic acid (0.1 mL, 1.48 mmol) was added to the tetrahydroisoquinoline **11** (100 mg, 0.24 mmol) in CH_2Cl_2 (5 mL) and the mixture was stirred at room temperature. After 4 h, the solvent was evaporated and aqueous NaOH (5 mL, 1 M) was added. The mixture was extracted with CH_2Cl_2 (2 × 5 mL). The combined extracts were dried ($MgSO_4$), evaporated, and purified by column chromatography on silica, eluting with CH_2Cl_2–MeOH (97:3), to give the amine **13** (50 mg, 87%) as an oil; R_f 0.34 [CH_2Cl_2–MeOH (9:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.71 (1H, s, CH), 6.59 (1H, s, CH), 3.86 (6H, s, 2 x CH_3), 3.20–2.96 (4H, m, 4 x CH), 2.66–2.50 (2H, m, 2 x CH), 2.38–2.27 (2H, m, 2 x CH), 1.97–1.92 (1H, m, CH), 1.76–1.70 (2H, m, 2 x CH), 1.56–1.42 (2H, m, 2 x CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 147.3, 147.1, 130.2, 126.6, 111.4, 108.1, 63.2, 56.9, 56.0, 55.8, 52.8, 31.5, 29.0, 25.4, 25.0; HRMS (ES) Found: MH^+, 248.1655. $C_{15}H_{21}NO_2$ requires MH^+ 248.1645; Data as reported.[10]

tert-Butyl 1-[3-(2-_tert_-Butoxycarbonyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)propyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate 14

n-BuLi (3.2 mL, 8.2 mmol, 2.5 M in hexane) was added to tetrahydroisoquinoline **2** (2.0 g, 6.8 mmol) in THF (28 mL) at –50 °C. After 4 min, $Br(CH_2)_3Br$ (0.3 mL, 3.4 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (99:1), to give the carbamate **14** (2.8 g, 64%) as a separable mixture of diastereomers (dr 1:1), each as an oil:

Isomer A: R_f 0.27 [petrol–EtOAc (90:10)]; ν_{max} (neat)/cm^{-1} 2970, 2935, 1685, 1520; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 6.63–6.55 (4H, m, 4 x CH), 5.12–5.10 (1H, m, CH), 4.98–4.96 (1H, m, CH), 4.22–4.19 (0.85H, m, CH), 3.97–3.92 (1.15H, m, CH), 3.85 (12H, br s, 4 x CH_3), 3.27–3.15 (2H, m, CH), 2.86–2.81 (2H, m, CH), 2.63–2.59 (2H, m, CH), 1.93–1.72 (4H, m, 2 x CH), 1.63–1.53 (2H, m, CH), 1.47 (18H, br s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ= 155.0 & 154.9, 147.6, 147.3, 130.6 & 130.1, 126.4 & 126.0, 111.6 & 111.4, 110.3 & 110.0, 79.7 & 79.2, 56.1, 55.9, 54.7 & 53.4, 38.4 & 38.2, 36.9 & 36.2, 28.5, 28.1 & 27.9, 23.5 & 23.2; HRMS (ES) Found: MNa^+, 649.3456. $C_{19}H_{25}NO_4Na$ requires MNa^+ 649.3433; LRMS *m/z* (ES) 649 (100%).

Isomer B: R_f 0.28 [petrol–EtOAc (90:10)]; ν_{max} (neat)/cm^{-1} 2970, 2935, 1685, 1520; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 6.63–6.55 (4H, m, 4 x CH), 5.12–5.10 (1H, m, CH), 4.98–4.96 (1H, m, CH), 4.22–4.19 (0.8H, m, CH), 4.03–3.94 (1.2H, m, CH), 3.85 (12H, br s, 4 x CH_3), 3.27–3.15 (2H, m, CH), 2.86–2.81 (2H, m, CH), 2.63–2.59 (2H, m, CH), 1.93–1.72 (4H, m, 2 x CH), 1.63–1.53 (2H, m, CH), 1.47 (18H, br s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ= 155.0 & 154.8, 147.5, 147.3, 130.5 & 130.0, 126.3 & 125.8, 111.6 & 111.4, 110.3 & 109.9, 79.7 & 79.2, 56.1, 56.0, 54.6 & 53.5, 38.3 & 38.0, 36.9 & 35.5, 28.5, 28.1 & 27.9, 23.6 & 23.2; HRMS (ES) Found: MNa^+, 649.3456. $C_{19}H_{25}NO_4Na$ requires MNa^+ 649.3433; LRMS *m/z* (ES) 649 (100%).

tert-Butyl 6,7-Dimethoxy-1-(prop-2-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate 15

n-BuLi (1.63 mL, 4.08 mmol, 2.5 M in hexane) was added to tetrahydroisoquinoline **2** (1.0 g, 3.4 mmol) in THF (14 mL) at –50 °C. After 4 min, propargyl bromide (0.36 mL, 4.1 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by

column chromatography on silica gel, eluting with petrol–EtOAc (99:1), to give the carbamate **15** (0.88 g, 78%) as an oil; R_f 0.1 [petrol–EtOAc (90:10)]; ν_{max} (neat)/cm^{-1} 2970, 2930, 1690, 1520, 1415; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 6.78 (1H, s, CH), 6.61 (1H, s, CH), 5.27–5.24 (0.5H, m, CH), 5.14 (0.5H, t, *J* 6, CH), 4.21–4.18 (0.5H, m, CH), 3.97–3.93 (0.5H, m, CH), 3.87 (6H, s, 2 x CH_3), 3.47–3.42 (0.5H, m, CH), 3.31–3.26 (0.5H, m, CH), 2.87–2.71 (4H, m, 4 x CH), 2.02–2.00 (1H, m, CH), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers, alkyne C atoms could not be observed) δ = 154.6 & 154.4, 147.9 & 147.8, 147.3, 127.8 & 127.6, 126.7 & 126.5, 111.4 & 111.2, 110.5 & 110.1, 80.1 & 79.8, 55.9 & 55.8, 53.1 & 52.4, 39.1 & 37.3, 28.4, 28.3 & 28.0, 26.5 & 26.1; HRMS (ES) Found: MNa^+, 354.1668. $C_{19}H_{25}NO_4Na$ requires MNa^+ 354.1681; LRMS *m/z* (ES) 354 (100%).

***tert*-Butyl 6,7-Dimethoxy-1-[(4-methoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate 16**

n-BuLi (1.6 mL, 4.1 mmol, 2.5 M in hexane) was added to tetrahydroisoquinoline **2** (1.0 g, 3.4 mmol) in THF (14 mL) at –50 °C. After 4 min, 4-methoxybenzyl chloride (0.6 mL, 4.1 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (92:8), to give the carbamate **16** (980 mg, 70%) as an oil; R_f 0.11 [petrol–EtOAc (90:10)]; ν_{max} (neat)/cm^{-1} 3005, 2990, 1675, 1510, 1415; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.05–7.02 (2H, m, 2 x CH), 6.85–6.80 (2H, m, 2 x CH), 6.63 (0.67H, s, CH), 6.60 (0.33H, s, CH), 6.34 (0.67H, s, CH), 6.20 (0.33H, s, CH), 5.22 (0.33H, t, *J* 7, CH), 5.07 (0.67H, t, *J* 7, CH), 4.15 (0.67H, ddd, *J* 12, 5, 3, CH), 3.87 (3H, s, OCH_3), 3.85–3.77 (0.33H, m, CH), 3.80 (3H, s, OCH_3), 3.75 (2H, s, OCH_3), 3.65 (1H, s, OCH_3), 3.37–3.22 (1H, m, CH), 3.10–3.00 (1H, m, CH), 2.96–2.72 (2H, m, 2 x CH), 2.65–2.55 (1H, m, CH), 1.45 (3H, s, *t*-Bu), 1.35 (6H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 158.3 & 158.1, 154.6 & 154.5, 147.6 & 147.5, 146.9 & 146.7, 130.8 & 130.6, 130.7 & 130.5, 128.8 & 128.6, 126.6 & 126.3, 113.7 & 113.5, 111.3 & 111.0, 110.7 & 110.3, 79.5 & 79.4, 56.5, 55.9 & 55.8, 55.7 & 55.6, 55.3 & 55.2, 42.0 & 41.8, 39.3 & 37.2, 28.5 & 28.3, 28.2; HRMS (ES) Found: MNa^+, 436.2103. $C_{24}H_{31}NO_5Na$ requires MNa^+ 436.2100; LRMS *m/z* (ES) 436 (100%).

***tert*-Butyl 1-[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate 17**

The tetrahydroisoquinoline **15** (500 mg, 1.5 mmol), benzyl azide (200 mg, 1.8 mmol), $CuSO_4{\cdot}H_2O$ (300 mg, 1.8 mmol), ascorbic acid (300 mg, 1.8 mmol), L-proline (200 mg, 1.81 mmol), and Na_2CO_3 (100 mg, 1.8 mmol) were heated at 65 °C in DMSO–water (10 mL, 9:1). After 18 h, the mixture was cooled to room temperature and saturated aqueous NH_4Cl (30 mL) was added. The precipitate was filtered and washed with water (100 mL). The combined extracts were dried ($MgSO_4$), evaporated, and purified by column chromatography on silica gel, eluting with petrol–EtOAc (60:40), to give the carbamate **17** (570 mg, 83%) as an oil; R_f 0.11 [petrol–EtOAc (50:50)]; ν_{max} (neat)/cm^{-1} 3000, 2970, 1690, 1365; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.35–7.15 (6H, m, 6 x CH), 6.66–6.56 (2H, m, 2 x CH), 5.55–5.36 (3H, m, 3 x CH), 4.28–4.21 (0.5H, m, CH), 3.98–3.91 (0.5H, m, CH), 3.85 (3H, s, OCH_3), 3.81 (1.7H, s, OCH_3), 3.76 (1.3H, s, OCH_3), 3.21–3.02 (2.5H, m, CH), 3.02–2.76 (1H, m, CH), 2.62–2.57 (1H, m, CH), 1.99–1.84 (0.5H, m, CH), 1.38 (3H, s, *t*-Bu), 1.26 (6H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 154.8 & 154.4, 147.8, 147.4, 145.2 & 144.8, 135.0 & 134.6, 129.1, 128.8, 128.7 & 128.6, 128.0 & 127.9, 126.2, 121.9, 111.4, 109.9, 79.7 & 79.5, 56.0 & 55.9, 54.4, 54.0, 53.1, 38.3 & 36.4, 32.8, 28.3 & 28.1, 28.0; HRMS (ES) Found: MNa^+, 487.2316. $C_{26}H_{32}N_4O_4Na$ requires MNa^+ 487.2325; LRMS *m/z* (ES) 487 (100%).

5-Benzyl-6-methyl-2H,5H,6H,7H,8H-[1,3]-dioxolo[4,5-g]isoquinoline 18

The carbamate **6b** (100 mg, 0.24 mmol) in THF (1 mL) was added to a suspension of $LiAlH_4$ (500 mg, 1.2 mmol) in THF (5 mL) at 0 °C under nitrogen. The mixture was stirred at room temperature for 1 h then was heated under reflux. After 16 h, the mixture was allowed to cool to room temperature. Aqueous NaOH (5 mL, 1 M) was added dropwise. The solids were removed by filtration though Celite and were washed with CH_2Cl_2–MeOH (9:1). The filtrate was evaporated and purified by column chromatography on silica, eluting with CH_2Cl_2–MeOH (95:5), to give the amine **18** (50 mg, 69%) as an oil; R_f 0.4 [CH_2Cl_2–MeOH (9.5:0.5)]; ν_{max} (neat)/cm^{-1} 2925, 2775, 1480; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.30–7.26 (2H, m, 2 x CH), 7.23–7.19 (1H, m, CH), 7.16–7.14 (2H, m, 2 x CH), 6.56 (1H, s, CH), 6.22 (1H, s, CH), 5.91–5.87 (2H, m, CH), 3.74 (1H, t, *J* 6, CH), 3.24–3.11 (2H, m, 2 x CH), 2.90–2.73 (3H, m, 3 x CH), 2.59–2.53 (1H, m, CH), 2.49 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 145.8, 145.3, 139.9, 130.6, 129.5, 128.1, 127.2, 126.0, 108.4, 107.8, 100.5, 65.2, 46.6, 42.6, 41.6, 25.7; HRMS (ES) Found: MH^+, 282.1491. $C_{18}H_{20}NO_2$ requires MH^+ 282.1494, LRMS *m/z* (ES) 282 (100%).

***tert*-Butyl 1-[2-(2H-1,3-Benzodioxol-5-yl)ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate 20**

n-BuLi (1.63 mL, 4.08 mmol, 2.5 M in hexane) was added to tetrahydroisoquinoline **2** (1.0 g, 3.4 mmol) in THF (14 mL) at –50 °C. After 4 min, bromide **19** (900 mg, 1.6 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (92:8), to give the carbamate **20** (1.08 g, 72%) as an oil; R_f 0.12 [petrol–EtOAc (80:20)]; ν_{max} (neat)/cm^{-1} 2970, 2930, 1685, 1515; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 6.75–6.58 (5H, m, 5 x CH), 5.93 (2H, s, OCH_2O), 5.18–5.01 (1H, m, CH), 4.28–4.26 (0.5H, m, CH), 4.05–4.00 (0.5H, m, CH), 3.86 (6H, s, 2 x CH_3), 3.29–3.17 (1H, m, CH), 2.98–2.59 (4H, m, 3 x CH), 2.10–2.00 (2H, m, 2 x CH), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 154.9, 147.7, 147.4, 145.6, 136.0 & 135.7, 130.1, 129.6, 126.3 & 125.9, 120.9, 111.6, 110.2 & 109.9, 108.7 & 108.1, 100.7, 79.9 & 79.4, 56.0 & 55.9, 54.4 & 53.6, 39.1 & 38.7, 36.9, 32.7, 28.5, 28.1 & 27.9; HRMS (ES) Found: MNa^+, 464.2032

$C_{25}H_{31}NO_6Na$ requires MNa^+ 464.2049, LRMS *m/z* (ES) 464 (100%).

Dysoxyline 21

In the same way as the amine **18**, the carbamate **20** (100 mg, 0.24 mmol) and $LiAlH_4$ (500 mg, 1.2 mmol) gave, after purification by column chromatography on silica, eluting with Et_2O–petrol (97.5:2.5), (±)-dysoxyline **21** (60 mg, 75%) as an oil; R_f 0.12 [Petrol–Et_2OH (90:10)]; ν_{max} (neat)/cm^{-1} 2935, 2780, 1515, 1490; ^1H NMR (400 MHz, $CDCl_3$) δ = 6.74–6.69 (2H, m, CH), 6.66–6.62 (1H, m, CH), 6.58 (1H, s, CH), 6.55 (1H, s, CH), 5.92 (2H, s, OCH_2O), 3.85 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.42 (1H, t, *J* 5, CH), 3.20–3.12 (1H, m, CH), 2.82–2.63 (4H, m, 4 x CH), 2.54–2.46 (1H, m, CH), 2.48 (3H, s, NCH_3), 2.05–2.00 (2H, m, 2 x CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.5, 147.3, 147.2, 145.4, 136.8, 129.7, 126.7, 121.0, 111.2, 110.0, 108.9, 108.1, 100.7, 62.6, 56.0, 55.8, 48.2, 42.7, 37.1, 31.3, 25.4; HRMS (ES) Found: MH^+, 356.1859. $C_{21}H_{26}NO_4$ requires MH^+ 356.1862. Data as reported.[12]

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