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TETRAHEDRON: *ASYMMETRY*

2-Substituted-1,2,3,4-tetrahydroisoquinolines and chiral 3-carboxyl analogues from *N*-benzotriazolylmethyl-*N*-phenethylamines

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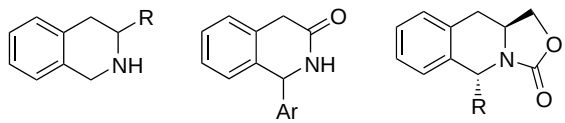
Abstract—*N*-Benzotriazolylmethyl-*N*-phenethylamines **5a–5c** and **11a–11c** cyclize in the presence of aluminum chloride to produce 1,2,3,4-tetrahydroisoquinolines **6a–6c** and **12a–12c** (70–89%) via electrophilic attack of a transient iminium cation X on the tethered phenyl ring. The Bt group in 2-benzotriazolylmethyl-1,2,3,4-tetrahydroisoquinolines **6a–6b** was replaced (i) with hydrogen by sodium borohydride to afford *N*-methyl-1,2,3,4-tetrahydroisoquinolines **7a–7b** or (ii) by nucleophiles, such as Grignard reagents, a silyl enol ether or triethyl phosphite, to furnish novel *N*-substituted-1,2,3,4-tetrahydroisoquinolines **13a–13c**, **14** or **15**, respectively. Optically active 3-substituted-1,2,3,4-tetrahydroisoquinolines **12a–12c** were similarly prepared in high yields without racemization.

1. Introduction

Many alkaloids possess 1,2,3,4-tetrahydroisoquinoline (THIQ) skeletons. Derivatives of THIQ play an important role in medicinal chemistry due to their significant biological and physiological activities,[1] e.g. in vitro inhibition of diazepam binding to rat cerebral cortical membranes.[2] A number of selective inhibitors of phenylethanolamine *N*-methyltransferase (PNMT, an enzyme that is involved in the biosynthesis of epinephrine in the central nervous system) contain the THIQ nucleus **1**.[3] Therefore, syntheses of substituted 1,2,3,4-tetrahydroisoquinolines continues to attract much interest.[4] Many of the classical methods for the preparation of THIQs are intermolecular cyclization reactions involving aromatic rings with electrophilic substituents; for example, cyclocondensation of 1-phenyl-2-aminopropane with formaldehyde gave 3-methyl-1,2,3,4-tetrahydroisoquinoline (43%).[5]

We previously reported the preparation of 1-aryl-1,4-dihydro-3-(2*H*)-isoquinolinones **2**,[6a] enantiopure oxazolo[3,4-*b*]tetrahydroisoquinolin-3-ones **3**[6b] and substituted 1,2,3,4-tetrahydroquinolines[6c,d] using benzotriazole methodology. Locher and Peerzada recently reported Lewis acid-promoted intramolecular Friedel–Crafts cyclizations to synthesize *N*-methyl-1,2,3,4-tetrahydroisoquinolines[7a] and *N*-benzotriazol-1-ylmethyl-1,2,3,4-tetrahydroisoquinolines.[7b] We now extend these methodologies to prepare THIQ derivatives **1** unsubstituted at C(1), including chiral derivatives without racemization.



1 **2** **3**

2. Results and discussion

2.1. Preparation of *N*-benzotriazolylmethyl-*N*-phenethylamines 5a–5c and their cyclizations in the presence of $AlCl_3$

We have investigated intensively Mannich reactions of benzotriazole, amines and formaldehyde (as well as other aldehydes).[8] Two methods were generally used for the condensation: (**A**) reactions of amines with benzotriazole and formaldehyde (37% aqueous solution); (**B**) reactions of amines with Bt^1CH_2OH. Generation of mono(benzotriazolylmethyl) products in good yields from primary amines requires hindered amines with a substituent at the α-position.[9] Reactions of unhindered primary amines with 2 equivalents of BtH and formaldehyde give bis(benzotriazolylmethyl) products.[10]

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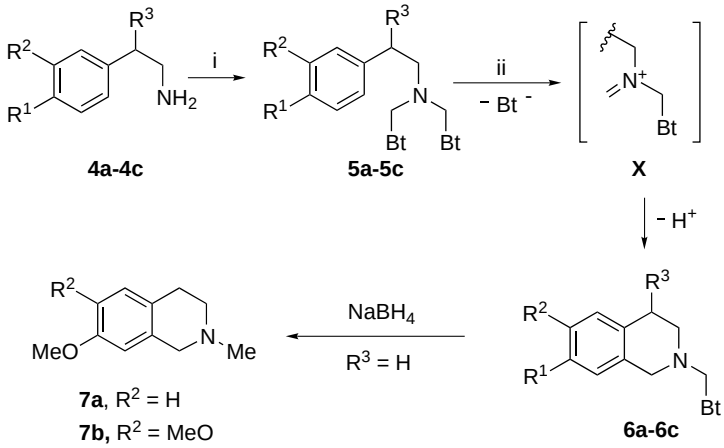
In the present work, using 1 equivalent of 4-methoxyphenethylamine **4a**, BtH and formaldehyde (37% aqueous solution), we obtained no *p*-$MeOC_6H_4CH_2CH_2NHCH_2Bt$; instead the crude ^1H NMR spectrum showed that bis(benzotriazolylmethyl) derivative **5a** was formed. When 2 equivalents of BtH and HCHO were used to react with **4a**, the bis(benzotriazolylmethyl) intermediate **5a** was furnished in 92% yield. Bis(benzotriazolylmethyl) intermediates **5b** and **5c** were obtained in 95 and 97% yields, respectively, by the reaction of the corresponding amines **4b** and **4c** with Bt^1CH_2OH in the presence of sodium sulfate. ^1H NMR spectral analysis showed that **5a**–**5b** were obtained as mixtures of Bt^1 and Bt^2 isomers with ratios of 22:1 and 4:1, respectively; while **5c** was obtained as a sole Bt^1 isomer. It is difficult to distinguish the proton and carbon NMR peaks of the minor Bt^2 isomers from the major Bt^1 isomers in **5a**–**5b** due to their overlap with each other; therefore we report only the ^1H and ^{13}C NMR data for the major Bt^1 isomers.

Treatment of **5a**–**5c** with aluminum chloride in refluxing CH_2Cl_2 was found to eliminate only one benzotriazolyl moiety to give 2-benzotriazolylmethyl-1,2,3,4-tetrahydroisoquinolines **6a**–**6c** in excellent yields (Scheme 1). Elimination of the benzotriazolyl anion in **5a**–**5c** generates the iminium cation **X**, which undergoes electrophilic substitution on the tethered phenyl ring to furnish 2-benzotriazolylmethyl-1,2,3,4-tetrahydroisoquinolines **6a**–**6c**. The ratios of Bt^1 and Bt^2 isomers for **6a**–**6c** changed to 5:1, 7:1 and 4:1, respectively. This is consistent with our previous reports that both Bt^1 and Bt^2 groups are good leaving groups in the presence of Lewis acids, such as $AlCl_3$, $ZnBr_2$, BF_3, etc.[11] For **6a** and **6b**, we report the individual ^1H and ^{13}C NMR (using attached proton test technique) data for each of their Bt^1 and Bt^2 isomers. The chemical shifts of the carbons attached to the benzotriazol-2-yl group appear at a lower field (76.7 ppm, for both **6a** and **6b**) compared to those of the carbons attached to the benzotriazol-1-yl group (68.9 ppm, for both **6a** and **6b**).[8e]

Treatment of 2-benzotriazolylmethyl-1,2,3,4-tetrahydroisoquinolines **6a**–**6b** with 2 equivalents of sodium borohydride in THF at room temperature readily replaced the benzotriazolyl group with hydrogen to give *N*-methyl-1,2,3,4-tetrahydroisoquinolines **7a**–**7b** in 83 and 87% yield, respectively (Scheme 1).

2.2. Preparation of optically active 3-substituted-1,2,3,4-tetrahydroisoquinolines 12a–12c

A similar methodology was used for the syntheses of optically active 3-substituted-1,2,3,4-tetrahydroisoquinolines **12a**,**12b** starting from chiral *N*-Boc-



Bt = benzotriazol-1-yl and -2-yl

i) For **5a**, using method **A**: BtH and HCHO (37%);

For **5b**, **5c**, using method **B**: Bt^1CH_2OH

ii) $AlCl_3/CH_2Cl_2$, reflux

Compd	R^1	R^2	R^3	Y^a (%) of **5**	Y^a (%) of **6**
a	MeO	H	H	92	86
b	MeO	MeO	H	95	89
c	H	H	Ph	97	82

[a] Isolated yield.

Scheme 1.

α-Phe **8**. Following a recently published procedure,[12] reaction of **8** with *iso*-butyl chloroformate in the presence of *N*-methylmorpholine generated the mixed anhydride, which with morpholine or *N*,*N*-dibutylamine afforded *N*-Boc-α-amino amides **9a**,**9b** in 92 and 89% yields, respectively. Treatment of crude **9a**,**9b** with HCl (ca. 1 M in EtOAc) readily removed the protecting *N*-Boc group. α-Amino amide **10a** was obtained as the hydrochloride salt in 87% yield; while **10b** was obtained as its free base in 92% yield. Compounds **10a**,**10b** were used directly for subsequent reactions without further purification. Reaction of **10a**–**10c** (**10c**, R = OMe, purchased from Aldrich) with 1 equivalent of benzotriazole and formaldehyde gave benzotriazolylmethyl intermediates **11a**–**11c** in 91, 93 and 92% yields, respectively. The ^{1}H NMR spectra showed that **11a**,**11b** were obtained as a mixture of Bt^1 and Bt^2 isomers in 6:1 and 8:1 ratio, respectively; while **11c** was obtained as a sole Bt^1 isomer.

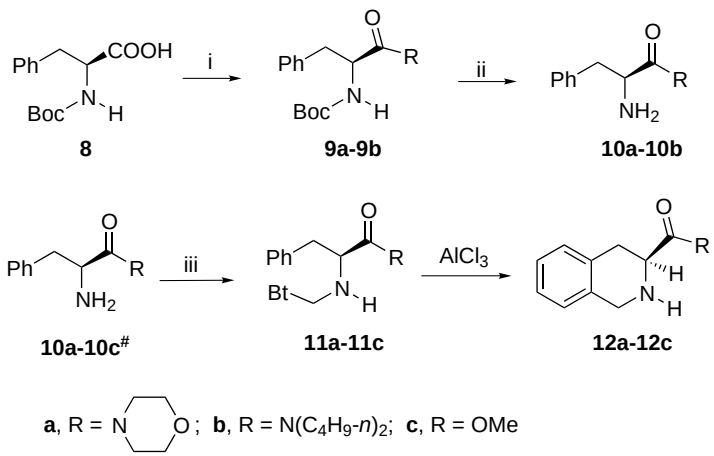
Subsequent treatment of **11a**–**11c** with aluminum chloride in refluxing CH_2Cl_2 readily eliminated the Bt anion to generate the iminium cation, which underwent electrophilic substitution on the tethered phenyl ring to furnish optically active 3-substituted-1,2,3,4-tetrahydroisoquinolines **12a**–**12c**. The optical activity of **12c** matches that reported earlier.[13] This indicates that no racemization occurred for all of the above transformations under the mild reaction conditions. An earlier paper reported that the treatment of phenylalanine with formaldehyde in the presence of concentrated hydrochloric acid afforded 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid; however, enantiopure phenylalanine was partially racemized under the strongly acidic conditions (Scheme 2).[3]

2.3. Nucleophilic substitution of 2-benzotriazolylmethyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline 6a with Grignard reagents, a silyl enol ether or triethyl phosphite

Nucleophilic substitution of **6a** with 2 equivalents of Grignard reagents (phenyl, *n*-pentyl or phenylethynyl magnesium bromide) in dry THF produced novel *N*-substituted-1,2,3,4-tetrahydroisoquinolines **13a**–**13c** (Scheme 3). The structures of **13a**–**13c** were clearly supported by their ^{1}H and ^{13}C NMR spectra and microanalysis or HRMS results. We further investigated the nucleophilic substitution reaction of **6a** with a silyl enol ether in the presence of $BF_3{\cdot}Et_2O$ and found that the benzotriazolyl group in **6a** can be easily substituted by such an organosilyl nucleophile to afford **14** in 63% yield. Treatment of **6a** with 1.2 equivalents of triethyl phosphite in the presence of $ZnBr_2$ furnished diethyl [7-methoxy-3,4-dihydro-2(1*H*)-isoquinolinyl]-methylphosphonate **15** in 80% yield.

3. Conclusion

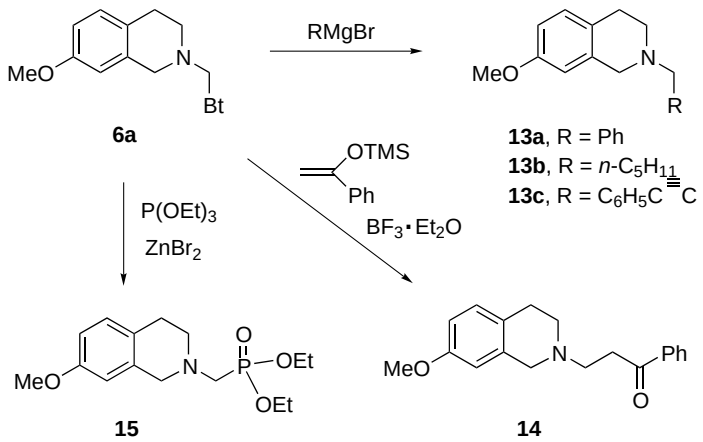
In summary, a simple and efficient approach to 1,2,3,4-tetrahydroisoquinolines has been reported by the treatment of *N*-benzotriazolylmethyl-*N*-phenethylamines **5a**–**5c** and **11a**–**11c** with aluminum chloride. No racemization was observed when chiral phenethylamines **10a**–**10c** were used as starting materials. Reduction of **6a**–**6b** with sodium borohydride easily replaces the benzotriazolyl group with hydrogen and nucleophilic substitutions of **6a** with Grignard reagents, a silyl enol ether or triethyl phosphite furnish novel *N*-substituted-1,2,3,4-tetrahydroisoquinolines **13a**–**13c**, **14** or **15**.



i) morpholine or $HN(C_4H_9\text{-}n)_2$; *N*-methylmorpholine, ClCOOBu-*i*;
ii) HCl/EtOAc; iii) BtH, HCHO (37%)

10a and **10c** (from Aldrich) were used as their hydrochloride salts. Therefore, one equivalent of NaOH was used in step iii).

Scheme 2.



Scheme 3.

4. Experimental

Melting points were determined using a Bristoline hot-stage microscope and are uncorrected. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Gemini 300 NMR spectrometer in $CDCl_3$ (with TMS for ^{1}H and chloroform-*d* for ^{13}C as the internal reference), unless otherwise stated. HRMS were measured on an AEI-30 mass spectrometer. Optical rotation values were measured on a Perkin–Elmer 341 polarimeter with the use of the sodium D line. Column chromatography was performed on silica gel (200–425 mesh). All of the reactions were carried out under N_2.

4.1. General procedure for the syntheses of bis(benzotriazolylmethyl) intermediates 5a–5c

Method **A**: Benzotriazole (2.38 g, 20 mmol) and an appropriate primary amine **4** (10 mmol) were stirred in MeOH (30 mL)/H_2O (5 mL) at 25°C for 10 min. Formaldehyde (37% aqueous solution, 1.62 g, 20 mmol) was added to the vigorously stirred mixture. After 4 h, a thick suspension was filtered and the precipitate was washed with cool MeOH to give the desired product.

Method **B**: A mixture of an appropriate amine **4** (10 mmol), Bt^1CH_2OH (20 mmol) and Na_2SO_4 (anhydrous, 4 g) was stirred in MeOH (40 mL) at 25°C for 10 h. The solid was filtered off and the solvent was evaporated in vacuo to give the desired product.

Bis(benzotriazolylmethyl) intermediates **5a**–**5c** can be used for the subsequent cyclization without further purification. For microanalysis purposes, the solid formed was recrystallized from appropriate solvents or the sticky oil was purified by column chromatography.

4.1.1. *N*,*N*-Bis(benzotriazolylmethyl)-*N*-(4-methoxyphenethyl)amine 5a. Method **A**: A mixture of Bt^1 and Bt^2 isomers in 22:1 ratio; colorless needles (from $CHCl_3$/Et_2O); yield 92%; mp 96–97°C; ^{1}H NMR δ (Bt^1) 8.07 (d, J=8.1 Hz, 2H), 7.54–7.36 (m, 6H), 6.90 (d, J=8.3 Hz, 2H), 6.68 (d, J=8.3 Hz, 2H), 5.61 (s, 4H), 3.74 (s, 3H), 3.11 (t, J=6.8 Hz, 2H), 2.75 (t, J=6.8 Hz, 2H); ^{13}C NMR δ (Bt^1) 158.0, 146.0, 133.1, 130.6, 129.4, 127.7, 124.1, 119.9, 113.8, 109.8, 64.4, 55.1, 52.3, 33.0. Anal. calcd for $C_{23}H_{23}N_7O$: C, 66.81; H, 5.61; N, 23.71. Found: C, 66.65; H, 5.63; N, 23.79%.

4.1.2. *N*,*N*-Bis(benzotriazolylmethyl)-*N*-(3,4-dimethoxyphenethyl)amine 5b. Method **B**: A mixture of Bt^1 and Bt^2 isomers in a 4:1 ratio; sticky oil; yield 95%; ^{1}H NMR δ (Bt^1) 8.07 (d, J=8.3 Hz, 2H), 7.55–7.36 (m, 6H), 6.65–6.52 (m, 2H), 6.43 (d, J=1.7 Hz, 1H), 5.64 (s, 4H), 3.80 (s, 3H), 3.49 (s, 3H), 3.13 (t, J=7.0 Hz, 2H), 2.73 (t, J=7.0 Hz, 2H); ^{13}C NMR (Bt^1) 148.6, 147.3, 145.8, 132.9, 131.1, 127.7, 124.1, 120.3, 119.8, 109.7, 64.6, 55.6, 55.5, 52.2, 33.5. Anal. calcd for $C_{24}H_{25}N_7O_2$: C, 65.00; H, 5.68; N, 22.11. Found: C, 64.64; H, 6.04; N, 21.71%.

4.1.3. *N*,*N*-Bis-(1*H*-1,2,3-benzotriazol-1-ylmethyl)-2,2-diphenyl-1-ethanamine 5c. Method **B**: colorless flakes (from $CHCl_3$/hexanes); yield 97%; mp 120–121°C; ^{1}H NMR δ 8.04 (d, J=8.2 Hz, 2H), 7.41–7.33 (m, 4H), 7.31–7.25 (m, 2H), 7.16–7.11 (m, 6H), 7.09–7.02 (m, 4H), 5.54 (s, 4H), 4.26 (t, J=8.1 Hz, 1H), 3.46 (d, J=8.1 Hz, 2H); ^{13}C NMR δ 146.0, 141.5, 133.0, 128.4, 127.8, 127.7, 126.6, 124.1, 119.8, 109.8, 64.7, 55.3, 49.1. Anal. calcd for $C_{28}H_{25}N_7$: C, 73.18; H, 5.48; N, 21.34. Found: C, 72.95; H, 5.29; N, 21.42%.

4.2. Preparation of *N*-benzotriazolylmethyl-1,2,3,4-tetrahydroisoquinolines 6a–6c via annulation of bis(benzotriazolylmethyl) intermediates 5a–5c

To a stirred solution of **5a**–**5c** (4 mmol) in dry CH_2Cl_2 (30 mL), $AlCl_3$ (2.13 g, 16 mmol) was added. The reaction mixture was refluxed for 10 h. After cooling, 2 M NaOH (20 mL) was added. The separated aqueous phase was extracted with CH_2Cl_2. The combined organic fractions were washed with 2 M NaOH, brine and dried over anhydrous $MgSO_4$. Removal of solvents in vacuo gave a solid, which was recrystallized from appropriate solvents to afford the pure products **6a**,**6b**.

4.2.1. 2-Benzotriazolylmethyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline 6a. A mixture of Bt^1 and Bt^2 isomers in 5:1 ratio; colorless prisms (from CH_2Cl_2/Et_2O); yield 86%; mp 127–129°C; ^{1}H NMR δ (Bt^1) 8.05 (d, $J=8.3$ Hz, 1H), 7.67 (d, $J=8.4$ Hz, 1H), 7.48 (dd, $J=7.2$, 7.2 Hz, 1H), 7.35 (dd, $J=7.6$, 7.6 Hz, 1H), 6.94 (d, $J=8.4$ Hz, 1H), 6.66 (dd, $J=8.4$, 2.5 Hz, 1H), 6.50 (d, $J=2.5$ Hz, 1H), 5.58 (s, 2H), 3.79 (s, 2H), 3.71 (s, 3H), 2.92 (t, $J=5.3$ Hz, 2H), 2.81 (t, $J=5.4$ Hz, 2H), [δ (Bt^2) 7.90–7.85 (m, 2H), 7.40–7.34 (m, 2H), 6.94 (d, $J=8.4$ Hz, 1H), 6.66 (dd, $J=8.4$, 2.5 Hz, 1H), 6.53 (d, $J=2.5$ Hz, 1H), 5.73 (s, 2H), 3.88 (s, 2H), 3.71 (s, 3H), 3.01 (t, $J=5.3$ Hz, 2H), 2.83 (t, $J=5.4$ Hz, 2H)]; ^{13}C NMR δ (Bt^1): 157.5 (q), 145.8 (q), 134.5 (q), 133.7 (q), 129.5, 127.4, 125.4 (q), 123.8, 119.7, 112.7, 110.9, 109.9, 68.9 (Bt^1CH_2), 55.1 (OCH_3), 52.3, 48.6, 28.2, [δ (Bt^2) 157.5 (q), 144.1 (q), 134.8 (q), 126.3, 125.5 (q), 118.1, 112.5, 110.8, 109.9, 76.7 (Bt^2CH_2), 55.1 (OCH_3), 51.7, 48.4, 28.5]. Anal. calcd for $C_{17}H_{18}N_4O$: C, 69.37; H, 6.16; N, 19.03. Found: C, 69.34; H, 6.02; N, 19.16%.

4.2.2. 2-Benzotriazolylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 6b. A mixture of Bt^1 and Bt^2 isomers in 7:1 ratio; colorless needles (from CH_2Cl_2/Et_2O); yield 89%; mp 136–137°C; ^{1}H NMR δ (Bt^1) 8.06 (d, $J=8.4$ Hz, 1H), 7.69 (d, $J=8.4$ Hz, 1H), 7.50 (dd, $J=7.2$, 7.2 Hz, 1H), 7.36 (dd, $J=7.5$, 7.5 Hz, 1H), 6.55 (s, 1H), 6.47 (s, 1H), 5.61 (s, 2H, Bt^1CH_2), 3.81 (s, 3H), 3.79 (s, 3H), 3.76 (s, 2H), 2.94 (t, $J=5.5$ Hz, 2H), 2.82 (t, $J=5.3$ Hz, 2H), [δ (Bt^2) 7.91–7.88 (m, 2H), 7.40–7.37 (m, 2H), 6.55 (s, 1H), 6.50 (s, 1H), 5.74 (s, 2H, Bt^2CH_2), 3.84 (s, 3H), 3.83 (s, 2H), 3.81 (s, 3H), 3.03 (t, $J=5.9$ Hz, 2H), 2.82 (t, $J=5.3$ Hz, 2H)]; ^{13}C NMR δ (Bt^1) 147.4 (q), 147.1 (q), 145.7 (q), 133.6 (q), 127.3, 125.1 (q), 125.0 (q), 123.7, 119.5, 111.1, 109.9, 109.1, 68.9 (Bt^1CH_2), 55.7, 51.8, 48.4, 28.6, [δ (Bt^2) 147.3 (q), 147.1 (q), 144.0 (q), 126.3, 125.5 (q), 125.1 (q), 118.1, 109.9, 109.1, 76.7 (Bt^2CH_2), 55.7, 51.1, 48.2, 28.9]. Anal. calcd for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.52; H, 6.45; N, 17.53%.

4.2.3. 2-(Benzotriazolylmethyl)-4-phenyl-1,2,3,4-tetrahydroisoquinoline 6c. A mixture of Bt^1 and Bt^2 isomers in 4:1 ratio; sticky oil; yield 82%; ^{1}H NMR δ (Bt^1) 8.04 (d, $J=8.2$ Hz, 1H), 7.51 (d, $J=8.2$ Hz, 1H), 7.43 (dd, $J=7.2$, 7.2 Hz, 1H), 7.34 (dd, $J=7.3$, 7.3 Hz, 1H), 7.26–7.20 (m, 3H), 7.20–7.00 (m, 5H), 6.86 (d, $J=7.5$ Hz, 1H), 5.55 (s, 2H), 4.27–4.21 (m, 1H), 3.94 (d, $J=5.6$ Hz, 2H), 3.25 (dd, $J=11.5$, 5.1 Hz, 1H), 2.98 (dd, $J=11.5$, 6.4 Hz, 1H). ^{13}C NMR (Bt^1) 145.9, 144.4, 136.5, 133.9, 129.6, 128.9, 128.2, 127.5, 126.5, 126.4, 126.3, 126.2, 123.9, 119.8, 118.3, 110.0, 69.2, 56.6, 52.7, 45.6. Anal. calcd for $C_{22}H_{20}N_4$: C, 77.62; H, 5.92. Found: C, 77.39; H, 6.24%.

4.3. General procedure for reduction of *N*-benzotriazolylmethyl-1,2,3,4-tetrahydroisoquinolines 6a–6b with $NaBH_4$

A mixture of **6a** or **6b** (2 mmol) and $NaBH_4$ (0.16 g, 4 mmol) was stirred in dry THF (15 mL) at 25°C overnight. The reaction mixture was quenched with water and extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4. After removal of the solvents in vacuo, the residue was purified by column chromatography with hexanes/EtOAc (2:1) as an eluent to give *N*-methyl-1,2,3,4-tetrahydroisoquinolines **7a**–**7b**.

4.3.1. 7-Methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline 7a. Colorless flakes; yield 83%; mp 50–51°C (lit.[14] bp 126°C/8 mmHg; mp 50–51°C); ^{1}H NMR δ 7.09 (d, $J=8.6$ Hz, 1H), 6.80 (dd, $J=8.4$, 2.3 Hz, 1H), 6.54 (d, $J=2.0$ Hz, 1H), 4.21 (d, $J=12.3$ Hz, 1H), 3.81 (d, $J=12.3$ Hz, 1H), 3.78 (s, 3H), 3.20 (t, $J=8.4$ Hz, 2H), 2.93 (t, $J=6.2$ Hz, 2H), 2.62 (s, 3H, NCH_3); ^{13}C NMR δ 148.2, 147.9, 122.4, 121.8, 110.9, 109.1, 61.0, 56.3, 55.7, 46.6, 23.9.

4.3.2. 6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline 7b. Colorless flakes; yield 87%; mp 83–84°C (lit.[15] mp 83–84°C); ^{1}H NMR δ 6.66 (s, 1H), 6.50 (s, 1H), 4.16 (d, $J=16.0$ Hz, 1H), 3.86 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.77 (d, $J=16.0$ Hz, 1H), 3.17 (t, $J=6.2$ Hz, 2H), 2.91 (t, $J=6.1$ Hz, 2H), 2.62 (s, 3H, NCH_3); ^{13}C NMR δ 148.1, 147.9, 122.4, 121.8, 110.9, 109.1, 61.0, 56.3, 55.8 (OCH_3), 55.7 (OCH_3), 46.6, 23.9.

4.4. Procedure for the preparation of chiral α-amino amides 9a,9b from *N*-Boc-Phe 8

To a cold solution (−15°C) of (2*S*)-2-({[(1,1-dimethylethyl)-oxy]carbonyl}amino)-3-phenylpropanoic acid (**8**, 2.65 g, 10 mmol) and 4-methylmorpholine (1.01 g, 10 mmol) in dry THF (30 mL), *iso*-butyl chloroformate (1.36 g, 10 mmol) in THF (5 mL) was added dropwise in 15 min. After stirring for another 15 min, morpholine (0.87 g, 10 mmol) or *N*,*N*-dibutylamine (1.29 g, 10 mmol) was added. Then, the reaction mixture was stirred at rt for 2 h. After evaporation of the solvent in vacuo, the residue was diluted with EtOAc (80 mL) and the organic phase was washed with 10% Na_2CO_3, 0.1 M HCl and brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent in vacuo gave **9a**,**9b**, which was used for the subsequent step without further purification.

4.4.1. *tert*-Butyl *N*-[(1*S*)-1-benzyl-2-morpholino-2-oxoethyl]carbamate 9a[12]. Colorless oil; yield 92%; ^{1}H NMR δ 7.32–7.19 (m, 5H), 5.49 (d, $J=8.6$ Hz, 1H), 4.84–4.76 (m, 1H), 3.67–3.38 (m, 5H), 3.33–3.25 (m, 1H), 3.06–2.84 (m, 4H), 1.43 (s, 9H); ^{13}C NMR δ 170.2, 155.0, 136.3, 129.5, 128.5, 127.0, 79.7, 66.4, 66.0, 50.7, 45.9, 42.1, 40.4, 28.3.

4.4.2. *tert*-Butyl *N*-[(1*S*)-1-benzyl-2-(dibutylamino)-2-oxoethyl]carbamate 9b. Colorless oil; yield 89%; $[\alpha]_D^{25}=+6.0$ (*c* 1.84, $CHCl_3$); ^{1}H NMR δ 7.27–7.19 (m, 5H), 5.35 (d, $J=8.9$ Hz, 1H), 4.78–4.70 (m, 1H), 3.47–3.38 (m, 1H), 3.07–2.85 (m, 5H), 1.41 (s, 9H), 1.35–1.81 (m, 8H), 0.95–0.83 (m, 6H); ^{13}C NMR δ 171.0, 154.8, 136.6, 129.4, 128.2, 126.6, 79.2, 51.3, 47.3, 45.9, 40.3, 30.8, 29.4, 28.1, 20.0, 19.8, 13.7, 13.6. Anal. calcd for $C_{22}H_{36}N_2O_3$: C, 70.18; H, 9.64; N, 7.44. Found: C, 69.97; H, 9.31; N, 7.62%.

To a stirred solution of **9a**,**9b** (10 mmol) in EtOAc (30 mL), HCl in EtOAc (ca. 1 M, 20 mL) was added. The mixture was stirred at rt until TLC showed disappearance of the starting material (about 15 h). For **10a**, the precipitate formed was filtered and washed with ether to give its hydrochloride salt. For **10b**, the clear solution was washed with 1 M NaOH, brine, dried over anhydrous K_2CO_3 and evaporated to give **10b**.

4.4.3. (2*S*)-1-Morpholino-1-oxo-3-phenyl-2-propanaminium chloride 10a. Colorless needles (from EtOH); yield 87%; mp 231–233°C; $[\alpha]_D^{25}=+69.5$ (*c* 1.73, EtOH); ^{1}H NMR δ (DMSO-d_6) 8.65 (br s, 3H), 7.37–7.24 (m, 5H), 4.64–4.59 (m, 1H), 3.49–3.22 (m, 7H), 2.96–2.87 (m, 2H), 2.71–2.68 (m, 1H); ^{13}C NMR δ (DMSO-d_6) 166.9, 134.7, 129.8, 128.6, 127.3, 65.6, 65.3, 49.4, 45.6, 42.0, 37.0. Anal. calcd for $C_{13}H_{19}ClN_2O_2$: C, 57.67; H, 7.07; N, 10.35. Found: C, 57.28; H, 7.20; N, 10.04%.

4.4.4. (2*S*)-2-Amino-*N*,*N*-dibutyl-3-phenylpropanamide 10b. Colorless oil; yield 92%; $[\alpha]_D^{25}=+50.7$ (*c* 1.81, EtOH); ^{1}H NMR δ 7.32–7.18 (m, 5H), 3.81 (t, $J=7.0$ Hz, 1H), 3.50–3.43 (m, 1H), 3.10–2.85 (m, 4H), 2.76 (dd, $J=13.2$, 7.3 Hz, 1H), 1.78 (s, 2H), 1.52–1.32 (m, 4H), 1.32–1.17 (m, 4H), 0.92 (t, $J=7.2$ Hz, 3H), 0.89 (t, $J=7.2$ Hz, 3H); ^{13}C NMR δ 174.2, 137.8, 129.2, 128.3, 126.5, 52.9, 47.0, 46.0, 42.9, 31.2, 29.6, 20.1, 19.9, 13.7, 13.6. Anal. calcd for $C_{17}H_{28}N_2O$: C, 73.87; H, 10.21; N, 10.13. Found: C, 73.92; H, 10.36; N, 9.97%.

4.5. General procedure for the preparation of Bt intermediates 11a–11c

To a solution of benzotriazole (0.36 g, 3 mmol), hydrochloride salt **10a**,**10c** (3 mmol) and NaOH (0.12 g, 3 mmol) in MeOH/H_2O (20/10 mL), formaldehyde (0.24 g, 3 mmol, 37% aqueous solution) was added. The mixture was stirred at rt for 5 h. For **11a**,**11c**, the precipitate formed was filtered, washed with cool H_2O and EtOH, and recrystallized from appropriate solvents. For **11b**, NaOH was not needed and, the clear solution was concentrated, extracted with CH_2Cl_2, and dried over anhydrous Na_2SO_4. Evaporation of solvents in vacuo afforded **11b**, which was used directly for the subsequent reaction.

4.5.1. (2*S*)-2-[(Benzotriazolylmethyl)amino]-1-morpholino-3-phenyl-1-propanone 11a. A mixture of Bt^1 and Bt^2 isomers in 6:1 ratio; colorless flakes (from EtOAc); yield 91%; mp 91–92°C; $[\alpha]_D^{25}=+151$ (*c* 2.39, EtOH); ^{1}H NMR δ (Bt^1) 8.01 (d, $J=8.2$ Hz, 1H), 7.60 (d, $J=8.2$ Hz, 1H), 7.48 (dd, $J=7.2$, 7.2 Hz, 1H), 7.36 (dd, $J=7.5$, 7.5 Hz, 1H), 7.28–7.13 (m, 3H), 7.10–7.02 (m, 2H), 5.50 (s, 2H), 3.90–3.78 (br s, 1H, NH), 3.35–3.00 (m, 6H), 2.91–2.82 (m, 2H), 2.77–2.59 (m, 3H); ^{13}C NMR δ (Bt^1) 171.4 (C=O), 146.0, 136.6, 132.2, 129.2, 128.3, 127.3, 126.8, 124.0, 119.3, 109.8, 65.8, 65.4, 61.9, 55.9, 45.1, 41.6, 41.0. Anal. calcd for $C_{20}H_{23}N_5O_2$: C, 65.73; H, 6.34; N, 19.16. Found: C, 66.05; H, 6.48; N, 19.20%.

4.5.2. (2*S*)-2-[(Benzotriazolylmethyl)amino]-*N*,*N*-dibutyl-3-phenylpropanamide 11b. A mixture of Bt^1 and Bt^2 isomers in 8:1 ratio; light yellow oil; yield 93%; $[\alpha]_D^{25}=+47.7$ (*c* 1.70, $CHCl_3$); ^{1}H NMR δ (Bt^1) 8.00 (d, $J=8.2$ Hz, 1H), 7.54 (d, $J=8.3$ Hz, 1H), 7.42 (dd, $J=7.3$, 7.3 Hz, 1H), 7.34 (dd, $J=7.3$, 7.3 Hz, 1H), 7.21–7.15 (m, 3H), 7.07 (d, $J=7.5$ Hz, 2H), 5.43 (br s, 2H), 3.80–3.74 (m, 1H), 3.20 (br s, 1H, NH), 3.10–3.04 (m, 1H), 3.00–2.93 (m, 1H), 2.87–2.82 (m, 2H), 2.79–2.74 (m, 2H), 1.19–1.08 (m, 4H), 0.95–0.87 (m, 4H), 0.82 (t, $J=7.7$ Hz, 6H); ^{13}C NMR δ (Bt^1) 172.4 (C=O), 146.3, 137.5, 132.4, 129.1, 128.2, 127.2, 126.5, 123.9, 119.6, 110.2, 62.1, 56.6, 47.1, 46.1, 40.6, 30.7, 29.4, 20.1, 20.0, 13.7, 13.6. Anal. calcd for $C_{24}H_{33}N_5O$: C, 70.73; H, 8.16. Found: C, 70.74; H, 8.48%.

4.5.3. Methyl (2*S*)-2-[(1*H*-1,2,3-benzotriazol-1-ylmethyl)amino]-3-phenylpropanoate 11c. Colorless needles (from $CHCl_3$); yield 92%; mp 96–97°C; $[\alpha]_D^{25}=+18.3$ (*c* 2.17, EtOH); ^{1}H NMR δ 8.03 (d, $J=8.3$ Hz, 1H), 7.42–7.38 (m, 2H), 7.38–7.32 (m, 1H), 7.19–7.13 (m, 3H), 7.02–7.00 (m, 2H), 5.56–5.41 (m, 2H), 3.70–3.60 (m, 1H), 3.46 (s, 3H), 2.97 (dd, $J=13.7$, 5.2 Hz, 1H), 2.79 (dd, $J=13.6$, 8.1 Hz, 1H), 2.69 (br s, NH, 1H); ^{13}C NMR δ 173.6 (C=O), 146.1, 136.4, 132.4, 128.9, 128.3, 127.3, 126.7, 123.9, 119.8, 109.4, 61.4, 59.4, 51.9, 39.2. Anal. calcd for $C_{17}H_{18}N_4O_2$: C, 65.79; H, 5.85; N, 18.05. Found: C, 65.77; H, 6.22; N, 18.13%.

4.6. General procedure for the preparation of chiral 3-substituted-1,2,3,4-tetrahydroisoquinolines 12a–12c via annulation of 11a–11c

A mixture of **11a**–**11c** (4 mmol) and $AlCl_3$ (2.13 g, 16 mmol) was refluxed in dry CH_2Cl_2 (30 mL) for 10 h. After cooling, 2 M NaOH (20 mL) was added. The separated aqueous phase was additionally extracted with CH_2Cl_2. The combined organic phase was washed with 2 M NaOH, brine and dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by column chromatography with hexanes/EtOAc/Et_3N (2:1:0.005) as an eluent to give **12a**–**12c**.

4.6.1. Morpholino[(3*S*)-(1,2,3,4-tetrahydro-3-isoquinolinyl)]methanone 12a. Colorless needles; yield 70%; mp 113–114°C; $[\alpha]_D^{25}=-89.4$ (*c* 2.03, EtOH); ^{1}H NMR δ 7.16–7.07 (m, 3H), 7.04–7.01 (m, 1H), 4.08 (s, 2H), 3.87 (dd, $J=11.1$, 4.4 Hz, 1H), 3.80–3.42 (m, 6H), 3.62–3.49 (m, 2H), 2.98 (dd, $J=16.3$, 11.2 Hz, 1H), 2.76 (dd, $J=16.4$, 4.2 Hz, 1H), 1.99 (br s, 1H, NH); ^{13}C NMR δ 171.3 (C=O), 135.2, 133.4, 129.2, 126.2, 126.1, 125.6, 66.7, 66.6, 53.0, 47.2, 45.8, 42.1, 31.3. Anal. calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.63; H, 7.73; N, 11.37%.

4.6.2. (3*S*)-*N*,*N*-Dibutyl-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide 12b. Colorless oil; yield 80%; $[\alpha]_D^{25}=-53.2$ (*c* 1.76, $CHCl_3$); ^{1}H NMR δ 7.18–7.03 (m, 4H), 4.11 (s, 2H), 3.83 (dd, $J=10.8$, 3.9 Hz, 1H), 3.40–3.25 (m, 4H), 3.01 (dd, $J=16.5$, 10.8 Hz, 1H), 2.74 (dd, $J=16.5$, 3.6 Hz, 1H), 1.89 (br s, 1H, NH), 1.60–1.53 (m, 4H), 1.37–1.26 (m, 4H), 0.93 (t, $J=7.3$ Hz, 6H); ^{13}C

NMR δ 172.4, 135.4, 133.9, 129.2, 126.1, 126.0, 125.6, 53.0, 47.4, 47.3, 45.8, 31.7, 31.6, 29.7, 20.1, 20.0, 13.8, 13.7. Anal. calcd for $C_{18}H_{28}N_2O$: C, 74.95; H, 9.78; N, 9.71. Found: C, 74.64; H, 10.07; N, 9.61%.

4.6.3. Methyl (3*S*)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylate 12c. Light yellow oil; yield 72%; $[\alpha]_D^{25}=-126$ (*c* 1.28, CH_2Cl_2), {lit.[13] $[\alpha]_D^{22}=-124$ (*c* 1.28, CH_2Cl_2)}; ^{1}H NMR δ 7.15–7.06 (m, 3H), 7.06–6.98 (m, 1H), 4.08 (d, $J=3.3$ Hz, 2H), 3.76 (s, 3H), 3.72 (dd, $J=10.1$, 4.8 Hz, 1H), 3.18–2.90 (m, 2H), 2.20 (br s, 1H, NH); ^{13}C NMR δ 173.4 (C=O), 134.7, 132.9, 129.0, 126.1, 126.0, 125.9, 55.7, 52.0, 47.2, 31.5; MS (EI): 191 (M^+, 3), 176 (M^+-CH_3, 3), 132 (M^+-COOMe, 100). Anal. calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85. Found: C, 69.10; H, 6.69%.

4.7. General procedure for the nucleophilic substitution of 6a with Grignard reagents

To a cold solution (−40°C) of 2-benzotriazolylmethyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**6a**, 0.88 g, 3 mmol) in dry THF (30 mL), an appropriate Grignard reagent (6 mmol) was added and the mixture was stirred at −40°C for 2 h and at rt for a further 10 h. The reaction mixture was washed with 2 M NaOH, and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After removal of solvents in vacuo, the residue was purified by column chromatography with hexanes/EtOAc (3:1) as an eluent to afford **13a**–**13c**.

4.7.1. 2-Benzyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline 13a. Colorless oil; yield 63%; ^{1}H NMR δ 7.40–7.26 (m, 5H), 6.99 (d, $J=8.4$ Hz, 1H), 6.70 (d, $J=8.4$ Hz, 1H), 6.51 (s, 1H), 3.72 (s, 3H), 3.67 (s, 2H), 3.59 (s, 2H), 2.81 (t, $J=5.3$ Hz, 2H), 2.74 (t, $J=5.4$ Hz, 2H); ^{13}C NMR δ 157.5, 138.3, 135.8, 129.5, 129.1, 128.3, 127.1, 126.4, 112.6, 111.1, 62.6, 56.2, 55.2, 50.8, 28.2. Anal. calcd for $C_{17}H_{19}NO$: C, 80.59; H, 7.56; N, 5.53. Found: C, 80.65; H, 7.74; N, 5.77%.

4.7.2. 2-Hexyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline 13b. Colorless flakes; yield 59%; mp 40–41°C; ^{1}H NMR δ 6.99 (d, $J=8.4$ Hz, 1H), 6.70 (dd, $J=8.4$, 2.7 Hz, 1H), 6.56 (d, $J=2.4$ Hz, 1H), 3.76 (s, 3H), 3.61 (s, 2H), 2.84 (t, $J=5.7$ Hz, 2H), 2.73 (t, $J=5.7$ Hz, 2H), 2.50 (t, $J=7.8$ Hz, 2H), 1.63–1.52 (m, 2H), 1.40–1.22 (m, 6H), 0.89 (t, $J=6.6$ Hz, 3H); ^{13}C NMR δ 157.5, 135.7, 129.5, 126.4, 112.5, 111.2, 58.4, 56.3, 55.2, 51.1, 31.8, 28.0, 27.3, 27.0, 22.6, 14.0; HRMS calcd for $C_{16}H_{26}NO$ 248.2014 (M+1), found 248.2006.

4.7.3. 7-Methoxy-2-(3-phenyl-2-propynyl)-1,2,3,4-tetrahydroisoquinoline 13c. Colorless oil; yield 74%; ^{1}H NMR δ 7.45–7.42 (m, 2H), 7.31–7.28 (m, 3H), 7.03 (d, $J=8.4$ Hz, 1H), 6.72 (dd, $J=8.7$, 2.7 Hz, 1H), 6.60 (d, $J=2.1$ Hz, 1H), 3.82 (s, 2H), 3.77 (s, 3H), 3.73 (s, 2H), 2.90 (s, 4H); ^{13}C NMR δ 157.6, 135.6, 131.7, 129.5, 128.2, 128.1, 125.9, 123.1, 112.6, 111.3, 85.5, 84.3, 55.3, 54.7, 50.1, 47.5, 28.4. Anal. calcd for $C_{19}H_{19}NO$: N, 5.05. Found: N, 5.21%. HRMS calcd for $C_{19}H_{20}NO$ 278.1545 (M+1), found 278.1542.

4.8. Procedure for the nucleophilic substitution of 6a with a silyl enol ether

To a solution of **6a** (0.59 g, 2 mmol) in dry THF (30 mL) at 0°C, 1-phenylvinyl trimethylsilyl ether (0.58 g, 3 mmol) and $BF_3{\cdot}Et_2O$ (2 mmol, 0.28 g) were added. The mixture was stirred at 0°C for 2 h and at room temperature for a further 10 h. The reaction mixture was washed with 2 M NaOH, brine and the aqueous phase was extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by column chromatography with hexanes/EtOAc (2:1) as an eluent to afford **14**.

4.8.1. 3-[7-Methoxy-3,4-dihydro-2(1*H*)-isoquinolinyl]-1-phenyl-1-propanone 14. Pale yellow oil; yield 63%; ^{1}H NMR δ 7.98 (d, $J=7.2$ Hz, 2H), 7.55 (t, $J=7.2$ Hz, 1H), 7.45 (dd, $J=7.6$, 7.6 Hz, 2H), 7.00 (d, $J=8.1$ Hz, 1H), 6.70 (dd, $J=8.4$, 2.7 Hz, 1H), 6.56 (d, $J=2.1$ Hz, 1H), 3.75 (s, 3H), 3.67 (s, 2H), 3.30 (t, $J=7.2$ Hz, 2H), 3.00 (t, $J=8.1$ Hz, 2H), 2.84–2.79 (m, 4H); ^{13}C NMR δ 199.0, 157.5, 136.9, 135.5, 133.0, 129.5, 128.5, 128.0, 126.2, 112.5, 111.2, 56.2, 55.2, 52.8, 51.3, 36.7, 28.2. Anal. calcd for $C_{19}H_{21}NO_2$: N, 4.74. Found: N, 4.79%. HRMS calcd for $C_{19}H_{22}NO_2$ 296.1651 (M+1), found 296.1655.

4.9. Procedure for the nucleophilic substitution of 6a with triethyl phosphite

To a solution of **6a** (0.59 g, 2 mmol) in dry THF (20 mL) at 0°C, $ZnBr_2$ (0.90 g, 4 mmol) was added. The solution was stirred for 20 min before triethyl phosphite (0.40 g, 2.4 mmol) was added dropwise. After stirring at room temperature for 10 h, most of the THF was evaporated. The residue was diluted with EtOAc, and the solution was washed with 2 M NaOH, water and dried over Na_2SO_4. After removal of solvent in vacuo, the residue was purified by column chromatography with hexanes/EtOAc (3:1–1:1) as an eluent to afford **15**.

4.9.1. Diethyl [7-methoxy-3,4-dihydro-2(1*H*)-isoquinolinyl]methylphosphonate 15. Light yellow oil; yield 80%; ^{1}H NMR δ 7.00 (d, $J=8.4$ Hz, 1H), 6.71 (dd, $J=8.4$, 2.7 Hz, 1H), 6.55 (d, $J=2.7$ Hz, 1H), 4.22–4.15 (m, 4H), 3.82 (s, 2H), 3.76 (s, 3H), 2.98–2.94 (m, 4H), 2.82 (t, $J=7.2$ Hz, 2H), 1.33 (t, $J=7.0$ Hz, 6H); ^{13}C NMR δ 157.5, 135.4, 129.5, 125.9, 112.6, 111.1, 62.1 (d, $J=6.8$ Hz), 57.4 (d, $J=10.8$ Hz), 55.2, 53.5 (d, $J=162.8$ Hz), 52.6 (d, $J=10.3$ Hz), 27.9, 16.5 ($J=5.7$ Hz). Anal. calcd for $C_{15}H_{24}NO_4P$: C, 57.50; H, 7.72; N, 4.47. Found: C, 57.84; H, 8.02; N, 4.68%.

References

1. (a) Herbert, R. B. In *The Chemistry and Biology of Isoquinoline Alkaloids*; Philipson, J. D.; Roberts, M. F.; Zenk, M. H., Eds.; Springer-Verlag: Berlin, 1985; p. 213; (b) Shamma, M. *Isoquinoline Alkaloids, Chemistry and Pharmacology*; Academic Press: New York, 1972.

2. (a) Guzman, F.; Cain, M.; Larscheid, P.; Hagen, T.; Cook, J. M.; Schweri, M.; Skolnick, P.; Paul, S. M. *J. Med. Chem.* **1984**, *27*, 564–570; (b) Dhar, N. C.; Maehr, R. B.; Masterson, L. A.; Midgley, J. M.; Stenlake, J. B.; Wastila, W. B. *J. Med. Chem.* **1996**, *39*, 556–561.
3. Grunewald, G. L.; Dahanukar, V. H.; Teoh, B.; Criscione, K. R. *J. Med. Chem.* **1999**, *42*, 1982–1990.
4. (a) Philippe, N.; Levacher, V.; Dupas, G.; Queguiner, G.; Bourguignon, J. *Org. Lett.* **2000**, *2*, 2185–2187; (b) Czombos, J.; Aelterman, W.; Tkachev, A.; Martins, J. C.; Tourwe, D.; Peter, A.; Toth, G.; Fulop, F.; De Kimpe, N. *J. Org. Chem.* **2000**, *65*, 5469–5475; (c) Davis, F. A.; Mohanty, P. K.; Burns, D. M.; Andemichael, Y. W. *Org. Lett.* **2000**, *2*, 3901–3903; (d) Monsees, A.; Laschat, S.; Dix, I.; Jones, P. G. *J. Org. Chem.* **1998**, *63*, 10018–10021; (e) Shinohara, T.; Takeda, A.; Toda, J.; Ueda, Y.; Kohno, M.; Sano, T. *Chem. Pharm. Bull.* **1998**, *46*, 918–927; (f) Alezra, V.; Bonin, M.; Micouin, L.; Husson, H.-P. *Tetrahedron Lett.* **2001**, *42*, 2111–2113; (g) Bois-Choussy, M.; Cadet, S.; Paolis, M. D.; Zhu, J. *Tetrahedron Lett.* **2001**, *42*, 4503–4506.
5. Grunewald, G. L.; Dahanukar, V. H.; Ching, P.; Criscione, K. R. *J. Med. Chem.* **1996**, *39*, 3539–3546.
6. (a) Katritzky, A. R.; Lan, X.; Zhang, Z. *J. Heterocycl. Chem.* **1993**, *30*, 381–387; (b) Katritzky, A. R.; Cobo-Domingo, J.; Yang, B.; Steel, P. J. *Tetrahedron: Asymmetry* **1999**, *10*, 255–263; (c) Katritzky, A. R.; Gordeev, M. F. *J. Org. Chem.* **1993**, *58*, 4049–4053; (d) Katritzky, A. R.; Cui, X.; Long, Q. *J. Heterocycl. Chem.* **1999**, *36*, 371–375.
7. (a) Locher, C.; Peerzada, N. *J. Chem. Soc., Perkin Trans. 1* **1999**, 179–184; (b) Locher, C.; Peerzada, N. *ARKIVOC* **2000**, *1*, 13–17.
8. (a) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409–548; (b) Katritzky, A. R.; Najzarek, Z.; Dega-Szafran, Z. *Synthesis* **1989**, 66–69; (c) Katritzky, A. R.; Fan, W.-Q. *J. Org. Chem.* **1990**, *55*, 3205–3209; (d) Katritzky, A. R.; Rachwal, B.; Rachwal, S.; Abboud, K. A. *J. Org. Chem.* **1996**, *61*, 3117–3126; (e) Katritzky, A. R.; Rachwal, S.; Wu, J. *Can. J. Chem.* **1990**, *68*, 446–455.
9. (a) Katritzky, A. R.; Noble, G.; Pilarski, B.; Harris, P. *Chem. Ber.* **1990**, *123*, 1443–1445; (b) Katritzky, A. R.; Pilarski, B.; Urogdi, L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 541–547.
10. Katritzky, A. R.; Yannakopoulou, K.; Lue, P.; Rasala, D.; Urogdi, L. *J. Chem. Soc., Perkin Trans. 1* **1989**, 225–233.
11. (a) Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683–2732; (b) Katritzky, A. R.; Qiu, G.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1998**, *63*, 6699–6709; (c) Katritzky, A. R.; Qiu, G.; He, H.-Y.; Yang, B. *J. Org. Chem.* **2000**, *65*, 3683–3689; (d) Katritzky, A. R.; Mehta, S.; He, H.-Y.; Cui, X. *J. Org. Chem.* **2000**, *65*, 4364–4369; (e) Katritzky, A. R.; Mehta, S.; He, H.-Y. *J. Org. Chem.* **2001**, *66*, 148–152.
12. Douat, C.; Heitz, A.; Martinez, J.; Fehrentz, J.-A. *Tetrahedron Lett.* **2000**, *41*, 37–40.
13. Monsees, A.; Laschat, S.; Kotila, S.; Fox, T.; Wuerthwein, E.-U. *Liebigs Ann.* **1997**, *3*, 533–540.
14. Clarke, C. B.; Pinder, A. R. *J. Chem. Soc.* **1958**, 1967–1976.
15. Bick, I. R. C.; Bremner, J. B.; Cava, M. P.; Wiriyachitra, P. *Aust. J. Chem.* **1978**, *31*, 321–326.