Synthesis of Optically Active Condensed Tetrahydropyridines from α-Amino Esters

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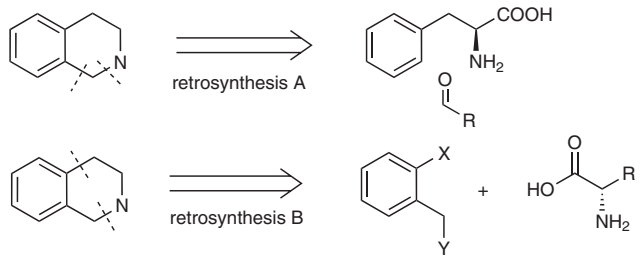
Abstract: Optically active condensed dihydropyridones **6** could be synthesized from α-amino esters **2** or **3** and *o*-bromobenzyl bromides or heterocyclic analogues **1**. These products resemble isoquinoline and β-carboline alkaloid structures and could be stereoselectively transformed into condensed 4-hydroxytetrahydropyridines **7** and **8** by reaction with Grignard reagents or reduction. Treatment of condensed 4-allyl or 4-homoallyl-4-hydroxypyridines **8** with *N*-iodosuccinimide undergoes halocyclization to bridged tricyclic tetrahydropyridines **9** and **10**.

Key words: amino acids, carbolines, isoquinolines, asymmetric synthesis, heterocycles

Condensed tetrahydropyridines such as tetrahydroisoquinolines or tetrahydro-β-carbolines are abundant in naturally occurring alkaloids and have gained pharmaceutical interest.[1,2] Biosynthesis of such compounds comprises a Pictet–Spengler-type cyclization of phenylalanine or tryptophane according to retrosynthesis A (see Scheme 1). Among such condensed *N*-heterocycles, compounds are found with an oxygen atom as carbonyl or hydroxy group in position 3 of the tetrahydropyridine ring, i.e. position 4 of the condensed system. Because of their importance, several syntheses were developed for such 3-functionalized condensed tetrahydropyridines. Thus intramolecular Friedel–Crafts acylation of benzylamino acids or α-heteroarylmethylamino acids[3–13] or of the corresponding esters and nitriles,[14–18] intramolecular Dieckmann condensation of *o*-ethoxycarbonylbenzylamino esters[19,20] or Grignard reaction of 4-hydroxyisoquinolinium salts[21] lead to condensed tetrahydropyridin-4-ones. With a few exceptions,[22,23] these syntheses result in racemic mixtures and often give unsatisfactory results. Condensed 3-hydroxytetrahydropyridines, e. g. 4-hydroxytetrahydroisoquinolines, were obtained either from corresponding condensed oxo compounds by reduction[5,18,19,22–26] or by addition of organometallics,[5,17–19,25] by cyclization of 2-benzylaminoacetaldehyde acetals[27] or by Pictet–Spengler-type reaction.[28]



Scheme 1

We found an efficient way to condensed dihydropyridones. It starts from α-amino acids like in the biosynthesis, but only the C–C–N unit of the amino acid is incorporated into the final pyridine ring while a C-3 unit is contributed by an *o*-halobenzyl halide or a heterocyclic analogue (retrosynthesis B in Scheme 1, X,Y = Hal).[29–31] After primary alkylation of the amino group of the N-protected α-amino ester **3**, the resulting *N*-(α-bromobenzyl)amino esters **5** were submitted to a bromo-lithium exchange by *n*-BuLi or *t*-BuLi resulting in a cyclization to dihydroisoquinolin-4-ones or their heterocyclic analogues **6** (Scheme 2, Tables 1 and 2). Low temperatures (down to –100 °C) were necessary to prevent racemization during the final cyclization step. Occasionally, addition of the alkyllithium to the carbonyl group of the product was observed as side reaction resulting in the corresponding 4-alkyl-4-hydroxyisoquinolines and heterocyclic analogues **8** (see also footnotes in Table 2).[29] By choosing oxazole or thiazole as the annulated heterocyclic 6π-ring, the corresponding condensed dihydropyridones **6** (6π-system is 1,3-oxazole or 1,3-thiazole) could be transformed into aminoglycitol derivatives. Here, up to three new stereogenic centers were created in a highly selective way.[30,31] This overall transformation of α-amino esters into aminoglycitols provided a novel way to amino sugars starting from α-amino acids.[30,31]

Similar starting materials **1** and **2** and reactions could be used in an interesting synthesis of optically active polycyclic bridged condensed tetrahydropyridines. N-Unsubstituted α-amino esters **2** were dibenzylated by *o*-bromobenzyl bromides or heterocyclic analogues **1**. The resulting products **5** (R^2 = *o*-bromobenzyl or heterocyclic analogue) were submitted to a double cyclization via bromo-lithium exchange. Alternatively, condensed dihydropyridones **6** with an *o*-bromobenzyl or heterocyclic analogous substituent R^2 could be treated with butyllithium.[32,33] The products exhibited a novel mode of HIV-inhibition by blocking the RNase-H and DNA-polymerase activity of the reverse transcriptase.[32,33]

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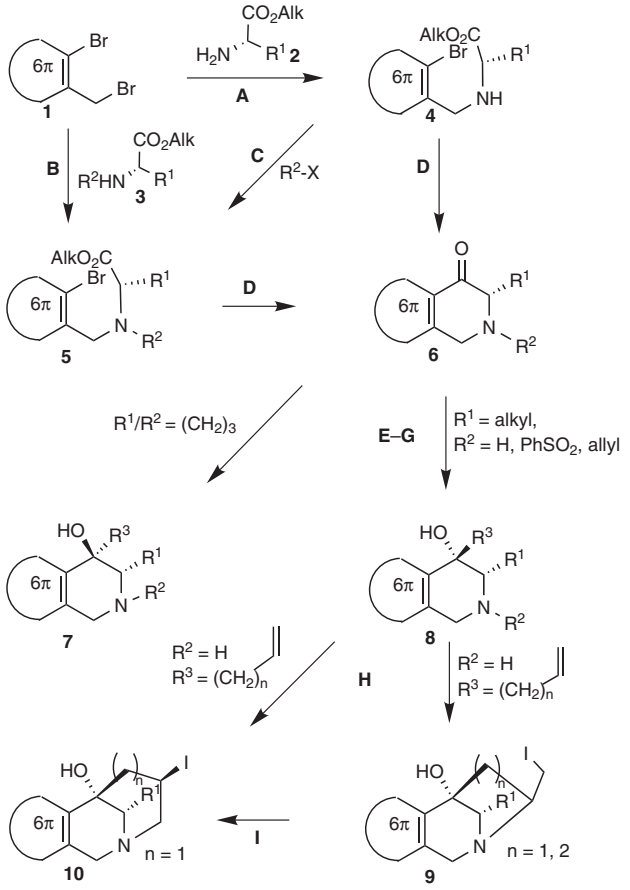


Scheme 2 *Reagents and conditions*: Method A: MeCN, K_2CO_3, reflux, 5 h, 52–95%; Method B: MeCN, K_2CO_3, reflux, 5 h, 63–93%; Method C, C1: MeCN or CH_2Cl_2, $NaHCO_3$, reflux, 4–8 h or C2: r.t. 8 h, 87–95%; Method D: BuLi THF, –100 °C, 3–6 h (argon), 12–81%; Method E: R_3MgBr (5–7 equiv), THF, 0 °C–r.t., 8–12 h (argon), 18–97%; Method F: $NaBH_4$, EtOH, 0 °C–r.t., 5–10 h, 47–57%; Method G: $LiAlH_4$, THF, 0 °C–r.t., 12–20 h (argon), 22–93%; Method H: NIS, THF, 0 °C–r.t., 12–20 h (argon), 56–66%; Method I: THF, 60 °C, 3 h, 98%

Here we give a full report on the synthesis of condensed dihydropyridones **6** and their precursors i.e., the N-protected amino esters **5** and the N-unprotected members **4**. Furthermore, reactions of the condensed dihydropyridones **6** with organometallics and with reducing reagents resulting in a transformation of the carbonyl group into hydroxy compounds **7** or **8** and halocyclization of allyl and homoallyl compounds **8** to 1,3-bridged cyclization products **9** and **10** are reported (Scheme 2).

A variety of α-amino esters **5** could be synthesized by straightforward alkylation of N-protected amino esters or proline ester with *o*-bromobenzyl bromides or heterocyclic analogues **1** (see Table 1, Method B). When N-unsubstituted α-amino esters **2** were reacted with the alkylating reagents **1** to synthesize N-monosubstituted amino esters **4** (Method A), double alkylation occurred as side reaction affording small amounts of dibenzylated products (see footnotes in Table 1, compounds **4a**, **4d–h**) although the amino esters **2** were used in small excess. Reaction of amino esters **2** with two equivalents of the alkylation reagent **1** promotes the double alkylation to become the major reaction.[32,33] The N-monobenzylated amino esters **4** could be *N*-Cbz-protected (**5j**) or allylated (**5c**, **5n**) in high yields providing an access (Method C) to products **5** as an alternative to direct Route B.

Regardless of the kind of N-substituent at position 2, a cyclization of the N-alkylation products **5** via bromo-lithium exchange to condensed dihydropyridones **6** was possible. When R^2 was H, i. e. **4** was used as starting material, two equivalents of butyllithium had to be applied. Lowering of the temperature from –78 to –100 °C increased the yield (see product **6i**). The use of *t*-BuLi instead of *n*-BuLi was advantageous in some cases (see products **6i** and **6m**) but gave rise to unwanted addition to the carbonyl group yielding the corresponding hydroxy products **8** (R^3 = *t*-Bu, see **6b**, **6g**) in other cases. The transformation of the NH-containing amino ester **4d** into the carbazole **6b** would require three equivalents of *t*-BuLi. However, this resulted in the formation of the corresponding *tert*-butyl-hydroxytetrahydro-β-carboline **8** (R^3 = *t*-Bu) almost to the same extent (29%) as the envisaged β-carbolinone **6b** (33%). Thus it was better to use only two equivalents of *t*-BuLi resulting in an increase of the yield from 33 to 52% (see Table 2). Formation of the 4-alkyl-4-hydroxy product **8** in the course of the cyclization of **5** to **6** was also observed when *n*-BuLi was applied to a lesser extent than with *t*-BuLi. For example, cyclization of **5b** with *n*-BuLi gave 12% of the isoquinolinone **6g** and 46% of the corresponding 4-butyl-4-hydroxyisoquinoline **7**. With *t*-BuLi no **6g** could be obtained at all, but only the 4-*tert*-butyl-4-hydroxyisoquinoline (58%). The conditions of the transformation of amino esters **5** to condensed dihydropyridones **6** did not violate the optical integrity as shown by the β-carbolinone **6j**, where only the enantiomer **6j** could be detected by HPLC (>99% ee, CHIRALCEL OD). The structure of this compound could also be proved by X-ray crystal analysis (Figure 1).

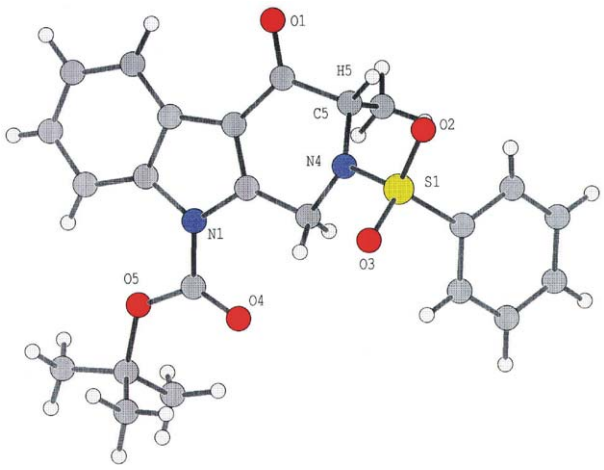


Figure 1 X-ray crystal structure of **6j**

Table 1 (*S*)-*N*-(*o*-Bromobenzyl)amino Esters and Heterocyclic Analogues **4** and **5** Prepared

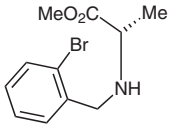
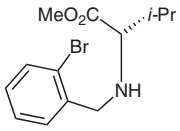
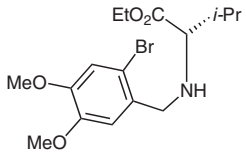
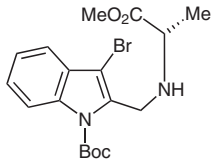
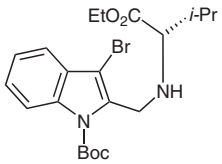
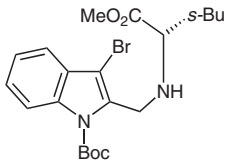
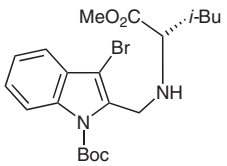
No.	Product[a]	Yield (%) Method Time	^{1}H NMR ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ, *J* (Hz)
4a		89 A 5 h[b]	1.27 (d, 3 H, *J* = 7.0, CH_3), 1.93 (s, 1 H, NH), 3.34 (q, 1 H, *J* = 7.0, CHN), 3.63 (s, 3 H, CH_3O), 3.70 (d, 1 H, *J* = 13.9, CH_2N), 3.83 (d, 1 H, *J* = 13.9, CH_2N), 7.04–7.07 (m, 1 H, CH_{ar}), 7.18–7.23 (m, 1 H, CH_{ar}), 7.34 (dd, 1 H, *J* = 7.6, 1.6, CH_{ar}), 7.46 (dd, 1 H, *J* = 7.9, 1.2, CH_{ar})	19.1 (CH_3), 51.8 (CH_2N), 51.9 (CH_3O), 56.0 (CHN), 124.0 (C_{ar}–Br), 127.5 (CH_{ar}), 128.7 (CH_{ar}), 130.1 (CH_{ar}), 132.8 (CH_{ar}), 138.8 (C_{ar}), 175.9 (C=O)
4b		89 A 5 h[c]	0.85–0.90 (m, 6 H, 2 CH_3), 1.18–1.91 [m, 2 H, C*H*(CH_3)$_2$, NH], 2.95 (d, 1 H, *J* = 6.1, CHN), 3.61 (s, 3 H, OCH_3), 3.63 (d, 1 H, *J* = 14.1, CH_2N), 3.81 (d, 1 H, *J* = 14.1, CH_2N), 6.99–7.05 (m, 1 H, CH_{ar}), 7.17–7.22 (m, 1 H, CH_{ar}), 7.36 (dd, 1 H, *J* = 7.5, 1.1, CH_{ar}), 7.44 (d, 1 H, *J* = 7.9, CH_{ar})	19.0 (CH_3), 19.7 (CH_3), 32.1 [*C*H(CH_3)$_2$], 51.8 (OCH_3), 52.8 (CH_2N), 67.2 (CHN), 124.5 (C_{ar}–Br), 127.7 (CH_{ar}), 128.9 (CH_{ar}), 130.5 (CH_{ar}), 133.1 (CH_{ar}), 139.5 (C_{ar}), 175.8 (C=O)
4c		69 A 5 h	0.88 (d, 6 H, *J* = 6.7, 2 CH_3), 1.17 (t, 3 H, *J* = 7.1, C*H*$_3$CH$_2$O), 1.71–1.93 [m, 2 H, C*H*(CH_3)$_2$, NH], 3.57 (d, 1 H, *J* = 7.0, CHN), 3.51 (d, 1 H, *J* = 14.2, CH_2N), 3.65 (d, 1 H, *J* = 14.2, CH_2N), 3.70 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 4.09 (q, 2 H, *J* = 7.1, OC*H*$_2$CH$_3$), 6.84 (s, 1 H, CH_{ar}), 6.93 (s, 1 H, CH_{ar})	14.3 (*C*H$_3$CH$_2$O), 18.6 (CH_3), 19.4 (CH_3), 31.7 [*C*H(CH_3)$_2$], 51.8 (CH_2N), 55.9 (OCH_3), 56.1 (CH_3O), 60.4 (OC*H*$_2$CH$_3$), 66.5 (CHN), 112.8 (CH_{ar}), 113.7 (C_{ar}–Br), 115.3 (CH_{ar}), 131.1 (C_{ar}), 148.2 (C_{ar}), 148.4 (C_{ar}), 175.0 (C=O)
4d		68 A 2 h[d]	1.28 (d, 3 H, *J* = 7.0, CH_3), 1.71 (s, 9 H, *t*-C_4H_9), 2.59 (s, 1 H, NH), 3.35 (s, 3 H, CH_3O), 3.38 (q, 1 H, *J* = 7.0, CHN), 4.19 (d, 1 H, *J* = 14.6, CH_2N), 4.28 (d, 1 H, *J* = 14.6, CH_2N), 7.21–7.34 (m, 2 H, CH_{ar}), 7.42–7.51 (m, 1 H, CH_{ar}), 8.08 (d, 1 H, *J* = 8.1, CH_{ar})	19.6 (CH_3), 28.2 [(*C*H$_3$)$_3$C], 43.8 (CH_2N), 51.6 (CH_3O), 54.9 (CHN), 85.0 [*C*(CH_3)$_3$], 102.4 (C_{ar}–Br), 115.8 (CH_{ar}), 119.4 (CH_{ar}), 123.3 (CH_{ar}), 125.5 (CH_{ar}), 128.0 (C_{ar}), 135.3 (C_{ar}), 135.4 (C_{ar}), 149.8 (*C*O$_2$Bu-*t*), 175.9 (*C*O$_2$Me)
4e		52 A 3 h[e]	0.96 (d, 3 H, *J* = 6.7, CH_3), 0.98 (d, 3 H, *J* = 6.3, CH_3), 1.05 (t, 3 H, *J* = 7.1, C*H*$_3$CH$_2$O), 1.79 (s, 9 H, *t*-C_4H_9), 1.89–2.02 [m, 1 H, C*H*(CH_3)$_2$], 2.65 (s, 1 H, NH), 3.09 (d, 1 H, *J* = 5.3, CHN), 3.61–3.89 (m, 2 H, OC*H*$_2$CH$_3$), 4.24 (d, 1 H, *J* = 14.7, CH_2N), 4.39 (d, 1 H, *J* = 14.7, CH_2N), 7.32–7.39 (m, 2 H, CH_{ar}), 7.55 (d, 1 H, *J* = 7.4, CH_{ar}), 8.16 (d, 1 H, *J* = 8.3, CH_{ar})	14.0 (*C*H$_3$CH$_2$), 18.4 [(*C*H$_3$)$_2$CH], 19.1 [(*C*H$_3$)$_2$CH), 28.2 [(*C*H$_3$)$_3$C], 32.0 [*C*H(CH_3)$_2$], 44.8 (CH_2N), 60.1 (CH_2O), 65.5 (CHN), 84.8 [*C*(CH_3)$_3$], 102.2 (C_{ar}–Br), 115.7 (CH_{ar}), 119.3 (CH_{ar}), 123.2 (CH_{ar}), 125.4 (CH_{ar}), 128.0 (C_{ar}), 135.5 (C_{ar}), 135.8 (C_{ar}), 149.8 (*C*O$_2$Bu-*t*), 174.9 (*C*O$_2$Et)
4f		60 A 3 h[f]	0.62 (d, 3 H, *J* = 6.8, CH_3), 0.64 (t, 3 H, *J* = 7.3, C*H*$_3$CH$_2$), 0.88–1.05 (m, 1 H, CH), 1.23–1.49 (m, 2 H, C*H*$_2$CH$_3$), 1.51 (s, 9 H, *t*-C_4H_9), 2.34 (s, 1 H, NH), 2.91 (d, 1 H, *J* = 5.8, CHN), 3.03 (s, 3 H, CH_3O), 3.95 (d, 1 H, *J* = 14.7, CH_2N), 4.09 (d, 1 H, *J* = 14.7, CH_2N), 7.05–7.12 (m, 2 H, CH_{ar}), 7.25–7.26 (m, 1 H, CH_{ar}), 7.85–7.89 (m, 1 H, CH_{ar})	11.9 (*C*H$_3$CH$_2$), 15.8 (CH_3), 25.8 (*C*H$_2$CH$_3$), 28.6 [(*C*H$_3$)$_3$C], 39.2 (CH), 45.1 (CH_2N), 51.4 (CH_3O), 64.8 (CHN), 85.2 [*C*(CH_3)$_3$], 102.7 (C_{ar}–Br), 116.1 (CH_{ar}), 119.7 (CH_{ar}), 123.6 (CH_{ar}), 125.8 (CH_{ar}), 128.4 (C_{ar}), 135.9 (C_{ar}), 136.1 (C_{ar}), 150.2 (*C*O$_2$Bu-*t*), 175.7 (*C*O$_2$Me)
4g		67 A 3 h[g]	0.74 (d, 3 H, *J* = 6.6, CH_3), 0.82 (d, 3 H, *J* = 6.6, CH_3), 1.23–1.41 (m, 2 H, C*H*$_2$CHN), 1.44–1.58 [m, 1 H, C*H*(CH_3)$_2$], 1.65 (s, 9 H, *t*-C_4H_9), 2.46 (s, 1 H, NH), 3.21–3.30 (m, 4 H, CH_3O, CHN), 4.12 (d, 1 H, *J* = 14.7, CH_2N), 4.24 (d, 1 H, *J* = 14.7, CH_2N), 7.11–7.28 (m, 2 H, CH_{ar}), 7.35–7.43 (m, 1 H, CH_{ar}), 7.98 (d, 1 H, *J* = 8.1, CH_{ar})	22.3 (CH_3), 23.2 (CH_3), 25.1 [*C*H(CH_3)$_2$], 28.6 [(*C*H$_3$)$_3$C], 43.5 (*C*H$_2$CHN), 44.7 (CH_2N), 51.8 (CH_3O), 58.7 (CHN), 85.2 [*C*(CH_3)$_3$], 102.8 (C_{ar}–Br, 116.1 (CH_{ar}), 119.8 (CH_{ar}), 123.7 (CH_{ar}), 125.8 (CH_{ar}), 128.4 (C_{ar}), 135.8 (C_{ar}), 135.9 (C_{ar}), 150.2 (*C*O$_2$Bu-*t*), 176.7 (*C*O$_2$Me)

Table 1 (*S*)-*N*-(*o*-Bromobenzyl)amino Esters and Heterocyclic Analogues **4** and **5** Prepared (continued)

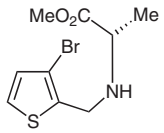
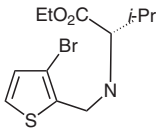
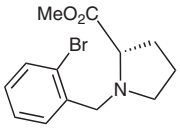
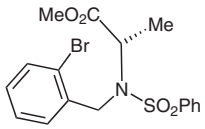
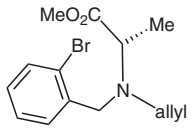
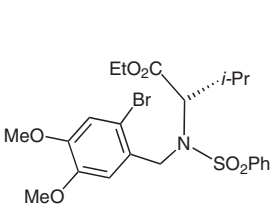
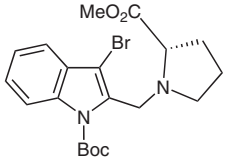
No.	Product[a]	Yield (%) Method Time	^{1}H NMR ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ, *J* (Hz)
4h		65 A 3 h[h]	1.26 (d, 3 H, *J* = 7.0, C*H*$_3$CH), 1.99 (s, 1 H, NH), 3.35 (q, 1 H, *J* = 7.0, CHN), 3.66 (s, 3 H, CH_3O), 3.76 (d, 1 H, *J* = 14.6, CH_2N), 3.91 (d, 1 H, *J* = 14.6, CH_2N), 6.84 (d, 1 H, *J* = 5.3, CH_{ar}), 7.13 (d, 1 H, *J* = 5.3, CH_{ar})	19.1 (*C*H$_3$CH), 45.6 (CH_2N), 51.9 (CH_3O), 55.6 (CHN), 108.6 (C_{ar}–Br), 124.7 (CH_{ar}), 129.9 (CH_{ar}), 138.2 (C_{ar}), 175.7 (*C*O$_2$Me)
4i		89 A 3 h[i]	0.89 (d, 6 H, *J* = 6.8, [C*H*$_3$)$_2$CH], 1.22 (t, 3 H, *J* = 7.1, C*H*$_3$CH$_2$O), 1.82–1.91 [m, 2 H, C*H*(CH$_3$)$_2$, NH], 2.97 (d, 1 H, *J* = 5.9, CHN), 3.86 (d, 1 H, *J* = 14.**7**, CH_2N), 3.94 (d, 1 H, *J* = 14.7, CH_2N), 4.13 (q, 2 H, *J* = 7.1, OC*H*$_2$CH$_3$), 6.84 (d, 1 H, *J* = 5.3, CH_{ar}), 7.13 (d, 1 H, *J* = 5.3, CH_{ar})	14.7 (*C*H$_3$CH$_2$O), 18.8 (CH_3), 19.7 (CH_3), 32.1 [*C*H(CH$_3$)$_2$], 46.8 (CH_2N), 60.9 (CH_2O), 66.6 (CHN), 108.6 (C_{ar}–Br), 125.0 (CH_{ar}), 130.2 (CH_{ar}), 139.3 (C_{ar}), 175.2 (*C*O$_2$Et)
5a		71 B 5 h[j]	1.64–1.96 (m, 4 H, 2 proline CH_2), 2.29–2.35 (m, 1 H, proline CH_2N), 2.91–2.92 (m, 1 H, proline CH_2N), 3.19–3.24 (m, 1 H, CHN), 3.48 (s, 3 H, OCH_3), 3.61 (d, 1 H, *J* = 14.0, CH_2N), 3.79 (d, 1 H, *J* = 14.0, CH_2N), 6.90–6.93 (m, 1 H, CH_{ar}), 7.06–7.11 (m, 1 H, CH_{ar}), 7.31–7.35 (m, 2 H, CH_{ar})	23.3 (CH_2), 29.3 (CH_2), 51.7 (CH_3O), 53.3 (CH_2N), 57.6 (CH_2N), 65.4 (CHN), 124.2 (C_{ar}–Br), 127.3 (CH_{ar}), 128.4 (CH_{ar}),131.0 (CH_{ar}),132.6 (CH_{ar}), 138.0 (C_{ar}), 174.6 (C=O)
5b		93 B 3 h[k]	1.21 (d, 3 H, *J* = 7.2, CH_3), 3.34 (s, 3 H, CH_3O), 3.34 (q, 1 H, *J* = 7.2, CHN), 4.51 (d, 1 H, *J* = 17.8, CH_2N), 4.62 (d, 1 H, *J* = 17.8, CH_2N), 7.02–7.08 (m, 1 H, CH_{ar}), 7.19–7.28 (m, 1 H, CH_{ar}), 7.41–7.62 (m, 5 H, CH_{ar}), 7.76–7.79 (m, 2 H, CH_{ar})	17.1 (CH_3), 49.6 (CH_2N), 52.5 (CH_3O), 55.9 (CHN), 122.5 (C_{ar}–Br), 127.8 (2 CH_{ar}), 128.9 (CH_{ar}), 129.2 (CH_{ar}), 129.4 (2 CH_{ar}), 128.0 (CH_{ar}), 132.8 (CH_{ar}), 133.3 (CH_{ar}), 137.4 (C_{ar}), 139.8 (C_{ar}), 171.7 (C=O)
5c		87 C1 8 h[l]	1.34 (d, 3 H, *J* = 7.2, CH_3), 3.20–3.35 (m, 2 H, NC*H*$_2$CH), 3.63 (q, 1 H, *J* = 7.2, CHN), 3.74 (s, 3 H, CH_3O), 3.84 (d, 1 H, *J* = 16.4, CH_2N), 3.90 (d, 1 H, *J* = 16.4, CH_2N), 5.11 (dd, 1 H, *J* = 10.1, 1.4, C*H*$_2$=CH), 5.23 (dd, 1 H, *J* = 17.2, 1.6, C*H*$_2$=CH), 5.77–5.90 (m, 1 H, C*H*=CH$_2$), 7.08–7.13 (m, 1 H, CH_{ar}), 7.28–7.33 (m, 1 H, CH_{ar}), 7.51–7.63 (m, 2 H, CH_{ar})	15.1 (CH_3), 51.3 (CH_3O), 53.9 (CH_2N), 54.2 (CH_2N), 57.4 (CHN), 117.2 (*C*H$_2$=CH), 123.9 (C_{ar}–Br), 127.2 (CH_{ar}), 128.1 (CH_{ar}), 130.1 (CH_{ar}), 132.5 (CH_{ar}), 136.4 (*C*H=CH$_2$), 139.2 (C_{ar}), 188.2 (C=O)
5d		79 B 3 h[m]	0.89–0.94 [m, 6 H, (C*H*$_3$)$_2$CH], 1.14 (t, 3 H, *J* = 7.1, C*H*$_3$CH$_2$O), 2.04–2.09 [m, 1 H, C*H*(CH$_3$)$_2$], 3.73–3.86 (m, 2 H, OC*H*$_2$CH$_3$), 3.88 (s, 3 H, CH_3O), 3.91 (s, 3 H, CH_3O), 4.22 (d, 1 H, *J* = 10.1, CHN), 4.64 (d, 1 H, *J* = 17.0, CH_2N), 5.06 (d, 1 H, *J* = 17.0, CH_2N), 6.99 (s, 1 H, CH_{ar}), 7.35 (s, 1 H, CH_{ar}), 7.52–7.66 (m, 3 H, CH_{ar}), 7.89 (d, 2 H, *J* = 7.9, CH_{ar})	13.8 (*C*H$_3$CH$_2$O), 19.4 (CH_3), 20.1 (CH_3), 28.7 [*C*H(CH$_3$)$_2$], 48.6 (CH_2N), 55.9 (CH_3O), 56.1 (CH_3O), 60.6 (O*C*H$_2$CH$_3$), 66.3 (CHN), 112.5 (C_{ar}–Br), 113.1 (CH_{ar}), 114.9 (CH_{ar}), 127.2 (2 CH_{ar}), 128.7 (2 CH_{ar}), 128.8 (C_{ar}), 132.7 (CH_{ar}), 139.6 (C_{ar}), 148.4 (C_{ar}), 148.6 (C_{ar}), 170.2 (C=O)
5e		86 B 2 h[n]	1.75 (s, 9 H, *t*-C$_4$H$_9$), 1.91–2.20 (m, 4 H, 2 CH_2), 2.64–2.76 (m, 1 H, proline NCH_2), 3.18–3.29 (m, 1 H, proline NCH_2), 3.42–3.47 (m, 1 H, CHN), 3.53 (s, 3 H, CH_3O), 4.34 (d, 1 H, *J* = 13.6, CH_2N), 4.51 (d, 1 H, *J* = 13.6, CH_2N), 7.32–7.39 (m, 2 H, CH_{ar}), 7.56–7.64 (m, 1 H, CH_{ar}), 8.07(dd, 1 H, *J* = 0.8, 8.4, CH_{ar})	23.8 (CH_2), 28.5 [(*C*H$_3$)$_3$C], 30.1 (CH_2), 48.5 (CH_2N), 51.8 (CH_3O), 53.6 (CH_2N), 64.3 (CHN), 84.6 [*C*(CH$_3$)$_3$], 102.2 (C_{ar}–Br), 115.5 (CH_{ar}), 119.8 (CH_{ar}), 123.3 (CH_{ar}), 125.6 (CH_{ar}), 128.2 (C_{ar}), 134.7 (C_{ar}), 136.2 (C_{ar}), 150.0 (*C*O$_2$Bu-*t*), 174.9 (*C*O$_2$Me)

Table 1 (*S*)-*N*-(*o*-Bromobenzyl)amino Esters and Heterocyclic Analogues **4** and **5** Prepared (continued)

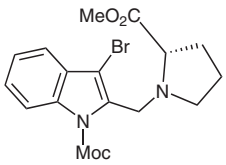
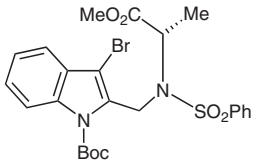
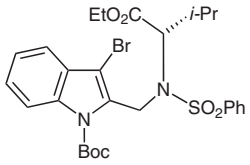
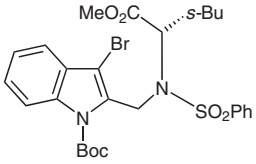
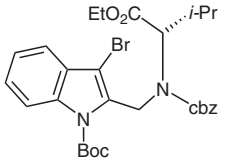
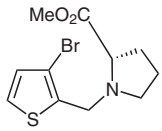
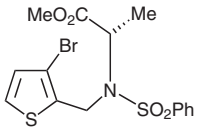
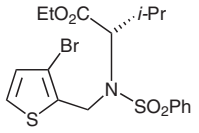
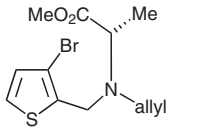
No.	Product[a]	Yield (%) Method Time	^{1}H NMR ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ, *J* (Hz)
5f		87 B 2 h[o]	1.67–2.06 (m, 4 H, proline CH_2), 2.52–2.60 (m, 1 H, proline NCH_2), 3.01–3.08 (m, 1 H, proline NCH_2), 3.29–3.34 (m, 1 H, CHN), 3.39 (s, 3 H, CH_3O), 3.97 (s, 3 H, CH_3O), 4.19 (d, 1 H, *J* = 13.6, CH_2N), 4.29 (d, 1 H, *J* = 13.6, CH_2N), 7.18–7.30 (m, 2 H, CH_{ar}), 7.43 (m, 1 H, CH_{ar}), 7.99 (dd, 1 H, *J* = 8.4, 0.8, CH_{ar})	23.6 (proline CH_2), 30.1 (proline CH_2), 49.2 (CH_2N), 51.9 (CH_3O), 53.9 (CH_2N), 54.3 (CH_3O), 65.1 (CHN), 103.1 (C_{ar}–Br), 115.9 (CH_{ar}), 119.9 (CH_{ar}), 123.8 (CH_{ar}), 126.0 (CH_{ar}), 128.4 (C_{ar}), 134.6 (C_{ar}), 136.1 (C_{ar}), 152.0 (NCO_2Me), 174.8 (CO_2Me)
5g		79 B 4 h[p]	1.38 (d, 3 H, *J* = 7.2, CH_3), 1.46 (s, 9 H, *t*-C_4H_9), 3.48 (s, 3 H, CH_3O), 4.22 (q, 1 H, *J* = 7.2, CHN), 4.77 (d, 1 H, *J* = 14.4, CH_2N), 4.87 (d, 1 H, *J* = 14.4, CH_2N), 6.88–7.09 (m, 5 H, CH_{ar}), 7.19–7.22 (m, 1 H, CH_{ar}), 7.39–7.42 (m, 2 H, CH_{ar}), 7.53–7.56 (m, 1 H, CH_{ar})	16.5 (CH_3), 28.6 [$(CH_3)_3C$], 45.2 (CH_2N), 52.7 (CH_3O), 58.8 (CHN), 85.3 [$C(CH_3)_3$], 105.3 (C_{ar}–Br), 115.7 (CH_{ar}), 120.1 (CH_{ar}), 123.6 (CH_{ar}), 126.3 (CH_{ar}), 127.5 (2 CH_{ar}), 128.1 (C_{ar}), 128.4 (2 CH_{ar}), 131.0 (C_{ar}), 132.2 (CH_{ar}), 135.7 (C_{ar}), 140.6 (C_{ar}), 149.6 (CO_2Bu-*t*), 172.1 (CO_2Me)
5h		68 B 4 h[q]	0.99 (d, 3 H, *J* = 6.4, CH_3), 1.18 (d, 3 H, *J* = 6.7, CH_3), 1.32 (t, 3 H, *J* = 7.1, CH_3CH_2O), 1.66 (s, 9 H, *t*-C_4H_9), 2.32–2.58 [m, 1 H, $CH(CH_3)_2$], 4.17–4.25 (m, 2 H, OCH_2CH_3), 4.42 (d, 1 H, *J* = 11.1, CHN), 4.84 (d, 1 H, *J* = 13.8, CH_2N), 5.16 (d, 1 H, *J* = 13.8, CH_2N), 6.93–6.98 (m, 2 H, CH_{ar}), 7.16–7.41 (m, 6 H, CH_{ar}), 7.81–7.84 (m, 1 H, CH_{ar})	14.5 (CH_3CH_2), 20.1 [$(CH_3)_2CH$], 20.3 [$(CH_3)_2CH$], 27.9 [$CH(CH_3)_3$], 28.6 [$(CH_3)_3C$], 41.5 (CH_2N), 61.4 (CH_2O), 66.9 (CHN), 85.2 [$C(CH_3)_3$], 106.2 (C_{ar}–Br), 115.7 (CH_{ar}), 119.9 (CH_{ar}), 123.4 (CH_{ar}), 126.2 (CH_{ar}), 127.2 (2 CH_{ar}), 127.8 (C_{ar}), 128.1 (2 CH_{ar}), 130.2 (C_{ar}), 131.9 (CH_{ar}), 135.7 (C_{ar}), 140.9 (C_{ar}), 149.6 (CO_2Bu-*t*), 169.9 (CO_2Et)
5i		74 B 4 h[r]	0.84–0.90 (m, 6 H, 2 CH_3), 0.99–1.11 (m, 1 H, $CH_3CHC_2H_5$), 1.59 (s, 9 H, *t*-C_4H_9), 1.79–2.07 (m, 2 H, CH_2CH_3), 3.64 (s, 3 H, CH_3O), 4.41 (d, 1 H, *J* = 10.9, CHN), 4.85 (d, 1 H, *J* = 19.9, CH_2N), 5.00 (d, 1 H, *J* = 19.9, CH_2N), 6.89–6.95 (m, 2 H, CH_{ar}), 6.93–7.36 (m, 6 H, CH_{ar}), 7.76 (d, 1 H, *J* = 8.2, CH_{ar})	11.3 (CH_3CH_2), 16.0 (CH_3), 25.3 (CH_2CH_3), 28.1 [$(CH_3)_3C$], 33.7 ($CH_3CHC_2H_5$), 41.4 (CH_2N), 51.8 (CH_3O), 65.5 (CHN), 84.8 [$C(CH_3)_3$], 105.7 (C_{ar}–Br), 115.3 (CH_{ar}), 119.5 (CH_{ar}), 123.0 (CH_{ar}), 125.8 (CH_{ar}), 126.9 (2 CH_{ar}), 127.5 (C_{ar}), 127.8 (2 CH_{ar}), 129.9 (C_{ar}), 131.6 (CH_{ar}), 135.4 (C_{ar}), 140.4 (C_{ar}), 149.2 (CO_2Bu-*t*), 170.0 (CO_2Me)
5j		95 C2 8 h[s]	–	14.3 [$(CH_3)_2CH$], 14.6 [$(CH_3)_2CH$], 19.4 (CH_3CH_2), 28.5 [$(CH_3)_3C$] 32.4 [$CH(CH_3)_2$], 45.1 (CH_2N), 60.9 (CH_2O), 64.8 (CHN), 67.9 (CH_2O), 84.9 [$C(CH_3)_3$], 92.4 (C_{ar}–Br), 115.9 (CH_{ar}), 119.9 (CH_{ar}), 123.6 (CH_{ar}), 126.2 (CH_{ar}), 127.6 (C_{ar}), 128.3 (CH_{ar}), 128.7 (2 CH_{ar}), 129.1 (2 CH_{ar}), 132.1 (C_{ar}), 137.3 (C_{ar}), 138.4 (C_{ar}), 149.9 (CO_2Bu-*t*), 156.4 ($CO_2C_7H_7$), 171.1 (CO_2Et)
5k		78 B 3 h[t]	1.75–1.91 (m, 4 H, proline CH_2), 2.49–2.53 (m, 1 H, proline CH_2N), 3.07–4.00 (m, 1 H, proline CH_2N), 3.31–3.36 (m, 1 H, CHN), 3.64 (s, 3 H, CH_3O), 3.86 (d, 1 H, *J* = 14.5, CH_2N), 4.00 (d, 1 H, *J* = 14.5, CH_2N), 6.84 (d, 1 H, *J* = 5.3, CH_{ar}), 7.19 (d, 1 H, *J* = 5.3, CH_{ar})	23.6 (proline CH_2), 29.7 (proline CH_2), 51.3 (CH_2N), 52.2 (CH_3O), 53.4 (CH_2N), 64.7 (CHN), 110.0 (C_{ar}–Br), 125.7 (CH_{ar}), 130.0 (CH_{ar}), 136.6 (C_{ar}), 174.6 (CO_2Me)

Table 1 (*S*)-*N*-(*o*-Bromobenzyl)amino Esters and Heterocyclic Analogues **4** and **5** Prepared (continued)

No.	Product[a]	Yield (%) Method Time	^{1}H NMR ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ, *J* (Hz)
5l		63 B 3 h[u]	1.33 (d, 3 H, *J* = 7.4, C*H*$_3$CH), 3.42 (s, 3 H, CH_3O), 4.55–4.69 (m, 3 H, CH_2N, CHN), 6.79 (d, 1 H, *J* = 5.3, thiophene CH_{ar}), 7.18 (d, 1 H, *J* = 5.3, thiophene CH_{ar}), 7.41–7.53 (m, 3 H, CH_{ar}), 7.77–7.80 (m, 2 H, CH_{ar})	17.2 (*C*H$_3$CH), 44.5 (CH_2N), 52.6 (CH_3O), 55.7 (CHN), 109.8 (C_{ar}–Br), 126.6 (CH_{ar}), 127.8 (2 CH_{ar}), 129.4 (2 CH_{ar}), 129.8 (CH_{ar}), 133.3 (CH_{ar}), 136.9 (C_{ar}), 139.9 (C_{ar}), 171.8 (*C*O$_2$Me)
5m		67 B 3 h[v]	0.78 (d, 3 H, *J* = 6.6, CH_3), 0.82 (d, 3 H, *J* = 6.6, CH_3), 1.05 (t, 3 H, *J* = 7.2, C*H*$_3$CH$_2$O), 2.05–2.13 [m, 1 H, C*H*(CH_3)$_2$], 3.66–3.86 (m, 2 H, OC*H*$_2$CH$_3$), 4.03 (d, 1 H, *J* = 10.3, CHN), 4.61 (d, 1 H, *J* = 16.9, CH_2N), 5.07 (d, 1 H, *J* = 16.9, CH_2N), 6.79 (d, 1 H, *J* = 5.3, thiophene CH_{ar}), 7.18 (d, 1 H, *J* = 5.3, thiophene CH_{ar}), 7.34–7.52 (m, 3 H, CH_{ar}), 7.74–7.77 (m, 2 H, CH_{ar})	14.3 (*C*H$_3$CH$_2$O), 19.8 (CH_3), 20.1 (CH_3), 29.3 [*C*H(CH_3)$_2$], 43.8 (CH_2N), 61.1 (CH_2O), 66.3 (CHN), 110.5 (C_{ar}–Br), 127.0 (CH_{ar}), 127.9 (2 CH_{ar}), 129.2 (2 CH_{ar}), 129.6 (CH_{ar}), 133.1 (CH_{ar}), 136.8 (C_{ar}), 140.0 (C_{ar}), 170.8 (*C*O$_2$Et)
5n		87 C1 5 h[w]	1.26 (d, 3 H, *J* = 7.2, C*H*$_3$CH), 3.19 (dd, 1 H, *J* = 13.2, 6.9, NC*H*$_2$CH), 3.28 (dd, 1 H, *J* = 13.2, 5.4, NC*H*$_2$CH), 3.56 (q, 1 H, *J* = 7.2, CHN), 3.65 (s, 3 H, CH_3O), 3.80 (d, 1 H, *J* = 15.6, CH_2N), 3.87 (d, 1 H, *J* = 15.6, CH_2N), 5.04 (dd, 1 H, *J* = 10.2, 1.3, C*H*$_2$=CH), 5.16 (dd, 1 H, *J* = 17.2, 1.5, C*H*$_2$=CH), 5.68–5.82 (m, 1 H, C*H*=CH$_2$), 6.82 (d, 1 H, *J* = 5.3, CH_{ar}), 7.12 (d, 1 H, *J* = 5.3, CH_{ar})	15.3 (*C*H$_3$CH), 48.7 (CH_2N), 51.3 (CH_3O), 54.2 (CH_2N), 57.2 (CHN), 107.9 (C_{ar}–Br), 117.4 (*C*H$_2$=CH), 124.8 (CH_{ar}), 129.8 (CH_{ar}), 136.1 (*C*H=CH$_2$), 140.2 (C_{ar}), 174.1 (*C*O$_2$Me)

[a] Satisfactory microanalyses obtained for **4a**,**b**,**d**–**i** and **5a**–**n**: C ± 0.38; H ± 0.15; Br ± 0.47; N ± 0.20; S ± 0.32.
[b] $[\alpha]_D^{20}$ –26.9 (*c* = 1.15, CH_2Cl_2); + 8% N,N-dialkylation product.
[c] $[\alpha]_D^{20}$ –47.8 (*c* = 1, $CHCl_3$).
[d] $[\alpha]_D^{20}$ –10.2 (*c* = 2.25, CH_2Cl_2). MS (90 eV): *m*/*z* (%) = 210 (36), 208 (35), 128 (20), 57 (100), 41 (39), 29 (10); + 9% N,N-dialkylation product.
[e] $[\alpha]_D^{20}$ +20.8 (*c* = 0.5, CH_2Cl_2); + 12% N,N-dialkylation product.
[f] Reactant ratio 1:1; + 13% N,N-dialkylation product.
[g] $[\alpha]_D^{20}$ –3.28 (*c* = 1.4, CH_2Cl_2); reactant ratio **1**/**2** = 1:2; + 8% N,N-dialkylation product.
[h] $[\alpha]_D^{20}$ –28.96 (*c* = 1.25, CH_2Cl_2); + 11% N,N-dialkylation product.
[i] $[\alpha]_D^{20}$ –41.44 (*c* = 1.25, CH_2Cl_2). MS (90 eV): *m*/*z* (%) = 320 (M^+, 1.16), 248 (24), 246 (24), 192 (13), 190 (14), 177 (100), 175 (96), 96 (16), 55 (12), 45 (18), 43 (14), 29 (19), 28 (15), 27 (11), 18 (13).
[j] $[\alpha]_D^{20}$ –38.0 (*c* = 1, CH_2Cl_2).
[k] $[\alpha]_D^{20}$ –29.12 (*c* = 1.25, CH_2Cl_2); mp 90–92 °C.
[l] $[\alpha]_D^{20}$ –52.13 (*c* = 1.5, CH_2Cl_2). MS (90 eV): *m*/*z* (%) = 312 (M^+, 1.13), 254 (17), 252 (17), 214 (21), 212 (23), 171 (97), 169 (100), 94 (20), 91 (29), 90 (50), 99 (41), 57 (18), 56 (35), 55 (27), 44 (17), 43 (29), 42 (21), 41 (28), 39 (15), 29 (18), 28 (22), 18 (17), 15 (29).
[m] $[\alpha]_D^{20}$ –19.9 (*c* = 1, CH_2Cl_2).
[n] $[\alpha]_D^{20}$ –32.0 (*c* = 1, CH_2Cl_2).
[o] $[\alpha]_D^{20}$ –14.5 (*c* = 1, CH_2Cl_2).
[p] $[\alpha]_D^{20}$ –21.6 (*c* = 1, MeOH); mp 115–117 °C. MS (90 eV): *m*/*z* = 311 (22), 309 (23), 210 (16), 208 (16), 129 (14), 128 (27), 77 (35), 57 (100), 56 (67), 41 (38), 29 (20), 18 (11).
[q] $[\alpha]_D^{20}$ –94.8 (*c* = 1.1, CH_2Cl_2); mp 109–111 °C. MS (90 eV): *m*/*z* = 397 (10), 395 (9), 353 (28), 351 (29), 210 (20), 208 (21), 129 (15), 128 (29), 77 (34), 57 (100), 43 (10), 41 (40), 29 (30), 18 (25).
[r] $[\alpha]_D^{20}$ –73.8 (*c* = 1, CH_2Cl_2); mp 113–115 °C.
[s] $[\alpha]_D^{20}$ –24.1 (*c* = 1, $CHCl_3$).
[t] $[\alpha]_D^{20}$ –62.0 (*c* = 1, CH_2Cl_2).
[u] $[\alpha]_D^{20}$ –36.3 (*c* = 1, CH_2Cl_2).
[v] $[\alpha]_D^{20}$ –47.8 (*c* = 1, $CHCl_3$).
[w] $[\alpha]_D^{20}$ –46.0 (*c* = 1.25, CH_2Cl_2).

Table 2 Condensed Tetrahydropyridones **6** Prepared

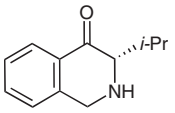
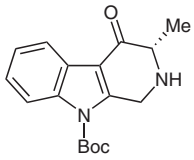
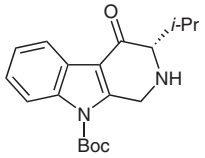
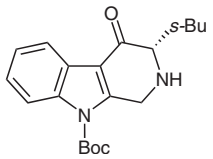
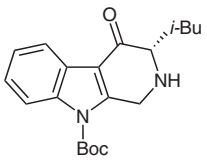
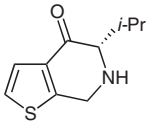
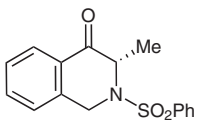
No.	Product[a]	Yield (%) BuLi Precursor	^{1}H NMR ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ, *J* (Hz)
6a		23[b] *n*-BuLi **4b**	0.89 (d, 3 H, *J* = 6.8, CH_3), 1.00 (d, 3 H, *J* = 6.9, CH_3), 2.21 (br s, 1 H, NH), 2.44–2.50 [m, 1 H, C*H*(CH_3)$_2$], 3.19 (d, 1 H, *J* = 4.8, CHN), 4.05 (d, 1 H, *J* = 16.5, CH_2N), 4.13 (d, 1 H, *J* = 16.5, CH_2N), 7.12 (d, 1 H, *J* = 7.6, CH_{ar}), 7.25–7.30 (m, 1 H, CH_{ar}), 7.38–7.44 (m, 1 H, CH_{ar}), 7.95 (dd, 1 H, *J* = 7.8, 1.1, CH_{ar})	17.6 (CH_3), 19.8 (CH_3), 27.2 [*C*H(CH_3)$_2$], 46.7 (CH_2N), 68.7 (CHN), 125.6 (CH_{ar}), 127.1 (CH_{ar}), 127.2 (CH_{ar}), 131.3 (C_{ar}), 133.3 (CH_{ar}), 143.7 (C_{ar}) 197.1 (C=O)
6b		52[c] *t*-BuLi **4d**	1.35 (d, 3 H, *J* = 6.9, CH_3), 1.63 (s, 9 H, *t*-C_4H_9), 1.98 (s, 1 H, NH), 3.45 (q, 1 H, *J* = 6.9, CHN), 4.35 (d, 1 H, *J* = 19.0, CH_2N), 4.57 (d, 1 H, *J* = 19.0, CH_2 N), 7.21–7.32 (m, 2 H, CH_{ar}), 7.98–8.05 (m, 1 H, CH_{ar}), 8.11–8.20 (m, 1 H, CH_{ar})	15.4 (CH_3), 28.2 [(*C*H$_3$)$_3$C], 43.9 (CH_2N), 57.6 (CHN), 85.8 [*C*(CH_3)$_3$), 115.0 (C_{ar}), 115.2 (CH_{ar}), 121.5 (CH_{ar}), 124.6 (CH_{ar}), 125.1 (CH_{ar}), 125.6 (C_{ar}), 135.6 (C_{ar}), 150.2 (*C*O$_2$Bu-*t*), 151.1 (C_{ar}), 196.3 (C=O)
6c		61[d] *t*-BuLi **4e**	0.95 (d, 3 H, *J* = 6.8, CH_3), 1.01 (d, 3 H, *J* = 6.9, CH_3), 1.63 (s, 9 H, *t*-C_4H_9), 2.06 (s, 1 H, NH), 2.36–2.49 [m, 1 H, C*H*(CH_3)$_2$], 3.10 (d, 1 H, *J* = 5.5, CHN), 4.29 (d, 1 H, *J* = 19.0, CH_2N), 4.54 (d, 1 H, *J* = 19.0, CH_2N), 7.25–7.28 (m, 2 H, CH_{ar}), 8.06–8.13 (m, 1 H, CH_{ar}), 8.17–8.21 (m, 1 H, CH_{ar})	18.5 (CH_3), 20.3 (CH_3), 27.1 [*C*H(CH_3)$_2$], 28.6 [(*C*H$_3$)$_3$C], 44.2 (CH_2N), 67.6 (CHN), 86.1 [*C*(CH_3)$_3$], 115.6 (CH_{ar}), 116.1 (C_{ar}), 121.9 (CH_{ar}), 124.9 (CH_{ar}), 125.5 (CH_{ar}), 126.1 (C_{ar}), 136.0 (C_{ar}), 149.9 (*C*O$_2$Bu-*t*), 151.3 (C_{ar}), 196.2 (C=O)
6d		41[e] *n*-BuLi **4f**	0.88 (t, 3 H, *J* = 7.4, C*H*$_3$CH$_2$), 0.98 (d, 3 H, *J* = 6.9, CH_3), 1.15–1.59 (m, 2 H, C*H*$_2$CH$_3$), 1.63 (s, 9 H, *t*-C_4H_9), 1.90 (br s, 1 H, NH), 2.11–2.24 (m, 1 H, CH), 3.16 (d, 1 H, *J* = 5.3, CHN), 4.28 (d, 1 H, *J* = 19.0, CH_2N), 4.54 (d, 1 H, *J* = 19.0, CH_2N), 7.19–7.28 (m, 2 H, CH_{ar}), 8.02–8.10 (m, 1 H, CH_{ar}), 8.14–8.23 (m, 1 H, CH_{ar})	12.3 (*C*H$_3$CH$_2$), 16.8 (CH_3), 25.6 (*C*H$_2$CH$_3$), 28.6 [(*C*H$_3$)$_3$C], 33.8 (CH), 44.2 (CH_2N), 67.1 (CHN), 86.1 [*C*(CH_3)$_3$], 115.6 (CH_{ar}), 116.2 (C_{ar}), 121.9 (CH_{ar}), 124.9 (CH_{ar}), 125.4 (CH_{ar}), 126.1 (C_{ar}), 136.0 (C_{ar}), 150.2 (*C*O$_2$Bu-*t*), 151.2 (C_{ar}), 196.4 (C=O)
6e		60[f] *n*-BuLi **4g** 62 *t*-BuLi **4g**	1.14 (d, 3 H, *J* = 6.5, CH_3), 1.17 (d, 3 H, *J* = 6.6, CH_3), 1.63–1.71 [m, 1 H, C*H*(CH_3)$_2$], 1.87 (s, 9 H, *t*-C_4H_9), 1.89–2.12 (m, 2 H, C*H*$_2$CHN), 2.21 (s, 1 H, NH), 3.56–3.61 (m, 1 H, CHN), 4.53 (d, 1 H, *J* = 19.1, CH_2N), 4.65 (d, 1 H, *J* = 19.1, CH_2N), 7.43–7.53 (m, 2 H, CH_{ar}), 7.26–7.29 (m, 1 H, CH_{ar}), 7.36–8.39 (m, 1 H, CH_{ar})	21.6 (CH_3), 23.4 (CH_3), 25.0 [*C*H(CH_3)$_2$), 28.2 [(*C*H$_3$)$_3$C], 38.0 (*C*H$_2$CHN), 43.1 (CH_2N), 59.9 (CHN), 85.7 [*C*(CH_3)$_3$], 115.0 (C_{ar}), 115.2 (CH_{ar}), 121.4 (CH_{ar}), 124.5 (CH_{ar}), 125.0 (CH_{ar}), 125.7 (C_{ar}), 135.6 (C_{ar}), 149.4 (*C*O$_2$Bu-*t*), 150.8 (C_{ar}), 196.9 (C=O)
6f		23[g] *t*-BuLi **4i**	0.89 (d, 3 H, *J* = 6.8, CH_3), 1.00 (d, 3 H, *J* = 6.9, CH_3), 2.30 (br s, 1 H, NH), 2.42–2.50 [m, 1 H, C*H*(CH_3)$_2$], 3.10 (d, 1 H, *J* = 4.9, CHN), 4.11 (d, 1 H, *J* = 17.2, CH_2N), 4.26 (d, 1 H, *J* = 17.2, CH_2N), 7.03 (d, 1 H, *J* = 5.2, CH_{ar}), 7.33 (d, 1 H, *J* = 5.2, CH_{ar}),	18.1 (CH_3), 20.3 (CH_3), 27.1 [*C*H(CH_3)$_2$], 44.0 (CH_2N), 68.1 (CHN), 123.9 (CH_{ar}), 125.3 (CH_{ar}), 136.7 (C_{ar}), 155.2 (C_{ar}), 193.5 (C=O)
6g		12[h] *n*-BuLi **5b**	1.35 (d, 3 H, *J* = 7.4, CH_3), 4.05 (q, 1 H, *J* = 7.4, CHN), 4.60 (d, 1 H, *J* = 17.9, CH_2N), 4.93 (d, 1 H, *J* = 17.9, CH_2N), 7.10–7.20 (m, 4 H, CH_{ar}), 7.27–7.44 (m, 2 H, CH_{ar}), 7.52–7.56 (m, 2 H, CH_{ar}), 7.63–7.66 (m, 1 H, CH_{ar})	15.4 (CH_3), 43.0 (CH_2N), 58.3 (CHN), 126.1 (CH_{ar}), 127.4 (2 CH_{ar}), 127.8 (CH_{ar}), 128.4 (CH_{ar}), 129.1 (C_{ar}), 129.4 (2 CH_{ar}), 133.1 (CH_{ar}), 134.6 (CH_{ar}), 138.1 (C_{ar}), 139.4 (C_{ar}), 194.4 (C=O)

Table 2 Condensed Tetrahydropyridones **6** Prepared (continued)

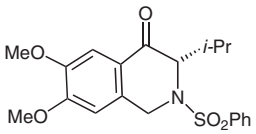
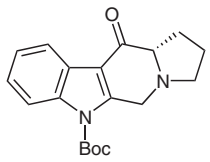
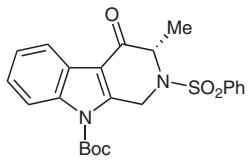
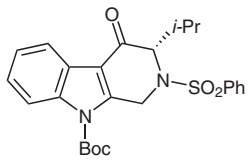
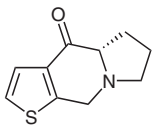
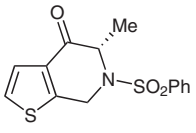
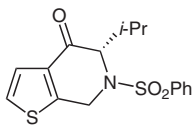
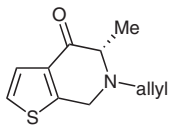
No.	Product[a]	Yield (%) BuLi Precursor	^{1}H NMR ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ, *J* (Hz)
6h		61[i] *t*-BuLi **5d**	0.92 [d, 3 H, *J* = 6.6, $(CH_3)_2CH$)], 1.09 [d, 3 H, *J* = 6.6, $(CH_3)_2CH$], 1.91–2.03 [m, 1 H, $CH(CH_3)_2$], 3.73 (s, 3 H, CH_3O), 3.85 (s, 3 H, CH_3O), 3.97 (d, 1 H, *J* = 10.2, CHN), 4.54 (d, 1 H, *J* = 18.6, CH_2N), 4.90 (d, 1 H, *J* = 18.6, CH_2N), 6.46 (s, 1 H, CH_{ar}) 7.03 (s, 1 H, CH_{ar}), 7.14–7.28 (m, 3 H, CH_{ar}), 7.49–7.52 (m, 2 H, CH_{ar})	19.0 (CH_3), 20.6 (CH_3), 27.9 [$CH(CH_3)_2$], 43.2 (CH_2N), 56.0 (CH_3O), 56.2 (CH_3O), 67.3 (CHN), 106.7 (CH_{ar}), 108.2 (CH_{ar}), 122.6 (C_{ar}), 126.9 (2 CH_{ar}), 128.8 (2 CH_{ar}), 132.2 (C_{ar}), 132.6 (CH_{ar}), 139.3 (C_{ar}), 148.5 (C_{ar}), 154.1 (C_{ar}), 191.7 (C=O)
6i		54[j] *n*-BuLi **5e** 59 *t*-BuLi **5e** 23 *n*-BuLi **5e** at –78 °C	1.64 (s, 9 H, *t*-C_4H_9), 1.78–1.84 (m, 2 H, proline CH_2), 2.04–2.31 (m, 2 H, proline CH_2), 2.59–2.63 (m, 1 H, CHN), 3.05–3.24 (m, 2 H, proline CH_2N), 4.03 (dd, 1 H, *J* = 18.3, 2.6, CH_2N), 4.69 (d, 1 H, *J* = 18.3, CH_2N), 7.25–7.28 (m, 2 H, CH_{ar}), 7.99–8.03 (m, 1 H, CH_{ar}), 8.15–8.17 (m, 1 H, CH_{ar})	24.2 (proline CH_2), 26.9 (proline CH_2), 30.5 [$(CH_3)_3C$], 52.7 (CH_2N), 55.5 (CH_2N), 70.0 (CHN), 88.2 [$C(CH_3)_3$], 117.6 (CH_{ar}), 118.4 (C_{ar}), 123.9 (CH_{ar}), 126.9 (CH_{ar}), 127.4 (CH_{ar}), 127.8 (C_{ar}), 128.3 (C_{ar}), 138.3 (C_{ar}), 151.9 (CO_2Bu-*t*), 196.7 (C=O)
6j		81[k] *n*-BuLi **5g**	1.34 (d, 3 H, *J* = 7.3, CH_3), 1.68 (s, 9 H, *t*-C_4H_9), 4.60 (q, 1 H, *J* = 7.3, CHN), 4.66 (d, 1 H, *J* = 19.8, CH_2N), 4.56 (d, 1 H, *J* = 19.8, CH_2N), 7.21–7.26 (m, 5 H, CH_{ar}), 7.61–7.64 (m, 2 H, CH_{ar}), 7.93–7.98 (m, 2 H, CH_{ar})	16.0 (CH_3), 28.6 [$(CH_3)_3C$], 41.1 (CH_2N), 58.1 (CHN), 87.1 [$C(CH_3)_3$], 114.3 (C_{ar}), 115.5 (CH_{ar}), 121.8 (CH_{ar}), 125.2 (C_{ar}), 125.3 (CH_{ar}), 126.1 (CH_{ar}), 127.1 (2 CH_{ar}), 129.5 (2 CH_{ar}), 133.3 (CH_{ar}) 135.9 (C_{ar}), 139.4 (C_{ar}), 145.5 (C_{ar}), 149.5 (CO_2Bu-*t*), 192.2 (C=O)
6k		65[l] *n*-BuLi **5h** 72 *t*-BuLi **5h**	0.94 (d, 3 H, *J* = 6.6, CH_3), 1.10 (d, 3 H, *J* = 6.6, CH_3), 1.68 (s, 9 H, *t*-C_4H_9), 1.89–2.01 [m, 1 H, $CH(CH_3)_2$], 4.01 (d, 1 H, *J* = 10.0, CHN), 4.67 (d, 1 H, *J* = 20.4, CH_2N), 5.53 (d, 1 H, *J* = 20.4, CH_2N), 7.14–7.24 (m, 5 H, CH_{ar}), 7.55–7.58 (m, 2 H, CH_{ar}), 7.90–7.95 (m, 2 H, CH_{ar})	19.5 (CH_3), 21.3 (CH_3), 28.6 [$(CH_3)_3C$], 29.1 [$CH(CH_3)_2$], 42.2 (CH_2N), 68.2 (CHN), 87.1 [$C(CH_3)_3$], 115.0 (C_{ar}), 115.4 (CH_{ar}), 121.8 (CH_{ar}), 125.0 (CH_{ar}), 125.3 (C_{ar}), 125.8 (CH_{ar}), 127.1 (2 CH_{ar}), 129.3 (2 CH_{ar}), 133.1 (CH_{ar}), 135.8 (C_{ar}), 139.3 (C_{ar}), 144.9 (C_{ar}), 149.5 (CO_2Bu-*t*), 192.2 (C=O)
6l		63[m] *n*-BuLi **5k**	1.75–1.86 (m, 2 H, proline CH_2), 2.05–2.13 (m, 2 H, proline CH_2), 2.52–2.61 (m, 1 H, CHN), 3.04–3.10 (m, 2 H, proline CH_2N), 3.83 (dd, 1 H, *J* = 15.9, 2.3, CH_2N), 4.29 (d, 1 H, *J* = 15.9, CH_2N), 7.06 (d, 1 H, *J* = 5.2, CH_{ar}), 7.34 (d, 1 H, *J* = 5.2, CH_{ar})	22.3 (proline CH_2), 25.0 (proline CH_2), 50.6 (CH_2N), 53.5 (CH_2N), 69.0 (CHN), 124.3 (CH_{ar}), 124.8 (CH_{ar}), 136.7 (C_{ar}), 153.3 (C_{ar}), 192.5 (C=O)
6m		66[n] *n*-BuLi **5l**	1.37 (d, 3 H, *J* = 7.4, CH_3CH), 4.56 (q, 1 H, *J* = 7.4, CHN), 4.62 (d, 1 H, *J* = 18.5, CH_2N), 5.18 (d, 1 H, *J* = 18.5, CH_2N), 6.95–6.99 (m, 2 H, CH_{ar}), 7.20–7.37 (m, 3 H, CH_{ar}), 7.54–7.57 (m, 2 H, CH_{ar})	17.0 (CH_3CH), 42.0 (CH_2N), 59.2 (CHN), 126.0 (CH_{ar}), 126.2 (CH_{ar}), 128.4 (2 CH_{ar}), 130.6 (2 CH_{ar}), 134.4 (CH_{ar}), 135.6 (C_{ar}), 140.2 (C_{ar}), 149.9 (C_{ar}), 191.0 (C=O)
6n		75[o] *t*-BuLi **5m**	0.94 (d, 3 H, *J* = 6.6, CH_3), 1.11 (d, 3 H, *J* = 6.6, CH_3), 1.56–2.10 [m, 1 H, $CH(CH_3)_2$], 3.95 (d, 1 H, *J* = 10.2, CHN), 4.60 (d, 1 H, *J* = 19.0, CH_2N), 5.19 (d, 1 H, *J* = 19.0, CH_2N), 6.90–6.94 (m, 2 H, CH_{ar}), 7.16–7.22 (m, 2 H, CH_{ar}), 7.28–7.33 (m, 1 H, CH_{ar}), 7.50–7.53 (m, 2 H, CH_{ar})	19.5 (CH_3), 20.2 (CH_3), 28.3 [$CH(CH_3)_2$], 41.9 (CH_2N), 68.1 (CHN), 124.8 (CH_{ar}), 125.0 (CH_{ar}), 127.2 (2 CH_{ar}), 129.3 (2 CH_{ar}), 133.2 (CH_{ar}), 135.2 (C_{ar}), 139.1 (C_{ar}), 148.3 (C_{ar}), 188.8 (C=O)

Table 2 Condensed Tetrahydropyridones **6** Prepared (continued)

No.	Product[a]	Yield (%) BuLi Precursor	^{1}H NMR ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ, *J* (Hz)
6o		53[p] *t*-BuLi **5n**	1.26 (d, 3 H, *J* = 7.1, C*H*$_3$CH), 3.21–3.24 (m, 2 H, NC*H*$_2$CH), 3.45 (q, 1 H, *J* = 7.1, CHN), 3.99 (d, 1 H, *J* = 17.1, CH$_2$N), 4.16 (d, 1 H, *J* = 17.1, CH$_2$N), 4.88–5.15 (m, 2 H, C*H*$_2$=CH), 5.73–5.82 (m, 1 H, C*H*=CH$_2$), 7.07 (d, 1 H, *J* = 5.2, CH$_{ar}$), 7.33 (d, 1 H, *J* = 5.2, CH$_{ar}$)	12.2 (*C*H$_3$CH), 45.8 (CH$_2$N), 56.3 (CH$_2$N), 62.8 (CHN), 118.9 (*C*H$_2$=CH), 123.9 (CH$_{ar}$), 124.6 (CH$_{ar}$), 134.4 (*C*H=CH$_2$), 151.4 (C$_{ar}$), 173.3 (C$_{ar}$), 193.5 (C=O)

[a] Satisfactory microanalyses obtained for **6a–m**: C ± 0.48; H ± 0.40; S ± 0.38. Exceptions: **6a**: C –0.58; **6b**: C –0.85; **6d**: H –0.57; **6h**: C –1.37.
[b] Plus 41% of the corresponding hydroxyisoquinoline **8** (R^3 = *n*-Bu); R_f 0.51 ($CHCl_3$–MeOH, 9:1).
[c] Plus 10% of the corresponding hydroxy-β-carboline **8** (R^3 = *t*-Bu); R_f 0.32 ($CHCl_3$–MeOH, 97:3); $[\alpha]_D^{20}$ +31.4 (*c* = 1, CH_2Cl_2).
[d] White solid; mp 168 °C; R_f 0.36 (CH_2Cl_2–acetone, 8:2); $[\alpha]_D^{20}$ –11.4 (*c* = 1, CH_2Cl_2). MS (90 eV): *m*/*z* (%) = 328 (M$^+$, 0.61), 229 (24), 201 (30), 157 (29), 129 (21), 128 (15), 72 (12), 57 (100), 55 (12), 43 (23), 41 (42), 39 (14), 29 (26), 28 (11), 27 (13).
[e] R_f 0.41 (CH_2Cl_2–acetone, 95:5); $[\alpha]_D^{20}$ –97.3 (*c* = 1, MeOH).
[f] White solid; mp 129–130 °C; R_f 0.50 (CH_2Cl_2–acetone, 95:5); $[\alpha]_D^{20}$ –9.3 (*c* = 1, CH_2Cl_2).
[g] Plus 18% of the debrominated starting material; R_f 0.26 (CH_2Cl_2–acetone, 95:5).
[h] Plus 46% of the alcohol **8** (R^3 = *n*-Bu). Use of *t*-BuLi gave no **6**, but 58% of the corresponding alcohol **8** (R^3 = *t*-Bu); R_f 0.25 (hexanes–EtOAc, 7:3).
[i] R_f 0.37 (hexanes–EtOAc, 1:1); $[\alpha]_D^{20}$ –44.0 (*c* = 1, CH_2Cl_2).
[j] Pale yellow solid; mp 143 °C; R_f 0.24 (CH_2Cl_2–acetone, 95:5); $[\alpha]_D^{20}$ +45.7 (*c* = 1, MeOH).
[k] R_f 0.69 (CH_2Cl_2–acetone, 95:5); ee >99.9% determined by HPLC (Chiracel OD; 0.5 mL/min, hexane–*i*-PrOH, 9:1); $[\alpha]_D^{20}$ –15.8 (*c* = 1, MeCN).
[l] R_f 0.2 (hexanes–EtOAc, 7:3); $[\alpha]_D^{20}$ –34.6 (*c* = 1, CH_2Cl_2).
[m] R_f 0.28 (CH_2Cl_2–acetone, 95:5).
[n] Plus 21% of the hydroxy product **8** (R^3 = *n*-Bu); white solid; mp 140–142 °C; R_f 0.84 (CH_2Cl_2–acetone, 95:5); $[\alpha]_D^{20}$ +24.8 (*c* = 1, CH_2Cl_2). MS (90 eV): *m*/*z* (%) = 307 (M$^+$, 1.17), 166 (53), 125 (39), 124 (100), 97 (36), 96 (56), 77 (47), 70 (18), 51 (27), 45 (19), 18 (15).
[o] R_f 0.26 (hexanes–EtOAc, 7:3); $[\alpha]_D^{20}$ –4.7 (*c* = 1, MeOH).
[p] Plus 22% of starting material; colorless oil; R_f 0.20 (hexanes–EtOAc, 7:3); $[\alpha]_D^{20}$ +31.3 (*c* = 1.15, CH_2Cl_2).

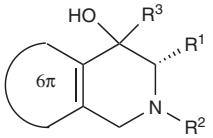
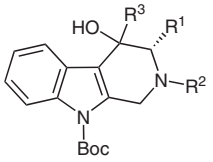
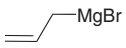
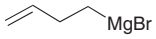
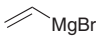
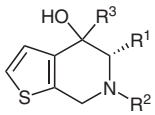
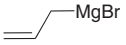
Since the chiral centre of the condensed dihydropyridones **6** is incorporated into a relatively rigid ring, an efficient asymmetric 1,2-induction can be expected in addition reactions to the adjacent carbonyl group. Thus, the incoming nucleophile should be directed opposite to the substituent R^1. Indeed, reaction with Grignard reagents gave the corresponding alcohols **8** as major diastereomers often in high diastereomeric ratios (Table 3, see also references 30 and 31). As expected, bulkier substituents R^1 are more effective than the methyl group (Table 3, compare **8c/8d**, **8f/8g**). In the case of the addition of homoallylmagnesium bromide to the methyl substituted dihydro-β-carbolinone **6b**, the two epimers **7f** and **8f** could be separated by column chromatography and characterized in pure form. In the other cases the major diastereomer was obtained in pure state by column chromatography. A similar effect of the size of the substituent R^1 on the stereoselectivity was observed when condensed dihydropyridones **6** were reduced with sodium borohydride or lithium aluminum hydride to condensed hydroxytetrahydropyridines **8** (R^3 = H, Table 4, Methods F, G). The *cis*-configuration of condensed hydroxytetrahydropyridines was proved with **8b** and **8l** by NOE effects showing the proximity of the substituent R^3 at position 4 and the H atom at the adjacent position 3. On the other hand, Grignard reactions and reductions of condensed dihydropyridones **6** [R^1/R^2 = (CH$_2$)$_3$] derived from proline gave the opposite diastereomers **7**, as found before with similar systems.[3,22,24,31]

The assignment of the reduction product of a 3-methyl-2-tosyl-1,2,3,4-tetrahydrobenzo[*h*]isoquinolin-4-one to the *trans*-series **7** by Gellert et al.[23] rather than to **8** seems to be questionable in light of our results. The authors owe further proof for the configuration of their product.

The NMR spectral data of compounds **7** and **8** prepared are listed in Table 5.

Blough et al. reported a halocyclization of racemic 4-allyl-1,2,3,4-tetrahydroisoquinoline in the presence of *N*-iodosuccinimide.[34] Interestingly, a five-membered ring was formed similar to **9** (R^1 = H) under kinetic control at 0–20 °C, which could be transformed into the six-membered product **10** (R^1 = H) by heating. Remarkably, the tetrahydro-β-carbolines **8c**, **8d**, **8e** gave the six-membered cyclization products **10** already at low temperatures (0–20 °C, Table 6, Method H). Obviously the substituent R^1 affects the outcome of the reaction. Possibly the bulk of the substituent R^1 hampers the formation of the five-membered ring thus directing the cyclization to the more spatial six-membered ring by 6-*endo-trig* mode. On the other hand, the iodocyclization of the thiophene derivative **8j** gave a separable mixture of the corresponding five-membered **9a** (27%) and the six-membered cyclization product **10a** (56%). The former could be transformed into the ring-expanded product **10a** by heating in THF at 60 °C for 3 hours (Method I) indicating that **9** can serve as intermediates for **10**. When lower homologous 4-vinyltetrahydro-β-carbolines **8h** and **8i** (R^3 = vinyl) were treated with *N*-io-

Table 3 Condensed 4-Alkyl-4-hydroxy-1,2,3,4-tetrahydropyridines **7** and **8** ($R^3 \neq H$) by Grignard Reaction

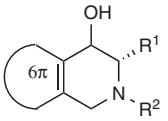
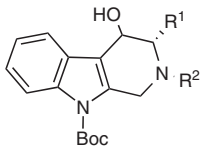
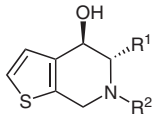
Product		R^2	R^1	R^3MgX	dr	Yield (%)[a]
						
7a		-$(CH_2)_3$-		EtMgBr	>95:5	74
8a		SO_2Ph	*i*-Pr		>95:5	53[b]
8b		H	Me	BnMgCl	76:24	58
8c		H	Me		82:18	63
8d		H	*i*-Pr		>95:5	67
8e		H	*s*-Bu		>95:5	81
8f/7f		H	Me		62:38	48[c]
8g		H	*i*-Pr		89:11	72
8h		H	Me		93:7	18[d]
8i		H	*i*-Pr		>95: 5	24[e]
7b		-$(CH_2)_3$-		EtMgBr	95:5	97[f]
7c		-$(CH_2)_3$-		PhMgBr	95:5	53[f]
8j		H	*i*-Pr		95:5	63

[a] Isolated yield after chromatography.
[b] Additional indole-deprotected product was obtained in 22%.
[c] Plus 26% starting material, diastereomers could be separated by flash chromatography.
[d] Plus 60% starting material.
[e] Plus 58% starting material.
[f] Racemic starting material was used.

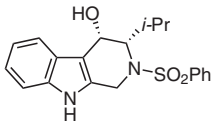
dosuccinimide, which would lead to four- or five-membered cyclization products **9** (n = 0) or **10** (n = 0) respectively, only the starting materials were re-isolated. This confirms that four-membered ring formation or 5-*endo-trig* cyclization is disfavored in these cases. On the other hand, the higher homologous (n = 2) 4-homoallyltetrahydro-β-carbolines **8f** and **8g** underwent entirely 6-*exo-trig* cyclization upon treatment with *N*-iodosuccinimide at low temperatures (0–20 °C) affording the smaller ring systems **9e** and **9f**. No ring expansion to **10** occurred under thermal treatment of these products **9e**, **9f** (THF, NaI, reflux). Obviously, no steric driving force is found in these larger six-membered rings **9**, which would have expanded to the seven-membered **10** (n = 2). Structures **9** and **10** can be easily differentiated by ^{13}C NMR spectroscopy where the CH_2I signals of **9** appear at 6 ppm while the CHI signal of the ring expanded product **10** resonances at 22–24 ppm. Products **9** and **10** were formed as single diastereomers. The configuration of **10** could be determined by NOESY. The configuration at the iodomethyl-substituted carbon atom of **9** could not be elucidated.

In summary, a series of optically active condensed tetrahydropyridines could be synthesized starting from α-amino esters and *o*-bromobenzyl bromides or heterocyclic analogues. Addition of Grignard reagents or reduction occurred with high stereoselectivity giving access to condensed hydroxypyridines. Allyl- and homoallyl-substituted condensed hydroxypyridines undergo iodocyclization to interesting new bridged condensed tetrahydropyridines. All these products represent new alkaloid-like structures.

Table 4 Condensed 4-Hydroxytetrahydropyridines **7** and **8** (R^3 = H) by Reduction

Product		R^1	R^2	Reducing Agent	Yield (%)	dr[a]
						
7d		-$(CH_2)_3$-		$LiAlH_4$/THF $NaBH_4$/EtOH	65 56	91:9 >95:5
8k		*i*-Pr	SO_2Ph	$LiAlH_4$/THF	22[b]	>95:5
8l		Me	allyl	$LiAlH_4$/THF $NaBH_4$/EtOH	66 57	87:13 91:9
8m		*i*-Pr	allyl	$LiAlH_4$/THF	93	>95:5
8n		*i*-Bu	allyl	$LiAlH_4$/THF $NaBH_4$/EtOH	61 47	92:8 94:6
7e		-$(CH_2)_3$-		$LiAlH_4$/THF	82	>95:5[c]

[a] Determined by NMR of the crude product.
[b] Additional N-deprotected product was obtained in 48% yield.



[c] Racemic starting material was used.

Table 5 NMR Data of Condensed 4-Alkyl-4-hydroxy-1,2,3,4-tetrahydropyridines **7** and **8** Prepared

Product[a]	^{1}H NMR ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ, *J* (Hz)
7a[b]	1.16 (t, 3 H, *J* = 7.5, C*H*$_3$CH$_2$), 1.85 (s, 9 H, *t*-C_4H_9), 2.01–2.39 (m, 4 H, proline CH_2), 2.56 (q, 2 H, *J* = 7.5, C*H*$_2$CH$_3$), 2.78–2.88 (m, 1 H, CHN), 3.32–3.51 (m, 2 H, proline CH_2), 3.53 (d, 1 H, *J* = 14.2, CH_2N), 4.28 (d, 1 H, *J* = 14.2, CH_2N), 7.09–7.14 (m, 2 H, CH_{ar}), 7.44 (d, 1 H, *J* = 7.6, CH_{ar}), 7.92 (d, 1 H, *J* = 7.5, CH_{ar})	9.6 (CH_3), 22.5 (CH_2), 23.3 (CH_2), 27.6 [C(*C*H$_3$)$_3$], 29.9 (CH_2), 51.4 (CH_2N), 55.6 (CH_2N), 73.9 (CHN), 75.1 (C_q–OH), 87.2 [*C*(CH$_3$)$_3$], 112.1 (CH_{ar}), 114.0 (C_{ar}), 116.2 (CH_{ar}), 121.8 (CH_{ar}), 122.1 (CH_{ar}), 127.9 (C_{ar}), 128.7 (C_{ar}), 138.6 (C_{ar}), 151.8 (*C*O$_2$Bu-*t*)
7b[c]	0.89 (t, 3 H, *J* = 7.6, C*H*$_3$CH$_2$), 1.77–2.03 (m, 8 H, proline CH_2, C*H*$_2$CH$_3$), 2.29–2.35 (m, 1 H, CHN), 2.49–2.58 (m, 1 H, proline CH_2N); 3.14–3.26 (m, 1 H, proline CH_2N), 3.37 (d, 1 H, *J* = 14.4, CH_2N), 4.11 (d, 1 H, *J* = 14.4, CH_2N), 7.02 (d, 1 H, *J* = 5.2, CH_{ar}), 7.08 (d, 1 H, *J* = 5.2, CH_{ar})	8.9 (*C*H$_3$CH$_2$), 22.8 (CH_2), 23.1 (CH_2), 29.1 (CH_2), 52.4 (CH_2N), 54.8 (CH_2N), 71.7 (CHN), 74.5 (C_q–OH), 122.5 (CH_{ar}), 125.8 (CH_{ar}), 135.3 (C_{ar}), 141.7 (C_{ar})
7c[d]	1.13–1.25 (m, 1 H, proline CH_2), 1.37–1.52 (m, 1 H, proline CH_2), 1.60–1.72 (m, 1 H, proline CH_2), 1.76–1.89 (m, 1 H, proline CH_2), 2.26–2.35 (m, 1 H, CHN), 2.67–2.72 (m, 1 H, proline CH_2N), 3.11–3.18 (m, 1 H, proline CH_2N), 3.49 (d, 1 H, *J* = 14.4, CH_2N), 4.27 (d, 1 H, *J* = 14.4, CH_2N), 6.74 (d, 1 H, *J* = 5.2, CH_{ar}), 7.06 (d, 1 H, *J* = 5.2, CH_{ar}), 7.16–7.28 (m, 3 H, CH_{ar}), 7.39–7.46 (m, 2 H, CH_{ar})	22.2 (CH_2), 24.3 (CH_2), 52.2 (CH_2N), 54.2 (CH_2N), 72.4 (CHN), 76.2 (C_q–OH), 123.7 (CH_{ar}), 125.3 (CH_{ar}), 126.8 (CH_{ar}), 127.2 (4 CH_{ar}), 135.7 (C_{ar}), 142.5 (C_{ar}), 142.6 (C_{ar})
7d[e]	–	24.4 (proline CH_2), 28.1 (proline CH_2), 28.6 [(*C*H$_3$)$_3$C], 52.2 (CH_2N), 54.5 (CH_2N), 68.4 (CHOH), 71.3 (CHN), 84.6 [*C*(CH$_3$)$_3$], 115.8 (CH_{ar}), 119.3 (C_{ar}), 120.3 (CH_{ar}), 123.2 (CH_{ar}), 124.2 (CH_{ar}), 128.1 (C_{ar}), 135.0 (C_{ar}), 136.6 (C_{ar}), 150.6 (*C*O$_2$Bu-*t*)

Table 5 NMR Data of Condensed 4-Alkyl-4-hydroxy-1,2,3,4-tetrahydropyridines **7** and **8** Prepared (continued)

Product[a]	^{1}H NMR ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ, *J* (Hz)
7e[f]	1.58–1.75 (m, 1 H, proline CH_2), 1.77–1.98 (m, 1 H, proline CH_2), 2.09–2.23 (m, 2 H, proline CH_2), 2.25–2.34 (m, 1 H, proline CH_2N), 2.48–2.59 (m, 1 H, CHN), 2.64 (br s, 1 H, OH), 3.12–3.19 (m, 1 H, proline CH_2N), 3.32 (d, 1 H, *J* = 14.3, CH_2N), 3.99 (d, 1 H, *J* = 14.3, CH_2N), 4.44 (d, 1 H, *J* = 7.8, C*H*OH), 6.99 (d, 1 H, *J* = 5.1, CH_{ar}), 7.10 (d, 1 H, *J* = 5.1, CH_{ar})	22.1 (proline CH_2), 28.4 (proline CH_2), 51.6 (CH_2N), 54.2 (CHN), 68.2 (*C*HC_q–OH), 72.6 (CHN), 123.6 (CH_{ar}), 124.1 (CH_{ar}), 135.2 (C_{ar}), 139.3 (C_{ar})
8a[g]	0.73 [d, 3 H, *J* = 6.9, $(CH_3)_2$CH], 0.95 (t, 3 H, *J* = 7.4, CH_3CH_2), 1.01 [d, 3 H, *J* = 6.6, $(CH_3)_2$CH], 1.61 (s, 9 H, *t*-C_4H_9), 1.76–1.87 [m, 1 H, C*H*$(CH_3)_2$], 1.92 (q, 2 H, *J* = 7.4, CH_2CH_3), 4.14 (d, 1 H, *J* = 6.5, CHN), 4.38 (d, 1 H, *J* = 18.1, CH_2N), 4.88 (d, 1 H, *J* = 18.1, CH_2N), 7.11–7.18 (m, 2 H, CH_{ar}), 7.42–7.47 (m, 3 H, CH_{ar}), 7.77–8.02 (m, 4 H, CH_{ar})	8.6 (CH_3CH_2), 21.6 [$(CH_3)_2$CH], 23.2 [$(CH_3)_2$CH], 28.6 [C$(CH_3)_3$], 29.6 [$(CH_3)_2$C*H*], 35.2 (CH_2CH_3), 43.3 (CH_2N), 63.4 (CHN), 75.6 (C_q–OH), 85.0 [*C*$(CH_3)_3$], 115.8 (CH_{ar}), 120.6 (C_{ar}), 121.5 (CH_{ar}), 123.3 (CH_{ar}), 124.5 (CH_{ar}), 127.2 (2 CH_{ar}), 127.9 (C_{ar}), 129.2 (C_{ar}), 129.4 (2 CH_{ar}), 132.9 (CH_{ar}), 136.4 (C_{ar}), 140.9 (C_{ar}), 150.3 (*C*O_2Bu-*t*)
8b[h]	1.17 (d, 3 H, *J* = 6.6, CH_3), 1.55 (s, 9 H, *t*-C_4H_9), 2.45 (br s, 1 H, OH), 2.79 (q, 1 H, *J* = 6.6, CHN), 3.09 (d, 1 H, *J* = 13.8, CH_2N), 3.66–3.72 (m, 2 H, CH_2COH), 3.94 (d, 1 H, *J* = 13.8, CH_2N), 6.76–6.79 (m, 2 H, CH_{ar}), 7.00–7.03 (m, 2 H, CH_{ar}), 7.17–7.24 (m, 3 H, CH_{ar}), 7.78–7.83 (m, 1 H, CH_{ar}), 8.11–8.18 (m, 1 H, CH_{ar})	14.3 (CH_3), 28.2 [C(*C*H_3)$_3$], 43.0 (*C*H_2COH), 44.3 (CH_2N), 54.4 (CHN), 72.7 (C_q–OH), 84.2 [*C*$(CH_3)_3$], 115.7 (CH_{ar}), 118.7 (C_{ar}), 120.3 (CH_{ar}), 123.0 (CH_{ar}), 123.8 (CH_{ar}), 126.4 (CH_{ar}), 127.9 (C_{ar}), 128.2 (2 CH_{ar}), 129.9 (2 CH_{ar}), 136.1 (C_{ar}), 136.9 (C_{ar}), 137.1 (C_{ar}), 150.0 (*C*O_2Bu-*t*)
8c[i]	1.16 (d, 3 H, *J* = 6.5, CH_3), 1.57 (s, 9 H, *t*-C_4H_9), 2.53–2.62 (m, 3 H, CH_2COH, OH), 2.91 (q, 1 H, *J* = 6.5, CHN), 3.15 (br s, 1 H, OH), 3.93 (s, 2 H, CH_2N), 4.80 (d, 1 H, CH_2=CH), 4.94 (d, 1H, CH_2=CH), 5.20–5.36 (m, 1 H, C*H*=CH_2), 7.16–7.20 (m, 2 H, CH_{ar}), 7.69–7.72 (m, 1 H, CH_{ar}), 8.08–8.11 (m, 1 H, CH_{ar})	14.0 (CH_3), 28.2 [(*C*H_3)$_3$C], 40.9 (*C*H_2COH), 45.3 (CH_2N), 55.1 (CHN), 71.2 (C_q–OH), 84.2 [*C*$(CH_3)_3$], 115.6 (CH_{ar}), 117.8 (*C*H_2=CH), 119.0 (C_{ar}), 120.0 (CH_{ar}), 122.9 (CH_{ar}), 123.7 (CH_{ar}), 127.4 (C_{ar}), 133.8 (*C*H=CH_2), 136.0 (C_{ar}), 136.8 (C_{ar}), 150.0 (*C*O_2Bu-*t*)
8d[j]	0.99 (d, 3 H, *J* = 6.8, CH_3), 1.04 (d, 3 H, *J* = 6.9, CH_3), 1.59 (s, 9 H, *t*-C_4H_9), 2.09 (s, 1 H, OH), 2.21–2.32 [m, 2 H, C*H*$(CH_3)_2$, OH], 2.59 (d, 1 H, CHN), 2.69–2.80 (m, 1 H, CH_2COH), 5.15–5.26 (m, 1 H, CH_2COH), 3.89 (d, 1 H, *J* = 17.5, CH_2N), 4.23 (d, 1 H, *J* = 17.5, CH_2N), 4.87 (d, 1 H, *J* = 10.1, CH_2=CH), 4.95 (d, 1 H, *J* = 16.8, CH_2=CH), 5.19–5.30 (m, 1 H, C*H*=CH_2), 7.16–7.19 (m, 2 H, CH_{ar}), 7.63–7.71 (m, 1 H, CH_{ar}), 8.10–8.18 (m, 1 H, CH_{ar})	15.7 (CH_3), 21.8 (CH_3), 24.2 [*C*H$(CH_3)_2$], 26.7 [(*C*H_3)$_3$C], 39.7 (*C*H_2COH), 44.9 (CH_2N), 62.0 (CHN), 72.1 (C_q–OH), 82.6 [*C*$(CH_3)_3$], 114.0 (CH_{ar}), 116.3 (*C*H_2=CH), 118.2 (C_{ar}), 118.3 (CH_{ar}), 121.3 (CH_{ar}), 122.2 (CH_{ar}), 125.9 (C_{ar}), 132.6 (*C*H=CH_2), 134.9 (C_{ar}), 136.7 (C_{ar}), 150.0 (*C*O_2Bu-*t*)
8e[k]	0.89 (t, 3 H, *J* = 7.2, CH_3CH$_2$), 1.04 (d, 3 H, *J* = 6.9, CH_3), 1,59 (s, 9 H, *t*-C_4H_9), 1.74–1.98 (m, 2 H, CHCH_2CH$_3$), 2.16–2.25 (m, 1 H, C*H*C_2H_5), 2.62 (s, 1 H, NH), 2.96–2.80 (m, 1 H, CH_2COH), 3.11–3.22 (m, 1 H, CH_2COH), 3.65 (d, 1 H, CHN), 3.87 (d, 1 H, *J* = 17.3, CH_2N), 4.26 (d, 1 H, *J* = 17.3, CH_2N), 4.79 (d, 1 H, *J* = 10.1, CH_2=CH), 4.93 (d, 1 H, *J* = 16.8, CH_2=CH), 5.14–5.29 (m, 1 H, C*H*=CH_2), 7.11–7.23 (m, 2 H, CH_{ar}), 7.69 (m, 1 H, CH_{ar}), 8.11 (m, 1 H, CH_{ar})	13.1 (CH_3CH_2), 19.6 (CH_3), 24.3 (CH_2CH_3), 28.6 [(*C*H_3)$_3$C], 33.5 (CH), 41.8 (*C*H_2COH), 46.8 (CH_2N), 64.9 (CHN), 73.7 (C_q–OH), 84.6 [*C*$(CH_3)_3$], 116.0 (CH_{ar}), 118.3 (*C*H_2=CH), 119.7 (C_{ar}), 120.3 (CH_{ar}), 123.2 (CH_{ar}), 124.2 (CH_{ar}), 127.6 (C_{ar}), 134.5 (*C*H=CH_2), 136.5 (2 C_{ar}), 150.5 (*C*O_2Bu-*t*)
8f[l]	1.17 (d, 3 H, *J* = 6.7, CH_3), 1.58 (s, 9 H, *t*-C_4H_9), 1.88–1.99 (m, 3 H, CH_2, OH), 2.04–2.28 (m, 3 H, CH_2COH, NH), 2.83 (q, 1 H, *J* = 6.7, CHN), 4.11 (d, 1 H, CH_2N), 4.25 (d, 1 H, CH_2N), 4.77–4.92 (m, 2 H, CH_2=CH), 5.61–5.79 (m, 1 H, C*H*=CH_2), 7.09–7.21 (m, 2 H, CH_{ar}), 7.68–7.76 (m, 1 H, CH_{ar}), 8.03–8.09 (m, 1 H, CH_{ar})	14.6 (CH_3), 28.2 [(*C*H_3)$_3$C], 29.4 (CH_2), 35.1 (*C*H_2COH), 44.8 (CH_2N), 59.2 (CHN), 73.5 (C_q–OH), 84.1 [*C*$(CH_3)_3$], 114.3 (*C*H_2=CH), 115.1 (CH_{ar}), 120.7 (C_{ar}), 120.0 (CH_{ar}), 122.7 (CH_{ar}), 123.6 (CH_{ar}), 127.9 (C_{ar}), 135.2 (C_{ar}), 135.9 (C_{ar}), 138.9 (*C*H=CH_2), 150.2 (*C*O_2Bu-*t*)
8g[m]	0.94 (d, 3 H, *J* = 6.8, CH_3), 1.01 (d, 3 H, *J* = 6.9, CH_3), 1.54 (s, 9 H, *t*-C_4H_9), 1.61–1.78 [m, 1 H, C*H*$(CH_3)_2$], 2.01–2.20 (m, 2 H, CH_2), 2.38–2.56 (m, 3 H, CH_2COH, NH), 3.42–3.60 (m, 1 H, CHN), 3.86 (d, 1 H, *J* = 17.5, CH_2N), 4.20 (d, 1 H, *J* = 17.5, CH_2N), 4.77–4.82 (m, 2 H, CH_2=CH), 5.50–5.68 (m, 1 H, CH=CH_2), 7.11–7.15 (m, 2 H, CH_{ar}), 7.59–7.68 (m, 1 H, CH_{ar}), 8.06 (d, 1 H, *J* = 7.6, CH_{ar})	17.4 (CH_3), 23.7 (CH_3), 25.9 [*C*H$(CH_3)_2$], 28.4 [C(*C*H_3)$_3$], 29.4 (CH_2), 35.3 (*C*H_2COH), 46.6 (CH_2N), 63.8 (CHN), 73.7 (C_q–OH), 84.1 [*C*$(CH_3)_3$], 114.4 (*C*H_2=CH), 115.5 (CH_{ar}), 119.6 (C_{ar}), 119.7 (CH_{ar}), 122.9 (CH_{ar}), 123.7 (CH_{ar}), 127.3 (C_{ar}), 136.0 (2 C_{ar}), 138.1 (*C*H=CH_2), 150.0 (*C*O_2Bu-*t*)
8h[n]	0.99 (d, 3 H, *J* = 6.6, CH_3), 1.48 (s, 9 H, *t*-C_4H_9), 2.28 (s, 1 H, OH), 2.70 (q, 1 H, *J* = 6.6, CHN), 3.98 (d, 1 H, *J* = 17.3, CH_2N), 4.09 (d, 1 H, *J* = 17.3, CH_2N), 5.24 (d, 1 H, *J* = 10.4, CH_2=CH), 5.43 (d, 1 H, *J* = 13.8, CH_2=CH), 5.69–5.82 (m, 1 H, C*H*=CH_2), 6.95–7.11 (m, 2 H, CH_{ar}), 7.50 (d, 1 H, CH_{ar}), 7.98 (d, 1 H, CH_{ar})	14.0 (CH_3), 28.2 [(*C*H_3)$_3$C], 45.8 (CH_2N), 57.5 (CHN), 71.8 (C_q–OH), 84.2 [*C*$(CH_3)_3$], 115.4 (CH_{ar}), 115.6 (*C*H_2=CH), 119.0 (C_{ar}), 120.1 (CH_{ar}), 122.7 (CH_{ar}), 123.8 (CH_{ar}), 127.4 (C_{ar}), 135.9 (C_{ar}), 136.4 (C_{ar}), 140.6 (*C*H=CH_2), 150.3 (*C*O_2Bu-*t*)

Table 5 NMR Data of Condensed 4-Alkyl-4-hydroxy-1,2,3,4-tetrahydropyridines **7** and **8** Prepared (continued)

Product[a]	^{1}H NMR ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ, *J* (Hz)
8i[o]	0.98 [d, 6 H, *J* = 6.9, $(CH_3)_2CH$], 1.59 (s, 9 H, *t*-C_4H_9), 2.09–2.18 [m, 1 H, $CH(CH_3)_2$], 2.45–2.53 (m, 1 H, CHN), 4.01 (d, 1 H, CH_2N), 4.53 (d, 1 H, CH_2N), 5.38 (d, 1 H, CH_2=CH), 5.57 (d, 1 H, CH_2=CH), 5.84–5.97 (m, 1 H, CH=CH_2), 7.02–7.19 (m, 2 H, CH_{ar}), 7.53–7.61 (m, 1 H, CH_{ar}), 8.07–8.12 (m, 1 H, CH_{ar})	18.3 (CH_3), 24.7 (CH_3), 26.9 [$CH(CH_3)_2$], 29.2 [$C(CH_3)_3$], 47.7 (CH_2N), 67.4 (CHN), 74.7 (C_q–OH), 84.1 [$C(CH_3)_3$], 116.3 (CH_{ar}), 116.4 (CH_2=CH), 120.6 (C_{ar}), 120.9 (CH_{ar}), 123.4 (CH_{ar}), 124.7 (CH_{ar}), 128.1 (C_{ar}), 136.8 (2 C_{ar}), 142.1 (CH=CH_2), 151.3 (CO_2Bu-*t*)
8j[p]	0.95 [d, 3 H, *J* = 7.2, $(CH_3)_2CH$], 0.98 (d, 3 H, *J* = 7.2, $(CH_3)_2CH$)], 2.18–2.44 [m, 2 H, $(CH_3)_2CH$, NH], 2.61–2.84 (m, 3 H, CH_2COH, CHN), 3.80 (d, 1 H, *J* = 15.8, CH_2N), 3.96 (d, 1 H, *J* = 15.8, CH_2N), 4.89 (d, 1 H, *J* = 10.1, CH_2=CH), 4.99 (d, 1 H, *J* = 17.1, CH_2=CH), 5.27–5.37 (m, 1 H, CH=CH_2), 6.98 (d, 1 H, *J* = 5.2, CH_{ar}), 7.05 (d, 1 H, *J* = 5.2, CH_{ar})	17.1 (CH_3), 23.2 (CH_3), 25.9 [$CH(CH_3)_2$], 42.1 (CH_2C_qOH), 46.0 (CH_2N), 63.5 (CHN), 72.4 (C_q–OH), 117.9 (CH_2=CH), 123.1 (CH_{ar}), 124.9 (CH_{ar}), 133.8 (CH=CH_2), 138.0 (C_{ar}), 140.4 (C_{ar})
8k[q]	0.81 (d, 3 H, *J* = 6.3, CH_3), 1.08 (d, 3 H, *J* = 6.6, CH_3), 1.59 (s, 9 H, *t*-C_4H_9), 2.15–2.28 [m, 1 H, $CH(CH_3)_2$], 2.39 (d, 1 H, *J* = 8.6, OH), 3.73–3.82 (m 1 H, CHN), 4.61 (d, 1 H, *J* = 17.1, CH_2N), 4.82 (d, 1 H, *J* = 17.1, CH_2N), 4.95–5.04 (m, 1 H, CHOH), 7.08–7.22 (m, 2 H, CH_{ar}), 7.35–7.50 (m, 3 H, CH_{ar}), 7.68–8.01 (m, 4 H CH_{ar})	21.6 (CH_3), 21.8 (CH_3), 27.2 [$CH(CH_3)_2$], 28.6 [$(CH_3)_3C$], 45.2 (CH_2N), 65.2 (CHOH), 66.8 (CHN), 85.1 [$C(CH_3)_3$], 115.8 (CH_{ar}), 117.7 (CH_{ar}), 120.6 (CH_{ar}), 123.4 (CH_{ar}), 124.7 (CH_{ar}), 127.3 (2 CH_{ar}), 128.4 (CH_{ar}), 129.5 (2 CH_{ar}), 133.1 (CH_{ar}), 136.2 (C_{ar}), 141.3 (2 C_{ar}), 150.2 (CO_2Bu-*t*)
8l[r]	1.26 (d, 1 H, *J* = 6.6, CH_3), 1.56 (s, 9 H, *t*-C_4H_9), 2.09 (br s, 1 H, OH), 2.78–2.84 (m, 1 H, CHN), 3.1 (dd, 1 H, *J* = 13.7, 7.2, CH_2N), 3.43 (dd, 1 H, *J* = 13.7, 5.9, CH_2N), 3.53 (d, 1 H, *J* = 17.4, CH_2N), 3.98 (d, 1 H, *J* = 17.4, CH_2N), 4.58 (d, 1 H, *J* = 2.2, CHOH), 5.12–5.22 (m, 2 H, CH_2=CH), 5.79–5.93 (m, 1 H, CH=CH_2), 7.15–7.24 (m, 2 H, CH_{ar}), 7.57–7.62 (m, 1 H, CH_{ar}), 8.07–8.10 (m, 1 H, CH_{ar})	13.9 (CH_3), 28.2 [$(CH_3)_3C$], 51.1 (CH_2N), 56.0 (CH_2N), 57.7 (CHN), 66.4 (CHOH), 83.9 [$C(CH_3)_3$], 115.6 (CH_{ar}), 117.8 (C_{ar}), 118.1 (CH_2=CH), 118.5 (CH_{ar}), 122.9 (CH_{ar}), 123.9 (CH_{ar}), 128.2 (C_{ar}), 134.8 (C_{ar}), 134.9 (CH=CH_2), 136.1 (C_{ar}), 150.1 (CO_2Bu-*t*)
8m[s]	1.05 (d, 1 H, *J* = 6.6, CH_3), 1.08 (d, 1 H, *J* = 6.5, CH_3), 1.57 (s, 9 H, *t*-C_4H_9), 2.13–2.28 [m, 1 H, $CH(CH_3)_2$], 2.32–2.40 (m, 1 H, CHN), 2.99–3.10 (m, 1 H, CH_2N), 3.41–3.49 (m, 1 H, CH_2N), 3.48 (d, 1 H, *J* = 18.1, CH_2N), 4.36 (d, 1 H, *J* = 18.1, CH_2N), 4.90 (d, 1 H, *J* = 2.4, CHOH), 5.03–5.13 (m, 2 H, CH_2=CH), 5.69–5.81 (m, 1 H, CH=CH_2), 7.16–7.25 (m, 2 H, CH_{ar}), 7.53–7.60 (m, 1 H, CH_{ar}), 8.09–8.18 (m, 1 H, CH_{ar})	20.6 (CH_3), 21.0 (CH_3), 26.1 [$CH(CH_3)_2$], 28.6 [$(CH_3)_3C$], 50.6 (CH_2N), 51.1 (CH_2N), 62.9 (CHN), 68.4 (CHOH), 84.4 [$C(CH_3)_3$], 116.0 (CH_{ar}), 116.6 (CH_2=CH), 118.1 (C_{ar}), 118.4 (CH_{ar}), 123.4 (CH_{ar}), 124.4 (CH_{ar}), 128.7 (C_{ar}), 136.1 (C_{ar}), 136.7 (C_{ar}), 138.1 (CH=CH_2), 150.7 (CO_2Bu-*t*)
8n[t]	0.86 (d, 3 H, *J* = 6.6, CH_3), 0.94 (d, 3 H, *J* = 6.5, CH_3), 1.40–1.51 (m, 1 H, CH_2CHN), 1.56 (s, 9 H, *t*-C_4H_9), 1.59–1.68 (m, 1 H, CH_2CHN), 1.80–1.94 [m, 1 H, $CH(CH_3)_2$], 2.18 (br s, 1 H, OH), 2.70–2.79 (m, 1 H, CHN), 3.19–3.32 (m, 2 H, CH_2N), 3.46 (d, 1 H, *J* = 17.1, CH_2N), 4.08 (d, 1 H, *J* = 17.1, CH_2N), 4.69 (d, 1 H, *J* = 2.3, CHOH), 5.02–5.19 (m, 2 H, CH_2=CH), 5.70–5.86 (CH=CH_2), 7.11–7.21 (m, 2 H, CH_{ar}), 7.52–7.60 (m, 1 H, CH_{ar}), 8.05–8.12 (m, 1 H, CH_{ar})	22.3 (CH_3), 23.8 (CH_3), 24.9 [$CH(CH_3)_2$], 28.2 [$(CH_3)_3C$], 36.7 (CH_2CHN), 51.0 (CH_2N), 54.4 (CH_2N), 59.6 (CHN), 63.4 (CHOH), 83.9 [$C(CH_3)_3$], 115.5 (CH_{ar}), 117.5 (CH_2=CH), 117.9 (C_{ar}), 118.4 (CH_{ar}), 123.0 (CH_{ar}), 123.9 (CH_{ar}), 128.3 (C_{ar}), 135.0 (C_{ar}), 135.9 (CH=CH_2), 136.1 (C_{ar}), 150.2 (CO_2Bu-*t*)

[a] Satisfactory microanalyses obtained for **8b**–**j**,**l**–**n** and **7d**,**e**: C ± 0. 0.42; H ± 0.22; N ± 0.49; S ± 0.31. Exceptions: **7d**: C –0.6; **8b**: C –0.73; **8c**: N –0.83; **8g**: C –0.75; **8h**: N –0.97; **8m**: H –0.81.
[b] Recorded in CD_3OD; R_f 0.48 ($CHCl_3$–MeOH, 9:1).
[c] R_f 0.45 ($CHCl_3$–MeOH, 9:1).
[d] R_f 0.49 ($CHCl_3$–MeOH, 9:1).
[e] R_f 0.17 ($CHCl_3$–MeOH, 9:1).
[f] R_f 0.34 ($CHCl_3$–MeOH, 9:1).
[g] R_f 0.59 (CH_2Cl_2–acetone, 95:5); $[\alpha]_D^{20}$ +29.6 (*c* = 1, CH_2Cl_2).
[h] R_f 0.21 ($CHCl_3$–MeOH, 9:1); $[\alpha]_D^{20}$ +76.2 (*c* = 1.25, CH_2Cl_2).
[i] R_f 0.23 ($CHCl_3$–MeOH, 9:1); $[\alpha]_D^{20}$ +85.5 (*c* = 1, CH_2Cl_2).
[j] R_f 0.54 ($CHCl_3$–MeOH, 9:1).
[k] R_f 0.53 ($CHCl_3$–MeOH, 9:1).
[l] R_f 0.26 ($CHCl_3$–MeOH, 9:1), $[\alpha]_D^{20}$ +50.0 (*c* = 1.1, CH_2Cl_2).
[m] R_f 0.13 ($CHCl_3$–MeOH, 9:1).
[n] R_f 0.21 ($CHCl_3$–MeOH, 9:1), $[\alpha]_D^{20}$ +29.7 (*c* = 1.65, CH_2Cl_2).
[o] R_f 0.50 ($CHCl_3$–MeOH, 9:1).
[p] R_f 0.23 ($CHCl_3$–MeOH, 9:1).
[q] R_f 0.25 (hexane–EtOAc, 7:3).
[r] R_f 0.25 ($CHCl_3$–MeOH, 97:3); $[\alpha]_D^{20}$ +39.9 (*c* = 1.2, CH_2Cl_2).
[s] R_f 0.44 (hexane–EtOAc, 7:3); $[\alpha]_D^{20}$ +33.9 (*c* = 1.3, CH_2Cl_2).
[t] R_f 0.46 (hexane–EtOAc, 7:3).

Table 6 Iodocyclization Products **9** and **10**[a]

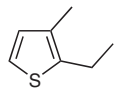
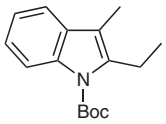
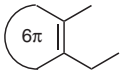
n	6π	R^1	**9** Yield (%) Method	**10** Yield (%) Method	^{1}H NMR ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ, *J* (Hz)
1		*i*-Pr	**9a** 27 H	–	0.93 (d, 3 H, *J* = 6.6, CH_3), 1.05 (d, 3 H, *J* = 6.5, CH_3), 1.62–1.68 [m, 1 H, C*H*(CH_3)$_2$], 1.93 (dd, 1 H, *J* = 12.2, 6.1, C*H*$_2$COH), 2.32 (dd, 1 H, *J* = 12.2, 10.2, C*H*$_2$COH), 2.75 (d, 1 H, *J* = 10.5, CHN), 3.04 (dd, 1 H, *J* = 9.4, 9.2, CH_2I), 3.18 (dd, 1 H, *J* = 9.4, 6.6, CH_2I), 3.79–3.88 (m, 1 H, C*H*CH_2I), 3.93 (d, 1 H, *J* = 18.2, CH_2N), 4.03 (d, 1 H, *J* = 18.2, CH_2N), 6.95 (d, 1 H, *J* = 5.0, CH_{ar}), 7.10 (d, 1 H, *J* = 5.0, CH_{ar})	5.7 (CH_2I), 19.8 (CH_3), 22.3 (CH_3), 25.9 [*C*H(CH_3)$_2$], 42.8 (*C*H_2COH), 51.0 (CH_2N), 61.7 (*C*HCH$_2$I), 75.1 (CHN), 79.8 (C_q–OH), 122.7 (CH_{ar}), 124.5 (CH_{ar}), 129.4 (C_{ar}), 145.2 (C_{ar})
1			–	**10a**[b] 56 H 98 I	0.89 (d, 3 H, *J* = 6.7, CH_3), 1.00 (d, 3 H, *J* = 6.6, CH_3), 1.53–1.67 [m, 1 H, C*H*(CH_3)$_2$], 1.95 (s, 1 H, OH), 2.21 (dd, 1 H, *J* = 12.2, C*H*$_2$COH), 2.35 (dd, 1 H, *J* = 12.2, C*H*$_2$COH), 2.49 (d, 1 H, *J* = 9.3, CHN), 3.16 (dd, 1 H, *J* = 12.7, C*H*$_2$CHI), 3.36 (dd, 1 H, *J* = 12.7, C*H*$_2$CHI), 3.62 (d, 1 H, *J* = 18.2, CH_2N), 3.74 (m, 1 H, CHI), 4.14 (d, 1 H, *J* = 18.1, CH_2N), 6.95 (d, 1 H, *J* = 5.1, CH_{ar}), 7.11 (d, 1 H, *J* = 5.1, CH_{ar})	21.7 (CH_3), 22.1 (CH_3), 23.3 (CHI), 27.5 [*C*H(CH_3)$_2$], 47.6 (*C*H_2COH), 53.2 (CH_2N), 66.6 (*C*H_2CHI), 70.6 (CHN), 76.6 (C_q–OH), 123.8 (CH_{ar}), 124.0 (CH_{ar}), 135.6 (C_{ar}), 139.5 (C_{ar})
1		Me	–	**10b** 66 H	1.06 (d, 3 H, *J* = 6.8, CH_3), 1.62 (s, 9 H, *t*-C_4H_9), 2.1 (s, 1 H, OH), 2.22 (dd, 1 H, *J* = 12.0, C*H*$_2$COH), 2.74 (dd, 1 H, *J* = 12.0, C*H*$_2$COH), 3.03 (q, 1 H, *J* = 6.8, CHN), 3.19–3.40 (m, 2 H, C*H*$_2$CHI), 3.81–3.99 (m, 2 H, CH_2N, CHI), 4.34 (d, 1 H, *J* = 18.4, CH_2N), 7.12–7.26 (m, 2 H, CH_{ar}), 7.76 (d, 1 H, CH_{ar}), 8.07 (d, 1 H, CH_{ar})	12.5 (CH_3), 22.6 (CHI), 28.3 [(*C*H_3)$_3$C$_q$], 47.6 (*C*H_2COH), 49.5 (CH_2N), 60.5 (CHN), 65.6 (*C*H_2CHI), 72.9 (C_q–OH), 84.6 [*C*(CH_3)$_3$], 115.6 (CH_{ar}), 116.9 (C_{ar}), 120.1 (CH_{ar}), 123.0 (CH_{ar}), 124.0 (CH_{ar}), 127.1 (C_{ar}), 134.8 (C_{ar}), 136.0 (C_{ar}), 150.2 (*C*O_2Bu-*t*)
1		*i*-Pr	–	**10c**[c] 62 H	0.93 (d, 3 H, *J* = 6.7, CH_3), 1.03 (d, 3 H, *J* = 6.5, CH_3), 1.62 (s, 9 H, *t*-C_4H_9), 1.68–1.80 [m, 1 H, C*H*(CH_3)$_2$], 1.98 (s, 1 H, OH), 2.22 (dd, 1 H, *J* = 12.1, C*H*$_2$COH), 2.49 (d, 1 H, *J* = 9.4, CHN), 2.71 (dd, 1 H, *J* = 12.1, C*H*$_2$COH), 3.18 (dd, 1 H, C*H*$_2$CHI), 3.39 (dd, 1 H, C*H*$_2$CHI), 3.73–3.91 (m, 2 H, CH_2N, CHI), 4.27 (d, 1 H, *J* = 18.6, CH_2N), 7.09–7.22 (m, 2 H, CH_{ar}), 7.83 (d, 1 H, CH_{ar}), 8.05 (d, 1 H, CH_{ar})	22.4 (CH_3), 22.7 (CH_3), 23.8 (CHI), 27.7 [*C*H(CH_3)$_2$], 28.7 [(*C*H_3)$_3$C], 48.5 (*C*H_2COH), 52.0 (CH_2N), 66.8 (*C*H_2CHI), 71.4 (CHN), 75.5 (C_q–OH), 84.8 [*C*(CH_3)$_3$], 115.9 (CH_{ar}), 118.1 (C_{ar}), 120.8 (CH_{ar}), 123.3 (CH_{ar}), 124.2 (CH_{ar}), 127.5 (C_{ar}), 135.8 (C_{ar}), 136.3 (C_{ar}), 150.9 (*C*O_2Bu-*t*)
1		*s*-Bu	–	**10d** 48 H	0.71 (t, 3 H, *J* = 7.2, C*H*$_3$CH$_2$), 0.99 (d, 3 H, *J* = 6.6, CH_3), 1.16–1.28 (m, 2 H, C*H*$_2$CH$_3$), 1.50–1.61 (m, 1 H, CH$_3$C*H*C$_2$H$_5$), 1.62 (s, 9 H, *t*-C_4H_9), 1.98 (s, 1 H, OH), 2.25 (dd, 1 H, *J* = 12.0, C*H*$_2$COH), 2.64 (d, 1 H, *J* = 9.1, CHN), 2.81 (dd, 1 H, *J* = 12.0, C*H*$_2$COH), 3.12 (dd, 1 H, C*H*$_2$CHI), 3.40 (dd, 1 H, C*H*$_2$CHI), 3.81–3.92 (m, 2 H, CH_2N, CHI), 4.26 (d, 1 H, *J* = 18.8, CH_2N), 7.11–7.25 (m, 2 H, CH_{ar}), 7.82 (d, 1 H, CH_{ar}), 8.08 (d, 1 H, CH_{ar})	10.9 (*C*H$_3$CH$_2$), 18.3 (CH_3), 23.8 (CHI), 27.5 (*C*H$_2$CH$_3$), 28.7 [(*C*H_3)$_3$C], 33.4 (CH$_3$*C*HC$_2$H$_5$), 48.6 (*C*H_2COH), 52.2 (CH_2N), 66.8 (*C*H_2CHI), 69.1 (CHN), 75.5 (C_q–OH), 84.8 [*C*(CH_3)$_3$], 115.9 (CH_{ar}), 118.2 (C_{ar}), 120.8 (CH_{ar}), 123.3 (CH_{ar}), 124.2 (CH_{ar}), 127.5 (C_{ar}), 135.9 (C_{ar}), 136.4 (C_{ar}), 150.7 (*C*O_2Bu-*t*)

Table 6 Iodocyclization Products **9** and **10**[a] (continued)

n		R[1]	**9** Yield (%) Method	**10** Yield (%) Method	^{1}H NMR ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ, *J* (Hz)
2		Me	**9e** 85 H	–	1.33 (d, 3 H, *J* = 7.0, CH_3), 1.61 (s, 9 H, *t*-C_4H_9), 1.72–2.02 (m, 4 H, 2 CH_2), 2.97 (q, 1 H, *J* = 7.0, CHN), 3.11–3.23 (m, 2 H, CH_2I), 3.83–4.09 (m, 2 H, CH_2N, C*H*CH_2I), 4.18 (d, 1 H, *J* = 18.4, CH_2N), 7.06–7.20 (m, 2 H, CH_{ar}), 7.67–7.73 (m, 1 H, CH_{ar}), 8.08 (d, 1 H, CH_{ar})	8.1 (CH_2I), 11.2 (CH_3), 27.5 (CH_2), 28.3 [C(*C*H_3)$_3$], 30.0 (*C*H_2COH), 45.8 (CH_2N), 53.8 (*C*HCH_2I), 61.1 (CHN), 69.9 (C_q–OH), 84.2 [*C*(CH_3)$_3$], 115.5 (CH_{ar}), 120.0 (CH_{ar}), 122.0 (C_{ar}), 122.8 (CH_{ar}), 123.7 (CH_{ar}), 126.5 (C_{ar}), 135.7 (C_{ar}), 136.0 (C_{ar}), 150.8 (*C*O_2Bu-*t*)
2		*i*-Pr	**9f**[d] 66 H	–	1.00–1.05 (m, 6 H, 2 CH_3), 1.14–1.22 [m, 1 H, C*H*(CH_3)$_2$] 1.62 (s, 9 H, *t*-C_4H_9), 1.72–2.05 (m, 4 H, 2 CH_2), 2.36 (q, 1 H, *J* = 9.5, CHN), 2.88–2.99 (m, 1 H, C*H*CH_2I), 3.10 (dd, 1 H, CH_2I), 3.22 (dd, 1 H, CH_2I), 3.68 (d, 1 H, *J* = 18.6, CH_2N), 3.96 (d, 1 H, *J* = 18.6, CH_2N), 7.09–7.20 (m, 2 H, CH_{ar}), 7.81 (d, 1 H, CH_{ar}), 8.08 (d, 1 H, CH_{ar})	9.0 (CH_2I), 22.0 (CH_3), 22.3 (CH_3), 27.5 (CH_2), 27.6 [*C*H(CH_3)$_2$], 28.3 [C(*C*H_3)$_3$], 37.7 (*C*H_2COH), 40.1 (CH_2N), 64.4 (*C*HCH_2I), 72.9 (C_q–OH), 73.3 (CHN) 84.1 [*C*(CH_3)$_3$], 115.4 (CH_{ar}), 118.4 (C_{ar}), 120.4 (CH_{ar}), 122.7 (CH_{ar}), 123.4 (CH_{ar}), 127.4 (C_{ar}), 135.1 (C_{ar}), 135.9 (C_{ar}), 150.9 (*C*O_2Bu-*t*)

[a] Satisfactory microanalyses obtained for **9a**,**f** and **10a–c**: C ± 0.48; H ± 0.35; N ± 0.27; S ± 0.38. Exception: **9f**: C + 0.6.
[b] $[\alpha]_D^{20}$ –76.9 (*c* = 1, CH_2Cl_2).
[c] $[\alpha]_D^{20}$ –39.3 (*c* = 1, CH_2Cl_2).
[d] $[\alpha]_D^{20}$ +88.0 (*c* = 1, CH_2Cl_2).

Starting materials were purchased from Aldrich, Lancaster, Acros, and Merck. TLC analysis was performed on Merck silica gel 60 F_{254} plates and visualized with UV illumination and charring with phosphomolybdic acid in EtOH (5%, v/v) or 0.3% ninhydrin in EtOH. Column chromatography was conducted with Merck silica gel 60 (400–639 mesh). Melting points were determined on a Boetius hot-stage apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, on a Bruker AC-300 in $CDCl_3$ with TMS as internal standard. Mass spectra were measured at 70 eV. Optical rotations were determined with a PerkinElmer polarimeter 241 (d = 2 mm). Enantiomeric purity was proved by analytical HPLC on cellulose carbamate (CHIRALCEL OD).

N-(2-Bromobenzyl)amino Esters and Heterocyclic Analogues 4; General Procedure

Method A: A mixture of *o*-bromobenzyl bromide or the corresponding heterocyclic analogue **1** (0.02 mol), K_2CO_3 (2.76 g, 0.02 mmol), amino ester **2** (0.026 mol) and MeCN (250 mL) was refluxed for 5 h. After cooling down to r. t., the suspension was filtered and the solution was concentrated in vacuo. The residue was purified by column chromatography.

N-(2-Bromobenzyl)amino Esters and Heterocyclic Analogues 5; General Procedures

Method B: Analogous to Method A, but using N-substituted amino ester **3**.

Method C1: $NaHCO_3$ (0.84 g, 0.01 mol) and allyl bromide (4.84 g, 0.04 mol) were added to a solution of the *N*-(*o*-bromobenzyl)amino ester or the corresponding heterocyclic analogue **4** (0.01 mol) in MeCN (150 mL). After reflux (4–8 h) the mixture was cooled to r.t. and filtered. The solution was concentrated in vacuo and the residue purified by column chromatography.

Method C2: A solution of the bromoindolmethylamino ester **4** (5 mmol) in CH_2Cl_2 (30 mL) was added under vigorous stirring to a solution of carbobenzyloxy chloride (0.89 g, 5.2 mmol) in sat. aq $NaHCO_3$. The mixture was stirred at r.t. for 8 h and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography.

Condensed Tetrahydropyridones 6; General Procedure

Method D: A solution of the N-alkylated amino ester **4** or **5** (2.5 mmol) in anhyd THF (120 mL) under argon was cooled to –100 °C. A 1.7 M solution of *t*-BuLi in pentane (5 mmol) or 1.6 M solution of *n*-BuLi in hexanes (3 mmol) was added dropwise while the temperature was maintained below –98 °C. After the addition, the solution was stirred at –100 °C for 3 to 6 h and then quenched with sat. aq NH_4Cl at this temperature. The mixture was stirred at r.t. until the appearing precipitate dissolved. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (5 ×). The combined organic layers were dried (Na_2SO_4), the solvent removed in vacuo and the residue purified by column chromatography.

Condensed 4-Alkyl-4-hydroxy-1,2,3,4-tetrahydropyridines and Heterocyclic Analogues 7 and 8 (R ≠ H) by Grignard Reaction; General Procedure

Method E: A solution of the condensed dihydropyridone **6** (0.80 mmol) in anhyd THF (15 mL) was kept under argon and cooled to 0 °C. The Grignard reagent R^3MgBr (4.0 mmol or 5.6 mmol for NH-containing **6**) was added dropwise. After stirring for 8 to 12 h, the mixture was poured onto ice and the organic phase separated. The aqueous phase was extracted with CH_2Cl_2 (5 ×). The combined organic layers were dried (Na_2SO_4) and the solvent removed in vacuo. The residue was purified by column chromatography.

Condensed 4-Hydroxy-1,2,3,4-tetrahydropyridines and Heterocyclic Analogues 7 and 8 (R = H) by Reduction; General Procedures

Method F: $NaBH_4$ (0.85 g, 2.25 mmol) was added to a solution of the condensed dihydropyridone **6** (1.5 mmol) in EtOH (60 mL) at 0 °C. The mixture was allowed to warm slowly to r.t. and was then

stirred for 5 to 10 h (TLC). After the reaction had gone to completion, the mixture was quenched with sat. aq NH_4Cl. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (5 ×). The combined organic layers were washed with H_2O and dried (Na_2SO_4). After evaporation of the solvent in vacuo, the remaining material was purified by column chromatography giving a solid.

Method G: A solution of the condensed dihydropyridone **6** (1.5 mmol) in anhyd THF (20 mL) was added to a solution of $LiAlH_4$ (0.068 g, 1.8 mmol) in anhyd THF (40 mL) under argon at 0 °C. The mixture was allowed to warm slowly to r.t. and was stirred for 12 to 18 h (TLC). After the reaction had gone to completion, the mixture was quenched with ice. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (5 ×). The combined organic layers were washed with water and dried (Na_2SO_4). After evaporation of the solvent in vacuo the remaining material was purified by column chromatography giving a solid.

Iodocyclization Products 9 and 10; General Procedure

Method H: A solution of the hydroxytetrahydropyridine **8** (1.3 mmol) in anhyd THF (5 mL) was added dropwise into a solution of *N*-iodosuccinimide (0.382 g, 1.7 mol) in anhyd THF (15 mL) under argon at 0 °C. The mixture was allowed slowly to warm up to r.t. and was stirred for 12 to 20 hours (TLC). The solvent was removed in vacuo and the remaining yellowish solid was purified by column chromatography.

Method I: A solution of the iodocyclization product **9a** (0.150 g, 0.413 mmol) in THF (10 mL) was stirred at 60 °C for 3 h. After evaporation of the solvent, the pure product was obtained in quantitative yield.

X-ray Crystal Data for the Dihydro-β-carboline 6j[35]

Empirical formula: $C_{23}H_{24}N_2O_5S$, formula weight: 440.50, temperature: 200 (2) K, wavelength: 0.71073 A, crystal system: monoclinic, space group: P 21, unit cell dimension: a = 10.704 (2) Å, α = 90°, b = 6.8991 (6) Å, β = 100.40 (2)°, c = 14.796 (2) Å, γ = 90 deg, volume: 1074.7 (2) Å^3, Z = 2, ρ_{calcd} = 1.361 Mg/m^3, absorption coefficient: 0.189 mm^{-1}, F (000): 464, crystal size: 0.45 × 0.42 × 0.30 mm, max. and min. transmission: 0.9456 and 0.9200, θ-range for data collection: 2.17 to 24.17 deg, index ranges: $-12 \le h \le 12$, $-7 \le k \le 7$, $-16 \le l \le 16$; reflections collected: 7595, independent reflections: 3351 [R(int) = 0.0795], refinement method: full-matrix least-squares on F^2, Data/restraints/parameters: 3351/1/376, goodness-of-fit on F^2: 0.998, final R indices [I > 2σ (I)]: $R1$ = 0.0303 $wR2$ = 0.0750, R indices (all data): $R1$ = 0.0332 $wR2$ = 0.0762, absolute structure parameter: –0.05 (6), largest diff.-map peak and hole: 0.157 and –0.160 e·A^{-3}.

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(35) Full details have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 606388. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK.