

Synthesis of homochiral propargyl amines from *N*-(Boc)-tetrahydro-2*H*-1,3-oxazines

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Alastair Rae,^a José L. Castro^b and Alethea B. Tabor^{*a}

^a Department of Chemistry, University College London, 20 Gordon Street, London, UK WC1H 0AJ

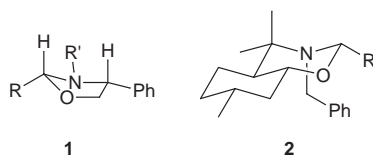
^b Merck Sharp and Dohme Research Laboratories, Terlings Park, Eastwick Road, Harlow, Essex, UK CM20 2QR

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The functionalisation of homochiral *N*-(Boc)-tetrahydro-2*H*-1,3-oxazines with the Grignard reagent of (trimethylsilyl)acetylene under Lewis acidic conditions is described. This leads directly to homochiral propargyl amines in good yields, under mild conditions, and with moderate to good enantioselectivities. The stereochemistry of the major enantiomer was determined to be (*R*) by correlation, and a mechanism for the ring opening reaction has been proposed on this basis.

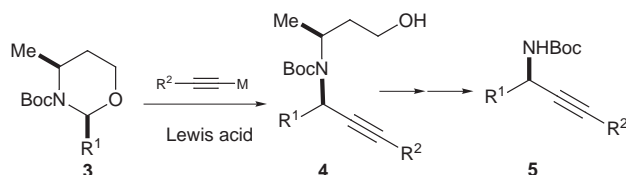
Introduction

The stereoselective synthesis of amines by ring-opening of *N,O*-acetals (aminals) by organometallic reagents has recently received attention from a number of groups.¹ For example, 2-aliphatic² and 2-aryl^{2,3} 1,3-oxazolidines **1** have been treated with aliphatic Grignard and other organometallic reagents, followed by cleavage *via* hydrogenolysis or oxidative methods to afford homochiral aliphatic and benzyl amines in moderate to good enantiomeric excesses (ee). Bicyclic *N*-benzyl-tetrahydro-2*H*-1,3-oxazines **2** derived from (+)-pulegone have also been



reacted with Grignard and organoaluminium reagents;⁴ subsequent treatment with P₂O₅, followed by hydrogenolysis, also led to homochiral aliphatic amines in high ee. However, these methods have not been used to access homochiral propargylic (prop-2-ynyl) amines, probably because the harsh conditions required for removal of the chiral auxiliary and the amine protecting groups would be incompatible with the sensitive functionality.

We wish to report a novel method for the synthesis of homochiral propargyl amines *via* the functionalisation of chiral *N*-(Boc)-tetrahydro-2*H*-1,3-oxazines **3**. Our approach (Scheme 1) involves ring-opening of the tetrahydrooxazines with an



Scheme 1

appropriate acetylenic nucleophile. This is followed by a mild, two step procedure which simultaneously removes the chiral directing group and the nitrogen protecting group, followed by reprotection of the amine.

Results and discussion

Ring opening of tetrahydro-2*H*-1,3-oxazines with acetylenic nucleophiles

In the preceding paper,⁵ we reported the synthesis of a series of *N*-(Boc)-tetrahydro-2*H*-1,3-oxazines **3** from (*S*)-*N*-(Boc)-3-aminobutan-1-ol and appropriate diethyl acetals. We also determined the structure, and the unusual conformation, adopted by these aminals, as the configuration at the 2-position is crucial to understanding the mechanism of the subsequent ring-opening reaction.

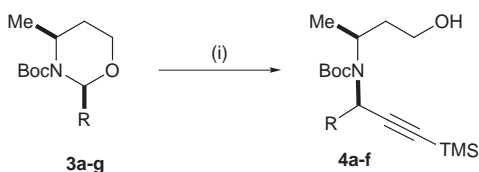
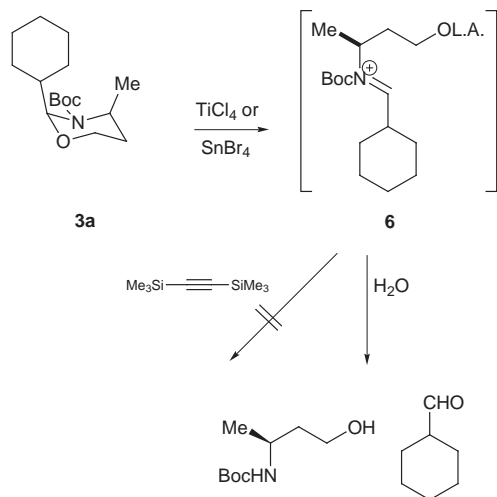
A few groups have previously reported reactions between aminals and a variety of acetylenic nucleophiles. Aminals derived from formaldehyde have been converted to simple propargyl amines with acetylenic Grignard reagents,⁶ lithiated acetylenes,⁷ or *via* cuprate catalysed acetylene addition.⁸ Alkynyllithiums, in the presence of BF₃·Et₂O, have been used to ring-open achiral tetrahydro-2*H*-1,3-oxazines⁹ in moderate yields, and acyclic aminals have been amidalkylated with (trimethylsilyl)acetylenes in the presence of TiCl₄,¹⁰ and (tributylstannyl)acetylenes in the presence of BF₃.¹¹ A considerable amount of work on the ring-opening of homochiral acetals by bis(trimethylsilyl)acetylene in the presence of TiCl₄ has also been carried out.¹² We therefore explored the reaction of a number of acetylenic nucleophiles and Lewis acids with *N*-(Boc)-tetrahydro-2*H*-1,3-oxazines **3**.

Ring opening reactions of aminal **3a** were initially attempted with bis(trimethylsilyl)acetylene, using either TiCl₄ or SnBr₄ as the Lewis acid. In both cases, cyclohexanecarbaldehyde and *N*-(Boc)-3-aminobutan-1-ol were recovered in high yield. These results suggest that complexation of the aminal to the Lewis acid occurs, giving iminium ion **6**; however, the insufficient nucleophilicity of bis(trimethylsilyl)acetylene means that no further reaction takes place. On aqueous workup, the iminium ion is hydrolysed to give the observed products (Scheme 2).

Further combinations of nucleophile and Lewis acid were attempted (Table 1). Although many of these had been previously reported to react with aminals or acetals,^{13–15} the reactions with aminal **3a** were unsuccessful. The failure of alkynyllithiums to give the desired ring opened product in the presence of BF₃·Et₂O was particularly surprising, as a similar reaction has recently been described.⁹

As aminals have previously been successfully functionalised with alkyl and aryl Grignard reagents,^{2,3,4} we next investigated

the use of acetylenic Grignard reagents. Pridgen^{2a} has shown that the reaction of Grignard reagents with 2-aryl-1,3-oxazolindines requires 2.5–3 equivalents of Grignard reagent, presumably leading to the formation of the Lewis acidic MgBr₂. We therefore treated aminals **3a–f** with an excess of the Grignard reagent derived from trimethylsilylacetylene, in the presence of BF₃·Et₂O (Scheme 3), to give the required ring opened alcohols **4a–f** in good yields (Table 2). Surprisingly, the 2-benzyl aminal **3g** failed to give any of the required product, giving only decomposition products. This may be due to deprotonation at the benzylic position by the Grignard reagent, leading to elim-



a R = cyclohexyl **e** R = ((CH₃)₂CH)₃SiOCH₂CH₂CH₂CH₂CH₂
b R = *n*-hexyl **f** R = ((CH₃)₂CH)₃SiOCH₂CH₂CH₂
c R = *n*-propyl **g** R = CH₂Ph
d R = *iso*-propyl

Scheme 3 Reagents and conditions: (i) Me₃SiC≡CMgBr (4 equiv.), BF₃·OEt₂ (1.2 equiv.), THF, 30 °C, 45 min.

Table 1

Aminal	Nucleophile	Lewis acid	Yield (%)	Reference
3a	TMSC≡CLi	TiCl ₄	5	—
3a	TMSC≡CLi	BF ₃ ·Et ₂ O	0 ^a	9
3a	TMSC≡CH	SnCl ₄	0 ^a	13
3a	(TMSC≡C) ⁻ (AlMe ₃ Li) ⁺	—	0 ^b	14
3a	TMSC≡CSnMe ₃	BF ₃ ·Et ₂ O	0 ^b	15

^a Starting material was consumed. ^b Starting material was recovered.

Table 2

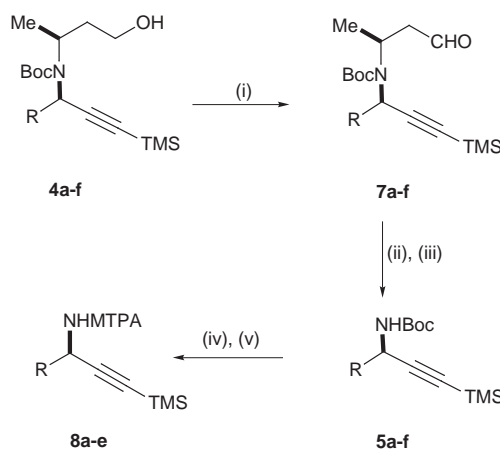
Aminal	de (%) ⁵	Alcohol	Yield (%)	Boc amine	Yield (%)	Mosher's amide	ee (%)
3a	96	4a	65	5a	69	8a	40
3b	72	4b	63	5b	65	8b	60
3c	72	4c	63	5c	46	8c	64
3d	78	4d	48	5d	60	8d	86
3e	80	4e	55	5e	31	8e	95
3f	100	4f	46	5f	77	11	52
3g	100	—	—	—	—	—	—

ination giving unknown by-products. This problem is probably enhanced by the relatively high temperatures required for the reaction.

Removal of the chiral directing group to give chiral propargyl amines

It was envisaged that removal of the chiral auxiliary could be effected by oxidation of the ring opened alcohol to the aldehyde followed by a retro-Michael β-elimination to reveal the required amine. Having introduced the acetylenic moiety, it was important that the chiral auxiliary could be removed without damaging both the triple bond and the new chiral centre; it was therefore desirable that strongly oxidising, basic or acidic conditions be avoided.

The Parikh–Doering variant¹⁶ of the Swern reaction gave smooth conversion of the alcohols to the aldehydes **7a–f**. All attempts to remove the chiral directing group under basic conditions¹² were unsuccessful, as was treatment with piperidinium acetate¹⁷ or acidic ion exchange resin. However, reaction of **7a–f** with aqueous 2 M HCl in THF at reflux for 3 hours allowed smooth cleavage of the auxiliary (Scheme 4), with con-

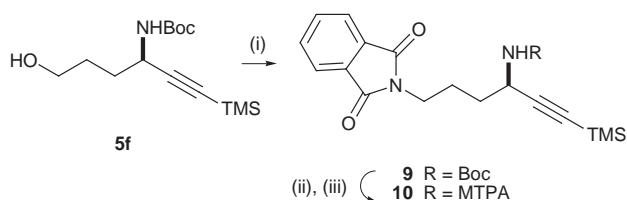


4a, 5a, 7a, 8a R = cyclohexyl
4b, 5b, 7b, 8b R = *n*-hexyl
4c, 5c, 7c, 8c R = *n*-propyl
4d, 5d, 7d, 8d R = *iso*-propyl
4e, 7e R = ((CH₃)₂CH)₃SiOCH₂CH₂CH₂CH₂CH₂
4f, 7f R = ((CH₃)₂CH)₃SiOCH₂CH₂CH₂
5e, 8e R = HOCH₂CH₂CH₂CH₂CH₂
5f R = HOCH₂CH₂CH₂

Scheme 4 Reagents and conditions: (i) DMSO, Et₃N, SO₃·pyridine, THF, N₂, 45 min; (ii) HCl (2 M), reflux, 3 h; (iii) Et₃N, (tBuOCO)₂O, CH₂Cl₂, 0 °C, 18 h; (iv) CF₃COOH, MeOH; (v) pyridine, (*S*)-MTPA-Cl, CH₂Cl₂, rt, 1 h.

comittant removal of the TIPS group from **7e** and **7f**. The amine hydrochloride salts were immediately reprotected as their Boc derivatives (**5a–f**), as unprotected propargyl amines have been shown to be unstable and prone to decomposition.¹⁸ The ee of **5a–e** were measured by removal of the Boc group and conversion to the (*S*)-Mosher's amides **8a–e** (Table 2).¹⁹

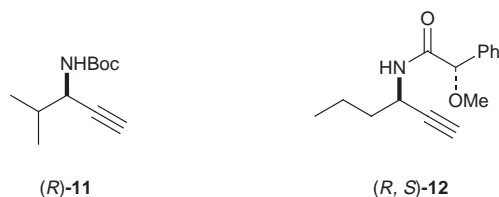
Propargyl amine **5f** was converted to phthalimide **9** prior to forming the (*S*)-Mosher's amide **10** (Scheme 5).



Scheme 5 Reagents and conditions: (i) Ph_3P , DEAD, phthalimide, THF, N_2 , 18 h; (ii) CF_3COOH , MeOH; (iii) pyridine, (*S*)-MTPA-Cl, CH_2Cl_2 , rt, 1 h.

Assignment of stereochemistry at the newly formed chiral centre

Assignment of the dominant absolute stereochemistry at the newly formed chiral centre of the amines **5a–f** was achieved by correlation to literature compounds. Amine **5d** was treated with 6 M HCl in order to remove the TMS and Boc groups; reprotection with Boc gave **11** in low yield. Comparison of the optical rotation with the literature values for this compound²⁰ indicated that the predominant enantiomer was the (*R*)-form.

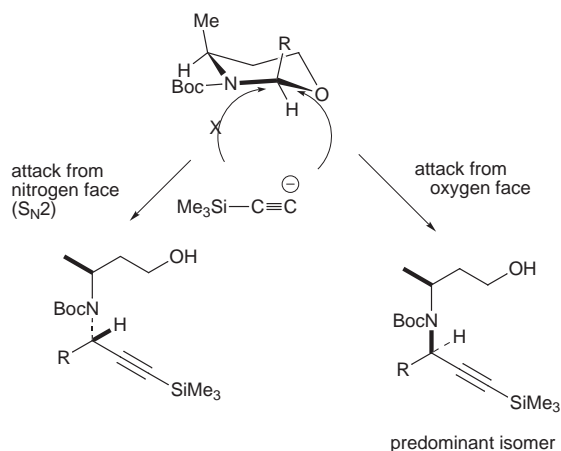


For confirmation, amine **5c** was also deprotected with 6 M HCl, and the resulting amine converted to the mandelamide **12** with (*S*)-(+)- α -methoxyphenylacetic acid. Comparison of the optical rotation of **12** with the literature value²¹ again indicated that the predominant enantiomer of amine **5c** was the (*R*)-form.

Mechanism of ring opening

Two factors control the stereochemistry of the newly formed chiral centre of the amines **5a–f**: the configuration of the chiral centre at C2 of the *N*-(Boc)-tetrahydro-2*H*-1,3-oxazines, and the direction of attack of the incoming nucleophile during the reaction with the Grignard reagents. The configuration at C2 is known from the structural work described in the preceding paper.⁵ The absolute stereochemistry of the amines described above, therefore, enables us to predict that the nucleophile predominantly attacks from the face of the oxygen atom, rather than the face of the nitrogen atom (Scheme 6).

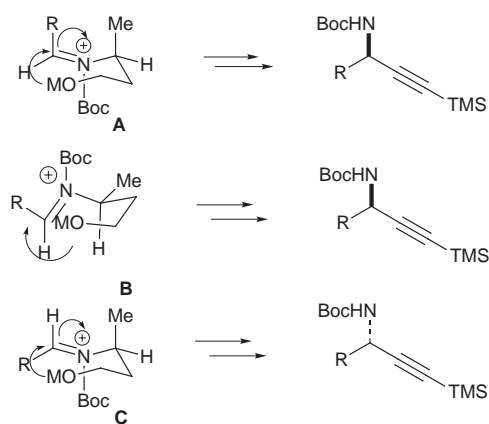
Previous work by Pedrosa on the ring-opening of *N*-benzyl-



Scheme 6

tetrahydro-2*H*-1,3-oxazines by Grignard reagents showed unambiguously that attack occurred from the face of the nitrogen atom, in an $\text{S}_{\text{N}}2$ -manner.^{4b} An equivalent stereochemical outcome was also reported by Takahashi for the ring-opening of *N*-methyl-1,3-oxazolidines by various organometallics, possibly indicating a similar mechanism.³ By contrast, Pridgen showed that the ring-opening of 1,3-oxazolidines without substituents on the nitrogen atom resulted in the opposite stereochemistry at the newly formed chiral centre;^{2a} this was attributed to equilibration of the 1,3-oxazolidine to the tautomeric imino alcohol, followed by attack of the nucleophile to a highly ordered, chelation complex resulting from the imino alcohol. The hypothesis that these unsubstituted 1,3-oxazolidines react *via* the imino alcohol is reinforced by studies on related imino ethers by Takahashi,^{3c} in which the stereochemical outcome is identical to that reported by Pridgen and opposite to that seen for the *N*-methyl-1,3-oxazolidines.

As the ring-opening reactions reported in this paper give the opposite stereochemistry to that reported by Pedrosa, and in addition, require an excess of the Grignard reagent, it is reasonable to assume that the reactions proceed *via* initial ring-opening to give an iminium ion, in line with the results reported by Pridgen. Furthermore, as the presence of one equivalent of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ is essential for ring opening to occur, it is possible that the reacting species is either an alkynylboron, for example, $\text{M} = \text{TMSC} \equiv \text{CBF}_2$, or an alkynylboronate, for example, $\text{M} = \text{TMSC} \equiv \text{CBF}_3^+ \text{MgBr}^-$. This would therefore lead us to consider some form of co-ordination mechanism, where the incoming nucleophile would be delivered by the oxygen to the iminium ion formed *via* initial ring opening. If this were the case then either conformer A (the immediate product of ring-opening) or conformer B (arising from rapid equilibration to the most stable allylic conformation)²² would furnish the observed major diastereomer (Scheme 7). A mechanism where



Scheme 7

$\text{BF}_3 \cdot \text{Et}_2\text{O}$ alone is acting as the Lewis acid and then directing the nucleophile by chelation is less likely, due to saturation of the coordination sphere of boron. Although the minor enantiomer could be accounted for by ring-opening of the minor tetrahydrooxazine diastereoisomer C (Scheme 7), the ee of the tetrahydrooxazine appears to be unrelated to the ee of the resulting amine (Table 2).⁵ This may suggest equilibration between major and minor tetrahydrooxazine diastereoisomers during the course of the reaction, or some other factor may be operational. Further studies, to elucidate the mechanism of this novel ring-opening reaction and to increase the enantioselectivity, are ongoing.

Experimental

Unless otherwise indicated, reagents were obtained from commercial suppliers and were used without further purification.

THF was distilled from sodium-benzophenone. CH_2Cl_2 was distilled from P_2O_5 and stored over 4 Å molecular sieves. DMSO, triethylamine and pyridine were distilled from CaH_2 and stored over 4 Å molecular sieves. Hexane is described as the fraction boiling between 67–70 °C unless otherwise stated. Flash column chromatography²³ was carried out using silica gel (particle size 40–63 µm) purchased from BDH. NMR spectra were recorded on Bruker AC 250 and Bruker AC 300 spectrometers operating at 250 and 300 MHz for ^1H ; 75 and 90 MHz for ^{13}C and 392 and 325.8 MHz for ^{19}F . Chemical shift (δ) values are measured in parts per million relative to the residual (undeuterated) solvent peak as an internal standard for ^1H and ^{13}C and relative to CFCl_3 for ^{19}F . J -Values are measured in Hz. Nominal and high resolution mass spectra were taken on a VG ZAB-SE spectrometer with sources for FAB and EI^+ . IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer. Optical rotations of chiral compounds were measured on a JASCO 600 spectrophotometer and an Optical Activity POLAAR 2000 polarimeter using sucrose as a standard and are given in units of 10^{-1} deg $\text{cm}^2 \text{g}^{-1}$. All rotations were taken as solutions in CHCl_3 unless otherwise stated.

General procedure for the ring-opening of tetrahydro-2H-1,3-oxazines 3a–f

To a stirred solution of EtMgBr (3 M in THF, 0.79 ml, 2.4 mmol) in anhydrous THF (2.5 ml) at 0 °C under N_2 was added trimethylsilylacetylene (0.33 ml, 2.42 mmol, 4.03 equiv.). A brown precipitate was formed which dissolved on heating to 30 °C. After 15 min a solution of the appropriate tetrahydro-2H-1,3-oxazine **3** (0.6 mmol) in THF (0.5 ml) was added, followed by $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.1 ml, 0.7 mmol, 1.17 equiv.). After 45 min the reaction was quenched with saturated NH_4Cl solution (5 ml) and extracted with EtOAc (3×25 ml). The combined organic layers were dried over Na_2SO_4 and the solvents removed *in vacuo* to give a viscous brown oil. Flash column chromatography over silica using the eluants indicated gave the required compounds.

(3S)-3-{N-(tert-Butoxycarbonyl)-N-[(1R)-3-trimethylsilyl-1-cyclohexylprop-2-ynyl]aminobutan-1-ol 4a. 65% (viscous yellow oil); $[a]_{\text{D}} +28.2$ (c 4.89 mg cm^{-3}); R_{F} 0.20 (20% EtOAc in hexane); ν_{max} (CHCl_3)/ cm^{-1} 3620 (O–H), 3020, 2153 ($\text{C}=\text{C}$), 1677 ($\text{C}=\text{O}$), 1271 (R–SiMe₃); δ_{H} (250 MHz; CDCl_3) 0.18 (9H, s, Si(CH₃)₃), 1.10–1.20 (3H, m, cyclohexyl), 1.21–1.30 (2H, m, cyclohexyl), 1.38 (3H, d, J 6.8, CH₃CH), 1.47 (9H, s, C(CH₃)₃), 1.61–1.81 (6H, m, cyclohexyl), 1.98–2.12 (3H, m, CH₂CH₂OH and CH₃CH), 3.52–3.74 (3H, m, CH₂CH₂OH and CHC≡C); δ_{C} (75 MHz; CDCl_3) 0.4, 20.3, 27.0, 29.2, 30.8, 32.1, 38.0, 42.4, 50.2, 55.5, 60.4, 61.3, 80.7, 81.4, 156.3; m/z (FAB) 382.2760 ($\text{M} + 1^+$). C₂₁H₄₀NO₃Si requires 382.2777, 382 ($\text{M} + 1$, 33%), 326 ($\text{M} - \text{tBu}$, 94%), 282 ($\text{M} - \text{Boc}$, 100%).

(3S)-3-{N-(tert-Butoxycarbonyl)-N-[(1R)-3-trimethylsilyl-1-hexylprop-2-ynyl]amino}butan-1-ol 4b. 63% (viscous yellow oil); $[a]_{\text{D}} +23.4$ (c 3.98 mg cm^{-3}); R_{F} 0.23 (20% EtOAc in hexane); ν_{max} (CHCl_3)/ cm^{-1} 3456 (O–H), 2960, 2930, 2172 ($\text{C}=\text{C}$), 1682 ($\text{C}=\text{O}$), 1250 (R–SiMe₃); δ_{H} (300 MHz; CDCl_3) 0.13 (9H, s, Si(CH₃)₃), 0.87 (3H, m, CH₃CH₂), 1.19–1.30 (10H, m, aliphatic), 1.28 (3H, d, J 6.8, CH₃CH), 1.45 (9H, s, C(CH₃)₃), 1.48–1.95 (3H, m, CH₂CH₂OH and CH₃CH), 3.59–3.76 (3H, m, CH₂CH₂OH and CHC≡C); δ_{C} (90 MHz; CDCl_3) –0.2, 13.9, 19.1, 22.4, 26.4, 28.4, 31.6, 35.1, 37.0, 47.4, 48.3, 58.6, 59.4, 80.1, 80.7, 105.2, 155.4; m/z (FAB) 384.2950 ($\text{M} + 1^+$). C₂₁H₄₂NO₃Si requires 384.2934 (ES⁺), 384 ($\text{M} + 1$, 10%), 328 ($\text{M} - \text{tBu}$, 100%), 284 ($\text{M} - \text{Boc}$, 16%).

(3S)-3-{N-(tert-Butoxycarbonyl)-N-[(1R)-3-trimethylsilyl-1-propylprop-2-ynyl]amino}butan-1-ol 4c. 63% (viscous yellow oil); $[a]_{\text{D}} +37.4$ (c 4.55 mg cm^{-3}); R_{F} 0.21 (20% EtOAc in hexane); ν_{max} (CHCl_3)/ cm^{-1} 3456 (O–H), 2963, 2934, 2171 ($\text{C}=\text{C}$), 1682 ($\text{C}=\text{O}$), 1251 (R–SiMe₃); δ_{H} (250 MHz; CDCl_3) 0.10 (9H, s, Si(CH₃)₃), 0.89 (3H, t, J 7.2, CH₃CH₂), 1.25–1.67 (4H, m, aliphatic), 1.28 (3H, d, J 6.8, CH₃CH₂), 1.44 (9H, s, C(CH₃)₃), 1.70–1.95 (3H, m, CH₂CH₂OH and CH₃CH), 3.49–3.65 (3H, m, CH₂CH₂OH and CHC≡C); δ_{C} (75 MHz; CDCl_3) 0.0, 13.8, 19.3, 19.9, 28.3, 28.6, 32.5, 37.6, 48.5, 60.5, 80.4, 105.3, 155.7; m/z (FAB) 342.2450 ($\text{M} + 1^+$). C₁₈H₃₆NO₃Si requires 342.2464 (ES⁺), 342 ($\text{M} + 1$, 9%), 286 ($\text{M} - \text{tBu}$, 100%), 242 ($\text{M} - \text{Boc}$, 94%).

(3S)-3-{N-(tert-Butoxycarbonyl)-N-[(1R)-3-trimethylsilyl-1-isopropylprop-2-ynyl]amino}butan-1-ol 4d. 48% (viscous yellow oil); $[a]_{\text{D}} +16.85$ (c 5.5 mg cm^{-3}); R_{F} 0.23 (20% EtOAc in hexane); ν_{max} (CHCl_3)/ cm^{-1} 3456 (O–H), 2967, 2172 ($\text{C}=\text{C}$), 1682 ($\text{C}=\text{O}$), 1250 (R–SiMe₃); δ_{H} (300 MHz; CDCl_3) 0.09 (9H, s, Si(CH₃)₃), 0.84 (3H, d, J 6.7, (CH₃)₂CH), 0.98–1.01 (3H, m, (CH₃)₂CH), 1.28 (3H, d, J 6.7, CH₃CH), 1.42 (9H, s, (CH₃)₃C), 1.81–2.18 (3H, m, (CH₃)₂CH and CH₂CH₂OH), 3.41–3.85 (4H, m, CH₂CH₂OH and CHC≡C and CH₃CH); δ_{C} (75 MHz; CDCl_3) –0.3, 19.4, 19.7, 20.7, 28.3, 32.2, 37.1, 47.6, 55.7, 58.6, 79.8, 84.8, 105.6, 155.6; m/z (FAB) 342.2450 ($\text{M} + 1^+$). C₁₈H₃₅NO₃Si requires 342.2464, 342 ($\text{M} + 1$, 40%), 241 ($\text{M} - \text{Boc}$, 70%), 198 (100%).

(3S)-3-{N-(tert-Butoxycarbonyl)-N-[(1R)-3-trimethylsilyl-1-(5-triisopropylsilyloxy-pentyl)prop-2-ynyl]amino}butan-1-ol 4e. 55% (viscous yellow oil); $[a]_{\text{D}} +15.7$ (c 3.89 mg cm^{-3}); R_{F} 0.23 (20% EtOAc in hexane); ν_{max} (CHCl_3)/ cm^{-1} 3457 (O–H), 2940, 2866, 2172 ($\text{C}=\text{C}$), 1682 ($\text{C}=\text{O}$), 1250 (R–SiMe₃), 1113 (RO–Si); δ_{H} (300 MHz; CDCl_3) 0.12 (9H, s, Si(CH₃)₃), 1.03 (21H, s, OSi(CH(CH₃)₂)₃), 1.10–1.59 (8H, m, aliphatic), 1.30 (3H, d, J 6.9, CH₃CH), 1.44 (9H, s, (CH₃)₃C), 1.60–2.05 (3H, m, CH₂CH₂OH and CH₃CH), 3.52–3.74 (3H, m, CH₂CH₂OH and CHC≡C), 3.64 (2H, t J 7.0, CH₂OSi), 4.12 (1H, br s, OH); δ_{C} (75 MHz; CDCl_3) –0.18, 11.92, 17.94, 19.05, 25.27, 25.33, 26.40, 28.44, 32.82, 35.28, 47.44, 48.34, 63.16, 80.20, 105.15, 155.43, either $1 \times \text{C}=\text{C}$ or (CH₃)₃CO missing; m/z (FAB) 564.3860 ($\text{M} + \text{Na}^+$). C₂₉H₅₉NO₄Si₂Na requires 564.3880, 564 ($\text{M} + \text{Na}$, 12%), 442 ($\text{M} - \text{Boc}$, 100%).

(3S)-3-{N-(tert-Butoxycarbonyl)-N-[(1R)-3-trimethylsilyl-1-(3-triisopropylsilyloxypropyl)prop-2-ynyl]amino}butan-1-ol 4f. 46% (yellow oil); $[a]_{\text{D}} +16.9$ (c 7.5 mg cm^{-3}); R_{F} 0.27 (20% EtOAc in hexane); ν_{max} (CHCl_3)/ cm^{-1} 3471 (O–H), 2943, 2867, 2172 ($\text{C}=\text{C}$), 1693 ($\text{C}=\text{O}$), 1250 (R–SiMe₃), 1114 (RO–Si); δ_{H} (300 MHz; CDCl_3) 0.19 (9H, s, Si(CH₃)₃), 1.14 (21H, s, OSi(CH(CH₃)₂)₃), 1.28–1.35 (2H, m, aliphatic), 1.33 (3H, d, J 6.8, CH₃CH), 1.52 (9H, s, (CH₃)₃C), 1.57–1.81 (2H, m, CH₂–CHC≡C), 1.98–2.01 (3H, m, CH₂CH₂OH and CH₃CH), 3.57–3.67 (2H, m, CH₂CH₂OH), 3.70–3.81 (3H, m, CHC≡C and CH₂OSi); δ_{C} (75 MHz; CDCl_3) –0.18, 11.92, 17.94, 19.05, 26.40, 28.44, 32.82, 35.28, 47.44, 48.34, 62.77, 80.15, 104.95, 155.48, either $1 \times \text{C}=\text{C}$ or tBuCO missing; m/z (FAB) 536.3580 ($\text{M} + \text{Na}^+$). C₂₇H₅₅NO₄Si₂Na requires 536.3567, 536 ($\text{M} + \text{Na}$, 11%), 414 ($\text{M} - \text{Boc}$, 100%).

General procedure for the synthesis of Boc-protected amines 5a–f

To a solution of alcohol **4** (1.94 mmol) in anhydrous THF (1.5 ml) under N_2 were added DMSO (13 ml) and triethylamine (1.94 ml). The $\text{SO}_3 \cdot \text{pyridine}$ complex (5.82 mmol; 3 equiv.) was added over 10 min. The reaction was stirred for 45 min, after which it was cooled to 0 °C, acidified with HCl (1 M; *ca.* pH = 4) and extracted with EtOAc –hexane (1 : 1; 3×20 ml). The combined organic layers were washed with water (40 ml) and dried over Na_2SO_4 . The solvents were removed *in vacuo* to give a clear oil. Column chromatography gave the desired aldehyde as a clear oil.

To a solution of the aldehyde (0.08 mmol) in THF (0.5 ml)

was then added HCl (2 M; 1.5 ml). The solution was heated at reflux for 3 hours, whereupon a brown precipitate was seen to form and TLC indicated the complete consumption of starting material. The solvents were removed *in vacuo* to give an off-white solid. This was dissolved in CH₂Cl₂ (1 ml) and cooled to 0 °C. Triethylamine (0.03 ml, 0.2 mmol, 2.53 equiv.) was added followed by a solution of di-*tert*-butyl dicarbonate (52.3 mg, 0.24 mmol, 3.0 equiv.) in CH₂Cl₂ (0.5 ml). The mixture was stirred overnight, then poured into water (2 ml) and extracted with CHCl₃ (3 × 2 ml). The combined organic layers were dried over Na₂SO₄ and the solvent removed *in vacuo* to give a yellow oil. Flash column chromatography over silica using the eluents indicated gave the required product. Yields are quoted over 3 steps.

The ee's of the Boc-protected amines **5a–e** were determined by conversion to the Mosher's amides, as follows. To a solution of **5** (1 mmol) in wet methanol (0.7 ml) was added trifluoroacetic acid (7 ml). The mixture was stirred until no starting material was detectable by TLC. Et₂O (10 ml) was added and the solvents were removed *in vacuo* to give an off-white solid. The solid was dissolved in CH₂Cl₂ (3 ml) and the solution was cooled to 0 °C. Pyridine (6 ml) was added followed by (*S*)-methoxytrifluoromethylphenylacetyl chloride (0.24 ml, 1.4 mmol, 1.4 equiv.). The mixture was stirred for 1 h, then poured into saturated NaHCO₃ solution (5 ml) and extracted with CH₂Cl₂ (3 × 5 ml). The combined organic layers were dried over Na₂SO₄ and the solvents removed to give the required Mosher's amides **8a–e**.

(1R)-N-(tert-Butoxycarbonyl)-3-(trimethylsilyl)-1-cyclohexylprop-2-yn-1-ylamine 5a. 69% (viscous oil); [α]_D +35.9 (*c* 2.9 mg cm⁻³); R_F 0.52 (20% EtOAc in hexane); ν_{\max} (CHCl₃)/cm⁻¹ 3619 (N–H), 3020, 2931, 2171 (C≡C), 1679 (C=O), 1215; δ_H (300 MHz; CDCl₃) 0.17 (9H, s, Si(CH₃)₃), 1.00–1.41 (6H, m, cyclohexyl), 1.46 (9H, s, C(CH₃)₃), 1.62–1.93 (5H, m, cyclohexyl), 4.35 (1H, m, *CHC*≡C), 4.72 (1H, m, NH); m/z (FAB) 332.2010 (M + Na⁺). C₁₇H₃₁NO₂SiNa requires 332.2022), 308.2030 (M – H⁺). C₁₇H₃₀NO₂Si requires 308.2046) 332 (M + Na), 308 (M – 1).

Mosher's amide derivative. δ_H (300 MHz; CDCl₃) 0.14 (9H, s, Si(CH₃)₃), 1.40–1.78 (11H, m, cyclohexyl), 3.56 (3H, s, OCH₃), 4.78 (1H, m, *CHC*≡C), 7.38–7.48 (5H, m, Ph); δ_F (325.8 MHz; CDCl₃) –69.13 (60%), –69.19 (40%).

(3R)-N-(tert-Butoxycarbonyl)-1-(trimethylsilyl)non-1-yn-3-ylamine 5b. 65% (viscous oil); [α]_D +23.0 (*c* 5 mg cm⁻³); R_F 0.53 (20% EtOAc in hexane); ν_{\max} (CHCl₃)/cm⁻¹ 3448 (N–H), 2961, 2929, 2254 (C≡C), 1708 (C=O), 1250 (R–SiMe₃); δ_H (300 MHz; CDCl₃) 0.18 (9H, s, Si(CH₃)₃), 0.92 (3H, t, *J* 7.0, CH₂CH₃), 1.23–1.40 (4H, m, CH₂CH₂CH₃ and CH₂CH₂CH₃), 1.49 (9H, s, C(CH₃)₃), 1.58–1.62 (6H, m, CH aliphatic), 4.41 (1H, m, *CHC*≡C), 4.70 (1H, br s, NH); δ_C (75 MHz; CDCl₃) 0.0, 13.7, 14.1, 18.9, 22.6, 25.6, 28.4, 28.2, 29.8, 31.7, 36.5, 105.8, 154.7; m/z (FAB) 312.2370 (M + H⁺). C₁₇H₃₄NO₂Si requires 312.2359), 312 (M + 1, 10%), 256 (100%).

Mosher's amide derivative. δ_H (300 MHz; CDCl₃) 0.14 (9H, s, Si(CH₃)₃), 0.84–0.94 (3H, m, CH₂CH₃), 1.20–1.38 (6H, m, aliphatic), 1.53–1.72 (4H, m, aliphatic), 3.56 (3H, s, OCH₃), 4.80 (1H, m, *CHC*≡C), 7.41–7.52 (5H, m, Ph); δ_F (325.8 MHz; CDCl₃) –69.07 (80%), –69.22 (20%).

(3R)-N-(tert-Butoxycarbonyl)-1-(trimethylsilyl)hex-1-yn-3-ylamine 5c. 46% (viscous oil); [α]_D +25.2 (*c* 4.7 mg cm⁻³); R_F 0.50 (20% EtOAc in hexane); ν_{\max} (CHCl₃)/cm⁻¹ 3448 (N–H), 2963, 2931, 2254 (C≡C), 1708 (C=O), 1250 (R–SiMe₃); δ_H (300 MHz; CDCl₃) 0.18 (9H, s, Si(CH₃)₃), 0.97 (3H, t, *J* 7.0, CH₂CH₃), 1.23–1.36 (2H, m, CH₂CH₂CH₃), 1.45 (9H, s, C(CH₃)₃), 1.58–1.65 (2H, m, CH₂CH₂CH₃), 4.40 (1H, m, *CHC*≡C), 4.70 (1H, br s, NH); δ_C (75 MHz; CDCl₃) 0, 13.70, 18.93, 28.43, 31.75, 67.16, 105.76, 154.68 ⁴BuCO and 1 × C≡C

missing; m/z (FAB) 270.1870 (M + H⁺). C₁₄H₂₈NO₂Si requires 270.1889), 270 (M + 1, 9%), 256 (80%), 214 (100%).

Mosher's amide derivative. δ_H (300 MHz; CDCl₃) 0.15 (9H, s, Si(CH₃)₃), 0.89–0.98 (3H, m, CH₂CH₃), 1.44–1.65 (4H, m, CH₂CH₂CH₃ and CH₂CH₂CH₃), 3.56 (3H, s, OCH₃), 4.80 (1H, m, *CHC*≡C), 7.31–7.44 (5H, m, Ph); δ_F (325.8 MHz; CDCl₃) –69.07 (82%), –69.22 (18%).

(3R)-N-(tert-Butoxycarbonyl)-1-trimethylsilyl-4-methylpent-1-yn-3-ylamine 5d. 60% (viscous oil); [α]_D +18.6 (*c* 5.15 mg cm⁻³); R_F 0.50 (20% EtOAc in hexane); ν_{\max} (CHCl₃)/cm⁻¹ 3448 (N–H), 2963, 2930, 2254 (C≡C), 1708 (C=O), 1250 (R–SiMe₃); δ_H (300 MHz; CDCl₃) 0.14 (9H, s, Si(CH₃)₃), 0.95 (6H, d, *J* 6.9, CH(CH₃)₂), 1.44 (9H, s, C(CH₃)₃), 1.87 (1H, octet, *J* 6.6, CH(CH₃)₂), 4.29 (1H, m, *CHC*≡C), 4.77 (1H, br s, NH); δ_C (75 MHz; CDCl₃) –0.2, 17.3, 18.6, 28.2, 33.0, 49.2, 88.1, 103.8, 154.8; m/z (FAB) 270.1880 (M + H⁺). C₁₄H₂₈NO₂Si requires 270.1889), 270 (M + 1, 14%), 214 (100%), 170 (M – Boc, 75%).

Mosher's amide derivative. δ_H (300 MHz; CDCl₃) 0.21 (9H, s, Si(CH₃)₃), 1.01 (6H, d, *J* 7.0, CH(CH₃)₂), 2.01 (1H, m, CH(CH₃)₂), 3.62 (3H, s, OCH₃), 4.66 (1H, m, *CHC*≡C), 7.35–7.69 (5H, m, Ph); δ_F (325.8 MHz; CDCl₃) –76.29 (93%), –76.32 (7%).

(6R)-6-[(tert-Butoxycarbonyl)amino]-8-trimethylsilyloct-7-yn-1-ol 5e. 31% (viscous oil); [α]_D +36.7 (*c* 1.2 mg cm⁻³); R_F 0.27 (20% EtOAc in hexane); ν_{\max} (CHCl₃)/cm⁻¹ 3620 (O–H), 3450 (N–H), 2961, 2929, 2254 (C≡C), 1708 (C=O), 1250 (R–SiMe₃); δ_H (300 MHz; CDCl₃) 0.16 (9H, s, Si(CH₃)₃), 1.41 (9H, s, C(CH₃)₃), 1.49–1.70 (6H, m, aliphatic), 1.78–1.82 (2H, m, CH₂CHC≡C), 3.50 (1H, br s, OH), 3.58 (2H, t, *J* 6.5, CH₂OH), 4.34 (1H, m, *CHC*≡C), 4.92 (1H, br d, *J* 8.2, NH); δ_C (75 MHz; CDCl₃) –0.2, 25.1, 28.3, 32.5, 36.0, 36.4, 43.3, 62.6, 70.9, 105.3, 154.8; m/z (FAB) 314.2140 (M + H⁺). C₁₆H₃₂NO₃Si requires 314.2151), 314 (M + 1, 15%), 258 (100%), 214 (M – Boc, 30%).

Bis-Mosher's amide derivative. δ_H (300 MHz; CDCl₃) 0.18 (9H, s, Si(CH₃)₃), 1.47–1.53 (6H, m, aliphatic), 1.65–1.82 (2H, m, aliphatic), 3.66 (6H, s, OCH₃), 4.35 (2H, t, *J* 8.0, CH₂OH), 4.76 (1H, m, *CHC*≡C), 7.30–7.67 (10H, m, Ph); δ_F (325.8 MHz; CDCl₃) {–75.20 (95%), –75.26 (5%)} (C¹F₃), –75.88 (100%) (C²F₃).

(4R)-4-[(tert-Butoxycarbonyl)amino]-6-trimethylsilylhex-5-yn-1-ol 5f. 77% (viscous oil); [α]_D +11.7 (*c* 62 mg cm⁻³); R_F 0.25 (20% EtOAc in hexane); ν_{\max} (CHCl₃)/cm⁻¹ 3621 (O–H), 3448 (N–H), 2961, 2929, 2254 (C≡C), 1708 (C=O), 1250 (R–SiMe₃); δ_H (300 MHz; CDCl₃) 0.14 (9H, s, Si(CH₃)₃), 1.44 (9H, s, C(CH₃)₃), 1.60–1.80 (4H, m, CH₂CH₂CH₂OH and CH₂CH₂CH₂OH), 2.10 (1H, br s, OH), 3.61–3.78 (2H, m, CH₂OH), 4.43 (1H, m, *CHC*≡C), 4.88 (1H, br d, *J* 6.2, NH); δ_C (75 MHz; CDCl₃) –0.4, 27.6, 32.4, 47.5, 64.3, 66.4, 81.7, 104.6, 154.6; m/z (FAB) 286.1850 (M + H⁺). C₁₄H₂₈NO₃Si requires 286.1838), 308 (M + Na, 20%), 286 (M + 1, 25%), 230 (100%), 186 (M – Boc, 30%).

(3R)-N-(tert-Butoxycarbonyl)-1-(trimethylsilyl)-6-phthalimido-hex-1-yn-3-ylamine 9

To a solution of (4R)-4-[(*tert*-butoxycarbonyl)amino]-6-trimethylsilylhex-5-yn-1-ol **5f** (0.135 g, 0.5 mmol), triphenylphosphine (0.150 g, 0.55 mmol, 1.1 equiv.) and phthalimide (0.082 g, 0.55 mmol, 1.1 equiv.) in THF (5 cm³) was added diethyl azodicarboxylate (0.11 cm³, 0.66 mmol, 1.32 equiv.) dropwise over 5 min. The mixture was stirred overnight (16 h) and then the solvents were removed *in vacuo*. Column chromatography (silica gel; 50% EtOAc in hexane; R_F 0.68) gave the title compound as a pale yellow solid (0.122 g; 60%); [α]_D +12.7 (*c* 39 mg cm⁻³); ν_{\max} (CHCl₃)/cm⁻¹ 3619 (N–H), 3020, 2400 (C≡C), 1711 (C=O), 1520 (C=C, Ar), 1216 (R–SiMe₃); δ_H (300

MHz; CDCl₃) 0.14 (9H, s, Si(CH₃)₃), 1.43 (9H, s, C(CH₃)₃), 1.63–1.75 (2H, m, C≡C–CHCH₂), 1.78–1.87 (2H, m, CH₂CH₂N), 3.73 (2H, t, *J* 7.0, CH₂CH₂N), 4.10 (1H, m, C≡C–CHCH₂), 4.49 (1H, br s, NH), 7.72 (2H, m, Ph), 7.84 (2H, m, Ph); δ_C (75 MHz; CDCl₃) –0.2, 24.9, 28.3, 33.6, 37.5, 43.3, 79.8, 87.9, 104.7, 123.2, 132.1, 133.8, 154.6, 168.2; *m/z* (FAB) 437.1860 (M + Na⁺. C₂₂H₃₀N₂O₄SiNa requires 437.1873), 437 (M + Na).

This was converted to the Mosher's amide **10** by the method described above; δ_H (300 MHz; CDCl₃) 0.18 (9H, s, Si(CH₃)₃), 1.65–1.97 (4H, m, C≡C–CHCH₂ and CH₂CH₂N), 3.10–3.15 (2H, m, CH₂CH₂N), 3.74 (3H, s, OCH₃), 4.18 (1H, m, *J* 8.5, C≡C–CHCH₂), 7.30–7.47 (5H, m, Ph), 7.50–7.60 (2H, m, Ph), 7.81–7.90 (2H, m, Ph); δ_F (392 MHz; CDCl₃) –69.33 (76%), –69.45 (24%).

Correlation of the stereocentre of Boc-protected amine **5d** by conversion to (3*R*)-*N*-(*tert*-butoxycarbonyl)-4-methylpent-1-yn-3-ylamine **11**

(3*R*)-*N*-(*tert*-Butoxycarbonyl)-1-trimethylsilyl-4-methylpent-1-yn-3-ylamine **5d** (2.9 mg, 0.011 mmol) was suspended in aqueous HCl (6 M; 1 ml) and heated at 100 °C for 2 h. The solvent was removed *in vacuo* and the white residue was dissolved in CH₂Cl₂ (0.4 ml). Triethylamine (0.5 ml) was added followed by a solution of di-*tert*-butyl dicarbonate (7.2 mg, 0.033 mmol, 3 equiv.) in CH₂Cl₂ (0.1 ml). The mixture was stirred for 24 h, after which the solvents were removed *in vacuo*. The residue was purified by column chromatography (silica gel; 20% EtOAc in hexane; *R*_F 0.45) to give the title compound as a clear oil (5 mg, 23%), spectroscopically identical with the literature.²⁰ [*a*]_D +24.0 (*c* 0.25 mg cm⁻³) [lit., for (*S*)-*N*-(*tert*-butoxycarbonyl)-4-methylpent-1-yn-3-ylamine²⁰ –45.3 (*c* 1.04 mg cm⁻³)]; δ_H (300 MHz; CDCl₃) 0.98 (6H, d, *J* 6.8, CH(CH₃)₂), 1.44 (9H, s, C(CH₃)₃), 1.89 (1H, octet, *J* 6.0, CH(CH₃)₂), 2.25 (1H, d, *J* 2.4, C≡CH), 4.31 (1H, m, C≡C–CHCH₂), 4.78 (1H, br s, NH).

Correlation of the stereocentre of Boc-protected amine **5c** by conversion to (2*S*)-*N*-[(3*R*)-hex-1-yn-3-yl]-2-methoxyphenylacetamide **12**

(3*R*)-*N*-(*tert*-Butoxycarbonyl)-1-(trimethylsilyl)hex-1-yn-3-ylamine **5c** (4.2 mg, 0.016 mmol) was suspended in aqueous HCl (6 M; 2 ml) and heated at 100 °C for 2 h. The solvent was removed *in vacuo* to give the hydrochloride salt of the free amine. To a solution of (*S*)-(+)-*α*-methoxyphenylacetic acid (5.3 mg, 0.032 mmol, 2 equiv.) in anhydrous CH₂Cl₂ (0.5 ml) was added triethylamine (0.005 ml, 0.032 mmol, 2 equiv.) and isobutyl chloroformate (0.004 ml, 0.032 mmol, 2 equiv.). The mixture was stirred at room temperature for 30 min, and the hydrochloride salt of the free amine and a further portion of triethylamine (0.005 ml, 0.032 mmol, 2 equiv.) then added in anhydrous CH₂Cl₂ (0.5 ml). The mixture was stirred for 24 h, after which the solvents were removed *in vacuo*. The residue was purified by column chromatography (silica gel; 20% EtOAc in hexane; *R*_F 0.24) to give the title compound **12** as a white solid (1.2 mg, 31%), spectroscopically identical with the literature,²¹ [*a*]_D +47.9 (*c* 0.48 mg cm⁻³, EtOH) (lit., for *N*-[(*S*)-hex-1-yn-3-yl]-(*R*)-2-methoxyphenylacetamide –141.6 (*c* 1.0 mg cm⁻³, EtOH); δ_H (300 MHz; CDCl₃) 0.90 and 0.99 (3H, 2 × t (major and minor diastereoisomers), *J* 7.2, CH₂CH₃), 1.25–1.65 (4H,

m, CH₂CH₂CH₃ and CH₂CH₂CH₃), 2.26 and 2.30 (1H, 2 × d (major and minor diastereoisomers), *J* 2.3, C≡CH), 3.38 (3H, s, OCH₃), 4.6 (1H, s, CHOCH₃), 4.65 (1H, m, C≡C–CHCH₂), 6.90 (1H, br m, NH), 7.25–7.44 (5H, m, Ph).

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