Novel, Regioselective Allylamine Construction; First Synthesis of Geranyllinaloisocyanide, a Diterpene from the Marine Sponge, *Halichondria Sp.*

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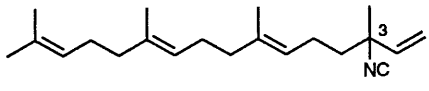
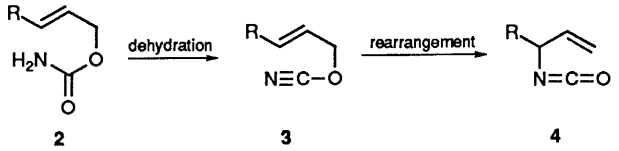
The first synthesis of the diterpene, 3-isocyano-3,7,11,15-tetramethylhexadeca-1,6,10,14-tetraene (geranyllinaloisocyanide, **1**), has been achieved through an allyl cyanate-to-isocyanate rearrangement. The crucial step in this synthesis is *in situ* transformation of allyl isocyanates into stable allyl acetamides with trimethylaluminium.

During a screening program for bioactive constituents of marine sponges, Scheuer and co-workers isolated the diterpenoid isocyanide, geranyllinaloisocyanide **1**, from a marine sponge (*Halichondria sp.*) as an active compound against *Staphylococcus aureus*.[1] This molecule is the isocyanide analogue of the known jasmine constituent geranyllinalool with characteristic isocyanide substituent at the sterically crowded C-3 position as shown below. In this report, we present the first synthesis of the novel isocyanide **1** by using an allyl cyanate-to-isocyanate rearrangement for construction of the nitrogen substituent at C-3 position.



1

An allyl cyanate-to-isocyanate rearrangement has been achieved by dehydration of the allyl carbamates **2** as shown in Scheme 1.[2] Dehydration of the allyl carbamates **2** provides the allyl cyanates **3**, which smoothly undergo [3,3] sigmatropic rearrangement to the isocyanates **4** below ambient temperature.

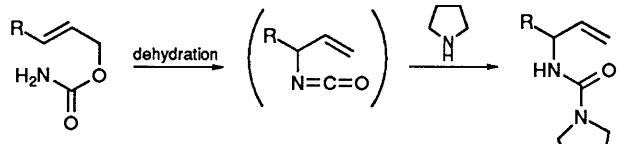


2 **3** **4**

Scheme 1

This reaction may offer a general approach to the regioselective synthesis of allylamines at sterically congested positions. However, the most serious problem with this reaction lies in the difficulty of isolating allyl isocyanates **4** due to the high reactivity of the isocyanate function. Indeed, secondary isocyanates react with water during aqueous work-up. Although tertiary isocyanates survive under careful aqueous work-up, purification by silica gel chromatography causes a decrease of isolated yields.

As a method to avoid these problems, we recently documented the conversion of the isocyanates **4** into the stable ureas **5** by reaction with pyrrolidine as shown in Scheme 2.[2] In this case, the yields of the reactions were determined as isolated yields of the ureas **5**. However, this reaction sequence has a drawback associated with the low reactivity of the ureas **5** which prevents their easy transformation into the corresponding amines. In this context, it was necessary to find a more reliable derivatization of the allyl isocyanates **4**.

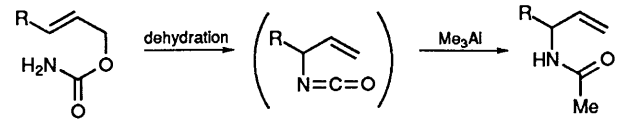


2 **4** **5**

Scheme 2

Results and Discussion

After a series of disappointing results, we realized an efficient transformation of the isocyanates **4** involving the use of trimethylaluminium (Me_3Al). Indeed, reaction of the isocyanates **4** with trimethylaluminium provided the acetamides **6** without isolation of the unstable isocyanates **4** as shown in Scheme 3.[3]



2 **4** **6**

Scheme 3

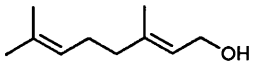
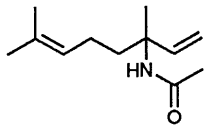
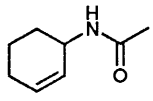
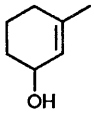
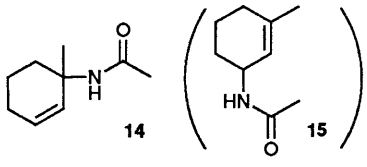
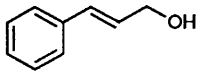
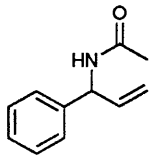
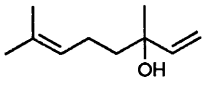
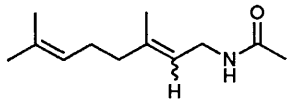
Scheme 4 outlines a typical example of this reaction sequence. Reaction of geraniol **7** with trichloroacetyl isocyanate followed by hydrolysis with potassium carbonate in aqueous methanol provided the carbamate **8**.[4] Treatment of this carbamate **8** with trifluoromethanesulfonic anhydride (Tf_2O) and diisopropylethylamine at −78 °C gave the isocyanate **9** which was transformed *in situ* into the acetamide **10** by reaction with trimethylaluminium. The acetamide **10** was isolated in 81% overall yield from geraniol **7** after chromatographic purification. The generality of this successful reaction sequence for the synthesis of allylamines is evident from five representative examples shown in Table 1.

Having achieved a highly efficient method for the synthesis of allylamines through an allyl cyanate-to-isocyanate rearrangement, we applied this method to the synthesis of geranyllinaloisocyanide **1** as shown in Scheme 5.

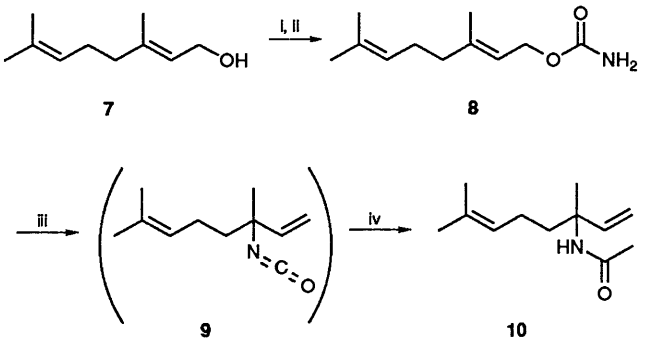
Transformation of geranylgeraniol* **20** to the allyl acetamide **22** was accomplished under similar conditions as those previously described in 59% overall yield. Conversion of the acetamide **22** to geranyllinaloisocyanide **1** was straightforward. Thus, treatment of **22** with Meerwein's reagent ($Et_3O^+ \cdot BF_4^-$) and then with acetic acid (AcOH) in aqueous tetrahydrofuran (THF) provided the corresponding amine,[6] which on treatment

* The authors thank Kuraray Co., Ltd. for supplying a sample of geranylgeraniol.

Table 1 Synthesis of allyl acetamide from allyl alcohol[a]

Entry	Substrate		Product		Yield (%)[b]
1		7		10	81
2		11		12	66
3		13		14 15	37(4)
4		16		17	71
5		18		19	62

[a] Reactions were performed according to the procedures reported in the Experimental section. [b] Isolated yields after chromatographic purification from starting allyl alcohols.



Scheme 4 *Reagents:* i, CCl_3CONCO; ii, K_2CO_3, aq. MeOH; iii, Tf_2O, Pr^i_2 NEt; iv, Me_3Al

with acetic formic anhydride furnished the formamide **23** in 84% overall yield from **22**.[7] Finally, the formamide **23** was smoothly transformed into **1** in 82% yield using triphenylphosphine, tetrabromomethane and diisopropylethylamine at −20 °C for 30 min.[8] Spectral data (^{1}H NMR and ^{13}C NMR) of synthetic **1** were in good agreement with those reported in the literature.[1]

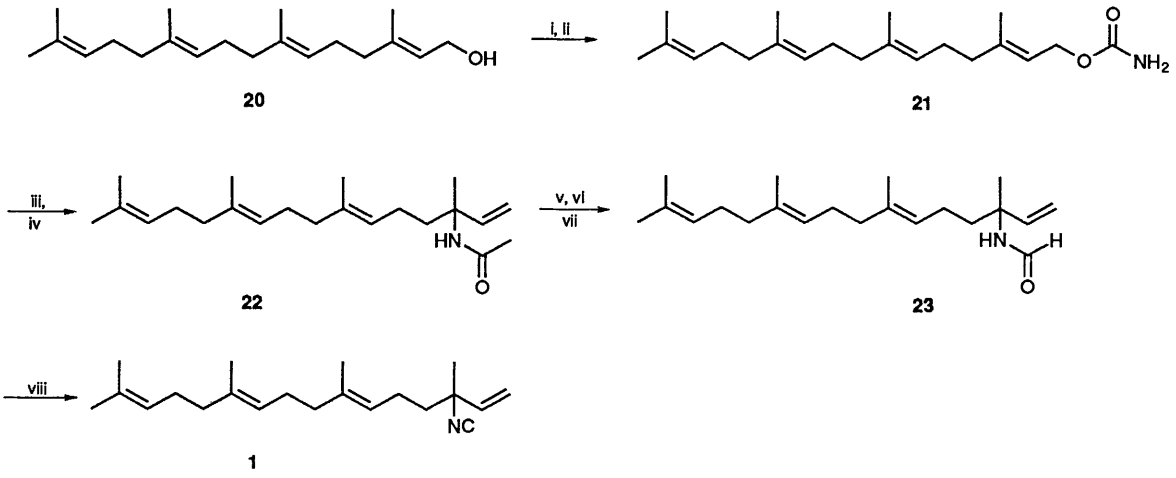
We have established that an allyl cyanate-to-isocyanate rearrangement is a useful method for the elaboration of a wide variety of allylamines. Efforts are presently underway to develop this reaction to the synthesis of optically active amines.[9]

Experimental

General Details.—M.p.s were determined on an oil bath apparatus and are uncorrected. IR spectra were recorded using a Shimadzu IR-420 infrared spectrometer for chloroform solution, and a JASCO FTIR-7000S for KBr unless otherwise stated. ^{1}H NMR spectra were determined using a JEOL EX 270 spectrometer operating at 270 MHz unless otherwise stated. ^{13}C NMR spectra were determined using the JEOL EX 270 instrument, operating at 67.80 MHz unless otherwise stated. Dilute solutions in [^{2}H]-chloroform were used throughout unless stated otherwise, with tetramethylsilane as the internal standard. All *J* values are in Hz. High-resolution mass spectra were recorded on a JMS-DX 705L instrument. Mass spectra (EI) were measured using a JEOL JMS D-100 spectrometer.

Dichloromethane was dried over active alumina. Trifluoromethanesulfonic anhydride was purified by distillation over phosphorus pentoxide. All reactions were carried out under argon. All organic solutions from work-ups were dried by brief exposure to anhydrous sodium sulfate. Column chromatography was performed on silica gel supplied by E. Merck (Art # 7734) and Fuji Davison (BW-820MH). Preparative TLC were made on plates prepared with a 2 mm layer of silica gel PF_{254} obtained from E. Merck (Art # 7747).

General Procedure: 3-Acetamido-3,7-dimethylocta-1,6-diene **10**.—To a solution of geraniol **7** (560 mg, 3.64 mmol) in dichloromethane (6 cm^3) cooled to 0 °C was added dropwise trichloroacetyl isocyanate (0.52 cm^3, 4.37 mmol). After the mixture had been stirred for 2 h, the dichloromethane was evaporated under reduced pressure and the resulting residue was dissolved in methanol (5 cm^3) and the solution cooled to 0 °C. Water (5 cm^3) and potassium carbonate (2.0 g, 14.5 mmol) were added to it and the cooling bath was removed. After the mixture had been stirred for 4 h at room temp., the methanol was evaporated and the aqueous residue was extracted with dichloromethane. The combined organic layers were dried and evaporated to afford the carbamate **8** (690 mg, 3.50 mmol, 96%), which was used in the next reaction without further purification.



Scheme 5 *Reagents and conditions:* i, CCl_3CONCO; ii, K_2CO_3, aq. MeOH; iii, Tf_2O, Pr^i_2NEt; iv, Me_3Al; v, Meerwein's reagent; vi, AcOH, aq. THF; vii, AcOCHO; viii, PPh_3, CBr_4, Pr^i_2NEt, −20 °C

Trifluoromethanesulfonic anhydride (0.83 cm^3, 3.50 mmol) was added dropwise to a stirred solution of the carbamate **8** (690 mg, 3.50 mmol) and diisopropylethylamine (2.6 cm^3, 15.0 mmol) in dichloromethane (30 cm^3) at −78 °C. After the mixture had been stirred at −78 °C for 2 h, trimethylaluminium (1 mol dm^{-3} solution in hexane; 14 cm^3, 14 mmol) was added to it, and the stirring was continued for a further 15 min. The cooling bath was removed, and the reaction temperature raised to 0 °C. The reaction mixture was treated cautiously with methanol until the evolution of gas had ceased then it was poured into water and extracted with dichloromethane. The combined extracts were washed with water and 1 mol dm^{-3} HCl, dried, and evaporated. Purification of the resulting residue by silica gel chromatography gave the title compound **10** (576 mg, 2.95 mmol, 81% overall yield from geraniol **7**); ν_{max}(KBr)/cm^{-1} 3292 (NH) and 1653 (CONH); δ_H 1.42 (3 H, s, CH_3), 1.59 (3 H, br s, C=C–CH_3), 1.67 (3 H, br s, C=C–CH_3), 1.93 (3 H, s, $NCOCH_3$), 5.0–5.16 (3 H), 5.76 (1 H, br, NH) and 5.95 (1 H, dd, *J* 17, 11, C*H*=CH_2); δ_C 17.7, 22.6, 24.3, 24.4, 25.7, 39.2, 57.3, 112.2, 124.1, 131.8, 143.1 and 169.3 (CO) (Found: M^+, 195.1624. $C_{12}H_{21}NO$ requires *M*, 195.1623).

3-*Acetamidocyclohex*-1-*ene* **12**.—Starting from cyclohex-2-enol **11** (291 mg, 2.97 mmol), trichloroacetyl isocyanate (0.42 cm^3, 3.53 mmol), dichloromethane (6 cm^3), potassium carbonate (1.6 g, 11.2 mmol), methanol (6 cm^3) and water (5 cm^3), the corresponding carbamate (394 mg) was obtained by the general procedure in 97% yield. This carbamate was transformed into 3-acetamidocyclohex-1-ene **12** (273 mg, 1.96 mmol) in 66% overall yield from cyclohex-2-enol **11** by employing trifluoromethanesulfonic anhydride (0.66 cm^3, 3.93 mmol), diisopropylethylamine (2.0 cm^3, 11.5 mmol), dichloromethane (25 cm^3) and trimethylaluminium (1 mol dm^{-3} solution in hexane, 14 cm^3, 14 mmol); m.p. 84 °C (from diethyl ether–hexane) (Found: C, 69.0; H, 9.6; N, 10.0. $C_8H_{13}NO$ requires C, 69.06; H, 9.35; N, 10.07%); ν_{max}(KBr)/cm^{-1} 3648, 3255 (NH) and 1638 (CON); δ_H 1.98 (3 H, s, $COCH_3$), 4.48 (1 H, br, CHN), 5.5–5.62 (2 H) and 5.86 (1 H, m).

3-*Acetamido*-3-*methylcyclohex*-1-*ene* **14**.—Starting from 3-methylcyclohex-2-enol **13** (317 mg, 2.83 mmol), trichloroacetyl isocyanate (0.40 cm^3, 3.36 mmol), dichloromethane (6 cm^3), potassium carbonate (1.2 g, 8.7 mmol), methanol (10 cm^3) and water (5 cm^3), the corresponding carbamate (320 mg) was obtained by the general procedure in 73% yield. This carbamate was transformed into 3-acetamidocyclohex-1-ene **14** (158 mg, 103 mmol) in 37% overall yield from 3-methylcyclohex-2-enol **3** by employing trifluoromethanesulfonic anhydride (0.48 cm^3, 2.86 mmol), diisopropylethylamine (1.5 cm^3, 8.6 mmol), dichloromethane (18 cm^3) and trimethylaluminium (1 mol dm^{-3} solution in hexane; 8.1 cm^3, 8.1 mmol). 3-Acetamidomethylcyclohex-1-ene **15** (24 mg, 4%) was also isolated. Compound **14** m.p. 81 °C (from diethyl ether–hexane) (Found: C, 70.5; H, 10.1; N, 9.1. $C_9H_{15}NO$ requires C, 70.59; H, 9.80; N, 9.15%); ν_{max}(KBr)/cm^{-1} 3294 (NH) and 1647 (CON); δ_H 1.46 (3 H, s, CH_3), 1.92 (3 H, s, $NCOCH_3$), 5.37 (1 H, br) and 5.7–5.8 (2 H); δ_C 19.0, 24.5, 24.9, 26.7, 34.1, 52.3, 128.7, 132.4 and 169.2 (CO).

3-*Acetamido*-1-*methylcyclohex*-1-*ene* **15**. ν_{max}(KBr)/cm^{-1} 3257 (NH) and 1634 (CON); δ_H 1.68 (3 H, br s, CH_3), 1.97 (3 H, s, $NCOCH_3$), 4.44 (1 H, br, CHN), 5.32 (1 H, br s, C=CH) and 5.42 (1 H, br, NH) (Found: M^+, 153.1176. $C_9H_{15}NO$ requires *M*, 153.1154).

3-*Acetamido*-3-*phenylprop*-1-*ene* **17**.—Starting from 3-phenylprop-2-en-1-ol **16** (261 mg, 1.95 mmol), trichloroacetyl isocyanate (0.28 cm^3, 2.35 mmol), dichloromethane (5 cm^3), potassium carbonate (0.81 g, 5.87 mmol), methanol (7 cm^3) and water (5 cm^3), the corresponding carbamate (340 mg) was isolated in 99% yield by the general procedure. This carbamate was transformed into 3-acetamido-3-phenylprop-1-ene **17** (243 mg, 1.39 mmol) in 71% overall yield from 3-phenylprop-2-en-1-ol **16** by using trifluoromethanesulfonic anhydride (0.48 cm^3, 2.86 mmol), diisopropylethylamine (1.5 cm^3, 8.6 mmol), dichloromethane (20 cm^3) and trimethylaluminium (1 mol dm^{-3} solution in hexane; 10 cm^3, 10 mmol); m.p. 66 °C (from diethyl ether–hexane) (Found: C, 75.2; H, 7.6; N, 7.95. $C_{11}H_{13}NO$ requires C, 75.43; H, 7.43; N, 8.00%); ν_{max}(KBr)/cm^{-1} 3242 (NHCHO) and 1651 (CON); δ_H 2.03 (3 H, s, $NCOCH_3$), 5.22 (1 H, d t, *J* 17, 1.5, CH=CH_{trans}), 5.26 (1 H, d t, *J* 10, 1, CH=CH_{cis}), 5.64 (1 H, m, PhC*H*$NCOCH_3$), 5.8 (1 H, br, NH), 6.01 (1 H, ddd, *J* 17, 10, 5, C*H*=CH_2) and 7.22–7.4 (5 H).

3-*Acetamido*-3,7,11,15-*tetramethylhexadeca*-1,6,10,14-*tetraene* **22**.—Starting from geranylgeraniol **20** (5.0 g, 17.1 mmol), trichloroacetyl isocyanate (2.6 cm^3, 21.9 mmol), dichloromethane (40 cm^3), potassium carbonate (7.0 g, 50.8 mmol), methanol (70 cm^3) and water (30 cm^3), the corresponding carbamate **21** (3.96 g) was obtained by the general procedure in 70% yield after purification by silica gel chromatography. This carbamate **21** (1.96 g, 5.89 mmol) was transformed into 3-acetamido-3,7,11,15-tetramethylhexadeca-1,6,10,14-tetraene **22** (1.63 g) in 84% yield by using trifluoromethanesulfonic anhydride (2.1 cm^3, 12.5 mmol), diisopropylethylamine (6.1

cm^3, 35.1 mmol), dichloromethane (40 cm^3) and trimethylaluminium (1 mol dm^{-3} solution in hexane; 44 cm^3, 44 mmol). $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 (NH) and 1660 (CONH); δ_H 1.44 (3 H, s, CH_3), 1.60 (9 H, s, $CH_3 \times 3$), 1.68 (3 H, s, CH_3), 1.95 (3 H, s, $NCOCH_3$), 5.02–5.13 (5 H), 5.42 (1 H, br s, NH) and 5.92 (1 H, dd, *J* 18, 11, C*H*=CH_2); δ_C 16.0, 17.7, 22.5, 24.3, 25.7, 26.6, 26.8, 39.3, 39.68, 39.71, 57.4, 112.3, 123.8, 124.1, 124.4, 131.3, 135.0, 135.6, 143.0 and 169.3 (CO) (Found: M^+, 331.2839. $C_{22}H_{37}NO$ requires *M*, 331.2875).

3-*Formamido*-3,7,11,15-*tetramethylhexadeca*-1,6,10,14-*tetraene* **23**.—To a solution of the acetamide **22** (822 mg, 2.48 mmol) dissolved in dichloromethane (25 cm^3) was added sodium carbonate (2.4 g) and a solution of triethyloxonium tetrafluoroborate (9 cm^3, *ca.* 1 mol dm^{-3} solution in dichloromethane). After being stirred at room temp. for 2 h, the reaction mixture was poured into water. The aqueous layer was extracted with two portions of dichloromethane, and the combined organic phases were dried and concentrated under reduced pressure. The resulting crude imino ether (0.96 g) was successively dissolved in a mixture of acetic acid (2 cm^3), water (2 cm^3) and tetrahydrofuran (20 cm^3). The solution was left *overnight* at room temp. and then evaporated to remove the tetrahydrofuran. Water was added to the residue and the solution was neutralized with sodium carbonate. It was then extracted with dichloromethane and the combined extracts were dried and concentrated under reduced pressure to afford the crude amine (746 mg). This crude amine was immediately dissolved in dichloromethane (10 cm^3) and treated with acetic formic anhydride (1.2 cm^3). The solution was stirred at room temp. for 2 h and then concentrated under reduced pressure. Chromatography of the residue on silica gel with diethyl ether–hexane (2:1, v/v) provided the formamide **23** (663 mg, 84%).

NMR analysis of **23** proved to be extremely difficult, because it exists as a 1:1 mixture of two rotational isomers. $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 (NH) and 1670 (NHCHO) (Found: M^+, 317.2730. $C_{21}H_{35}NO$ requires *M*, 317.2718).

3-*Isocyano*-3,7,11,15-*tetramethylhexadeca*-1,6,10,14-*tetraene* (*Geranyllinaloisocyanide*) **1**.—A solution of the formamide **23** (204 mg, 0.64 mmol), tetrabromomethane (594 mg, 1.79 mmol) and diisopropylethylamine (0.60 cm^3, 3.45 mmol) dissolved in dichloromethane (7 cm^3) was cooled to −20 °C. To this solution was added dropwise a solution of triphenylphosphine (423 mg, 1.33 mmol) in dichloromethane (*ca.* 1.5 cm^3). After being stirred at −20 °C for 30 min the reaction mixture was diluted with water. The aqueous layer was extracted with diethyl ether and the combined organic phases were washed with 0.5 mol dm^{-3} HCl, saturated aqueous sodium hydrogen carbonate and brine, dried, and concentrated under reduced pressure to afford the crude product (844 mg) which was purified by silica gel chromatography with diethyl ether–hexane (1:50, v/v) to provide the isocyanide **1** (156 mg, 82% yield); $\nu_{max}(CHCl_3)/cm^{-1}$ 2120 (NC), 980 and 920 [lit.,[1] $\nu_{max}(CCl_4)$ 2140, 990 and 930]; δ_H 1.48 (3 H, t, *J* 2, $CNCCH_3$), 1.6 (9 H, s, $CH_3 \times 3$), 1.68 (3 H, s, $NCOCH_3$), 5.04–5.14 (3 H), 5.21 (1 H, d, *J* 10, CH=CH_{cis}), 5.43 (1 H, d, *J* 17, CH=CH_{trans}) and 5.65 (1 H, ddt, *J* 17, 10, 2.5, C*H*=CH_2) [lit.,[1] δ_H(100 MHz; $CDCl_3$) 1.47 (t, *J* 1.5), 1.59 (s), 1.62 (s), 1.67 (s), 1.99 (br s), 5.0 (br) and 5.1–5.5 (several m)]; δ_C 16.0, 17.7, 22.7, 25.7, 26.5, 26.8, 28.4, 39.6, 39.7, 41.4, 62.6 (t, *J* 5, C–NC), 114.1, 122.4, 124.0, 124.4, 131.2, 135.0, 136.4, 138.2 and 155.8 (t, *J* 5, NC) [lit.,[1] δ_C(25 MHz, $CDCl_3$) 16.0 (2 C), 17.7, 22.8, 25.6, 26.8 (2 C), 28.4, 29.7, 39.7, 41.5, 62.5 (t, *J* 4.5, C–NC), 114.0, 122.3, 123.9, 131.0, 134.8, 136.2, 138.1 and 155.6 (t, *J* 4.5, NC)] (Found: M^+, 299.2646. $C_{21}H_{33}N$ requires *M*, 299.2613).

Acknowledgements

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