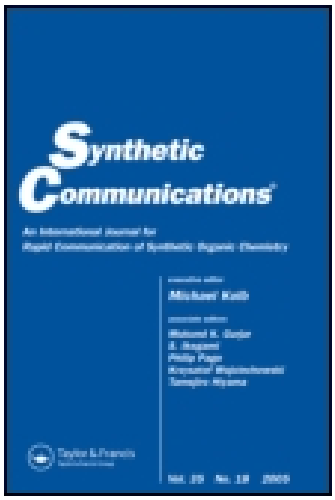

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PREPARATION OF 1,7-DISUBSTITUTED-1,2,3,4-TETRAHYDROISOQUINOLINES

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PREPARATION OF 1,7-DISUBSTITUTED-1,2,3,4-TETRAHYDROISOQUINOLINES

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ABSTRACT

A simple procedure for the preparation of 1,7-disubstituted-1,2,3,4-tetrahydroisoquinolines from 3,4-dihydroisoquinoline (**2**) is presented. This strategy overcomes the limitation of cyclisation approaches which generally require electron rich ring systems. A variety of 1-substituents has been incorporated using the appropriate organometallic or activated methylene nucleophile to prepare both electron rich (**7a**–**f**) and electron deficient 1,7-disubstituted-1,2,3,4-tetrahydroisoquinolines (**16**, **17**).

We were interested in the preparation of 1-substituted-2-methyl-7-amino-1,2,3,4-tetrahydroisoquinolines (**7a**–**f**) en route to anticonvulsant agents and preliminary details have been reported.[1] However, there are limited generic routes to 1-alkyl or 1-aryl 7-amino-1,2,3,4-tetrahydroisoquinolines. The 7-amino substituent is usually derived from a nitro group

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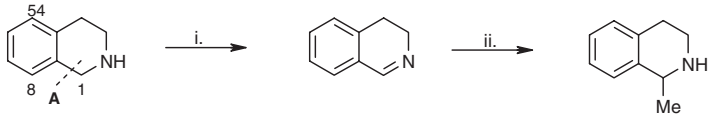
and classical synthetic approaches to isoquinolines (Pomerantz–Fritsch),[2] 3,4-dihydroisoquinolines (Bischler–Napieralski)[3] and 1,2,3,4-tetrahydroisoquinolines (Pictet–Spengler)[4] rely on cyclisation by intramolecular electrophilic substitution of an aromatic ring. Preparation of 1-substituted-7-nitro-1,2,3,4-tetrahydroisoquinolines by cyclisation (Scheme 1, **A** bond formation) is problematic as both the electrophile (nitrilium/iminium species) and the aromatic ring are deactivated.

Modification of an unsubstituted 1,2,3,4-tetrahydroisoquinoline is an alternative strategy. There is a wealth of literature detailing preparation of 1-substituted-1,2,3,4-tetrahydroisoquinolines by generation of a benzylic anion followed by reaction with an electrophile. Regiocontrol and stabilisation of a 1-benzylic anion is achieved by attachment of a suitable functional group to the nitrogen of tetrahydroisoquinoline. Directing/stabilising groups include amides,[5] carbamates[6] and amidines.[7] Borane adducts of tertiary amines have also been used to prepare 1,2-disubstituted tetrahydroisoquinolines.[8] A number of these strategies was examined but we found that they all failed with systems bearing substituents in the aromatic ring. This failure was presumably due to competing ortho-lithiation of sp^2 carbon atoms adjacent to a variety of nitrogen substituents present in the aromatic ring of our substrates.

Synthesis of 1-alkyl-1,2,3,4-tetrahydroisoquinolines can be achieved by nucleophilic addition of organometallic reagents to compounds derived from 3,4-dihydroisoquinoline (**2**) which can be prepared in high yield[9] from commercially available 1,2,3,4-tetrahydroisoquinoline. Unlike carbonyl chemistry, the reaction of imines with organometallic nucleophiles rarely proceeds efficiently without activation.[10] However, Lewis acid activation of 3,4-dihydroisoquinoline (**2**) yielded the 1-methyl derivative (**3**) in good yield (Scheme 1).

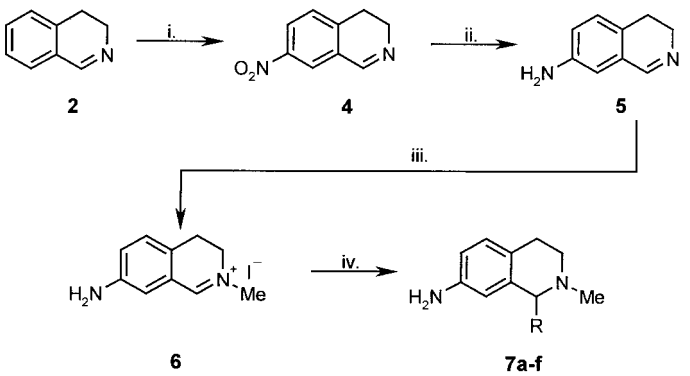
3,4-Dihydroisoquinoline activation by quaternisation of an imine intermediate with iodomethane is extremely useful for the preparation of 1-substituted-2-methyl-7-amino-1,2,3,4-tetrahydroisoquinolines (Scheme 2). The imine double bond serves not only to introduce the 1-substituent



1 **2** **3**

i. NBS, NaOH, CH_2Cl_2 (>95%), ii. $BF_3.OEt_2$, MeMgCl, CH_2Cl_2 (70%)

Scheme 1.



i. KNO_3, H_2SO_4 (76%), ii. $SnCl_2$, EtOH, HCl (88%), iii. MeI, acetone (0 > 95%), iv. RMgBr, thf, −78°C

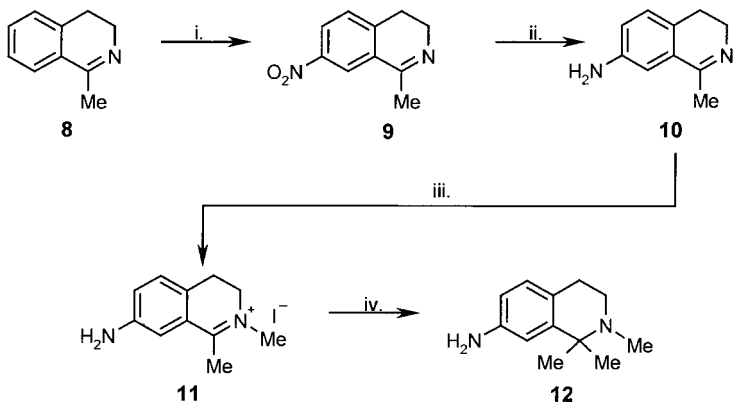
Scheme 2.

Table 1.

Compound	R	Yield (%)
(**7a**)	Methyl	67
(**7b**)	*i*-Propenyl	95
(**7c**)	Phenyl	75
(**7d**)	Benzyl	70
(**7e**)	*i*-Butyl	53
(**7f**)	Allyl	54

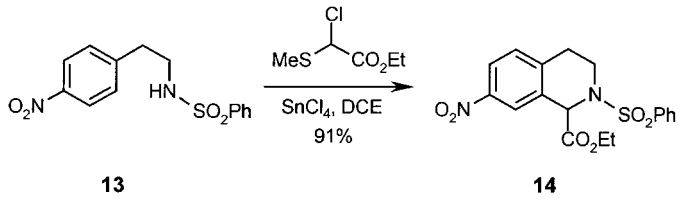
but also to control the regiochemistry of nitration, to give exclusively 7-nitro-3,4-dihydroisoquinoline (**4**).[9] A number of different Grignard reagents was used to prepare several 1-substituted compounds (**7a**–**f**) in good to excellent yield (Table 1).

This methodology can also be used to prepare tetrahydroisoquinolines bearing quaternary benzylic C-1 carbon atoms (**12**) (Scheme 3). Nitration of commercially available 1-methyl-3,4-dihydroisoquinoline (**8**) yielded exclusively 1-methyl-7-nitro-3,4-dihydroisoquinoline (**9**). Reduction followed by quaternisation with iodomethane gave the activated substrate (**11**) for the final alkylation reaction. However, when the iminium salt (**11**) was treated with an excess of methyl magnesium chloride only low to moderate yields of the target compound were obtained. Presumably, this is due to proton abstraction from the methyl substituent resulting in imine-enamine tauto-



i. KNO_3, H_2SO_4 (83%), ii. $SnCl_2$, EtOH, HCl (>95%),
iii.MeI, acetone (>95%), iv. MeMgCl, thf, -78°C (8-60%)

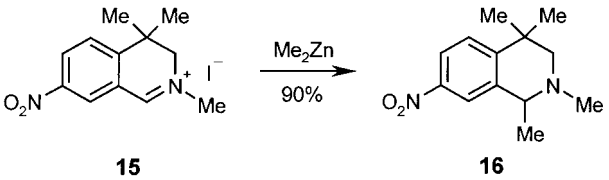
Scheme 3.



Scheme 4.

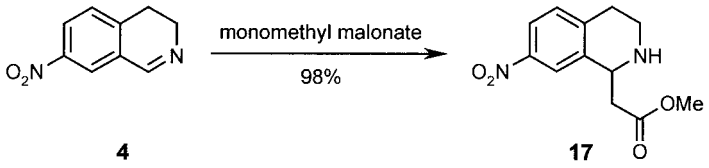
merism. Less basic, more nucleophilic reagents such as organocerium and alkylcopper reagents may overcome this limitation.[10]

As discussed earlier, synthesis of electron deficient tetrahydroisoquinolines by cyclisation strategies is difficult. One approach has been to use a modified Pictet–Spengler reaction involving reaction between a Lewis acid activated ethyl glyoxylate synthon and an *N*-phenylsulfonylated 4-nitrophenethylamine (**13**) (Scheme 4).[11] This approach is limited to a small range of 1-substituents that can be incorporated and removal of the phenylsulfonyl group can be troublesome. More recently electron deficient tetrahydroisoquinolines have been prepared from *tri*-substituted aromatic rings employing an N2–C3 cyclisation strategy.[12] However, the limitation of this strategy is that several synthetic transformations are required to prepare the cyclisation precursor.



15 **16**

Scheme 5.



4 **17**

Scheme 6.

Our 3,4-dihydroisoquinoline strategy was used to prepare electron deficient ring systems (e.g., **16**) (Scheme 5). Organo-zinc reagents were found to be more reliable than Grignard reagents in reactions with substrates bearing aromatic nitro groups. For example, dimethyl zinc was successfully employed in the preparation of 1,2,4,4-tetramethyl-7-nitro-1,2,3,4-tetrahydroisoquinoline (**16**), in excellent yield.

The advantage of this approach is that a variety of 1-alkyl-7-nitro-1,2,3,4-tetrahydroisoquinolines can be prepared with relative ease compared to existing procedures. For example, an activated methylene compound, monomethyl malonate, has also been used in place of an organo-zinc reagent to prepare an electron deficient tetrahydroisoquinoline (**17**) (Scheme 6).

In conclusion, 3,4-dihydroisoquinoline is a versatile precursor for the preparation of a number of novel 1,7-disubstituted-1,2,3,4-tetrahydroisoquinolines. This approach is superior to cyclisation strategies and tolerates aromatic ring substituents that limit approaches based on benzylic anion generation. Electron deficient 1,2,3,4-tetrahydroisoquinolines are accessible in a few steps and the attachment and removal of auxiliary activating groups is not required.

EXPERIMENTAL

Chromatography refers to flash chromatography through Merck Silica Gel 60 (less than 0.063 mm) and the eluent is stated. Infra red spectra

were recorded for dichloromethane solutions on a Perkin-Elmer 1600 FTIR. 1H NMR spectra were obtained using a Brucker AC250 and the solvent is stated. Accurate mass measurements were recorded by Analytical Sciences, SB, on a Jeol JMS DX303/DA 5000 at 70 eV. All solutions were dried over anhydrous magnesium sulfate unless stated otherwise. Solvents were removed under reduced pressure using a Buchi Rotavapor unless stated otherwise.

7-Amino-3,4-dihydroisoquinoline (5): 7-Nitro-3,4-dihydroisoquinoline[9] (0.6 g, 3.4 mmol) was dissolved in ethanol (100 mL) and heated to 60°C. This hot solution was treated with a solution of tin (II) chloride dihydrate (3.08 g, 13.7 mmol) in concentrated hydrochloric acid (10 mL) and heated at 60°C for 1 h. After cooling to room temperature, the resultant mixture was poured into ice-water (100 mL) and basified (pH 9) with potassium hydroxide pellets, liberating an oily residue. The residue was extracted into dichloromethane and dried. Chromatographic purification using a dichloromethane solution of ammonia in methanol (0.5%c. ammonia : 4.5% methanol : 95% dichloromethane) yielded 7-amino-3,4-dihydroisoquinoline (**5**) as a dark yellow oil (0.436 g, 88%); ν_{max}/cm^{-1} (CH_2Cl_2) 3685, 3383 and 1619; δ_H [250 MHz, $CDCl_3$] 2.63 (2H, t, $J = 7$Hz), 3.67 (2H, br.s), 3.73 (2H, dt, $J = 7$ and 2 Hz), 6.62 (1H, d, $J = 2$ Hz), 6.70 (1H, dd, $J = 8$ and 2 Hz), 6.95 (1H, d, $J = 8$ Hz), 8.24 (1H, s); Found: 146.0844. $C_9H_{10}N_2$ requires: 146.0844.

7-Amino-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline (7a): 7-Amino-3,4-dihydroisoquinoline (**5**) (0.4 g, 2.74 mmol) was dissolved in acetone (125 mL) and treated with iodomethane (0.5 mL, 8.03 mmol). The reaction mixture was left stirring at room temperature for 18 h. The resultant yellow precipitate (**6**) was collected by filtration and dried in vacuo at ambient temperature (0.726 g, 92%); m/z (API) 161(M^+, 100%). 7-Amino-2-methyl-3,4-dihydroisoquinolinium iodide (**6**) (0.5 g, 1.7 mmol) was suspended in anhydrous tetrahydrofuran (50 mL) and cooled to –78°C under an argon atmosphere. The cooled solution was treated with methyl magnesium chloride (2.14 mL of a 3 M solution in tetrahydrofuran, 6.96 mmol), added as a single portion. The reaction was stirred at ambient temperature for 18 h before pouring into water (50 mL). The organic solvent was removed and the organic product extracted into dichloromethane and dried. Evaporation under reduced pressure furnished 7-amino-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline (**7a**) as a pale yellow oil (0.3 g, 98%). For ease of handling, the product was converted into the mono hydrochloride by the addition of 1 molar equivalent of ethereal hydrogen chloride followed by solvent evaporation under reduced pressure; ν_{max}/cm^{-1} (CH_2Cl_2) 3621 and 3421; δ_H [250 MHz, $CDCl_3$ hydrochloride salt] 1.37 (3H, d, $J = 7$ Hz), 2.46 (3H, s), 2.54–2.83 (3H, m), 2.96–3.06 (1H, m),

3.45–3.55 (3H, m), 6.45 (1H, d, $J = 2$ Hz), 6.51 (1H, dd, $J = 8$ and 2 Hz), 6.88 (1H, d, $J = 8$ Hz); Found: 176.1314. $C_{11}H_{16}N_2$ requires: 176.1314.

7-Amino-1-isopropenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (7b): Prepared according to the procedure for **7a** using isopropenyl magnesium bromide (0.5 M solution in tetrahydrofuran). The title compound (**7b**) was isolated in 95% yield; ν_{max}/cm^{-1} (CH_2Cl_2) 3655 and 3466; δ_H [250 MHz, $CDCl_3$] 1.52 (3H, s), 2.31 (3H, s), 2.36–2.63 (2H, m), 2.78–3.14 (2H, m), 3.48 (2H, br.s), 3.58 (1H, br.s), 5.06 (2H, d, $J = 1$ Hz), 6.49–6.53 (2H, m), 6.87–6.90 (1H, m); Found: 202.1470. $C_{13}H_{18}N_2$ requires: 202.1470.

7-Amino-2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (7c): Prepared according to the procedure for **7a** using phenyl magnesium bromide (3 M solution in tetrahydrofuran). The title compound (**7c**) was isolated in 75% yield; ν_{max}/cm^{-1} (CH_2Cl_2) 3662, 3453 and 3390; δ_H [250 MHz, $CDCl_3$] 2.21 (3H, s), 2.54–2.76 (2H, m), 3.06–3.20 (2H, m), 3.41 (2H, br.s), 4.18 (1H, s), 5.95 (1H, d, $J = 2$ Hz), 6.49 (1H, dd, $J = 8$ and 2 Hz), 6.67 (1H, dd, $J = 8$ and 1 Hz), 6.92 (1H, d, $J = 8$ Hz), 7.18–7.33 (4H, m); Found: 238.1474. $C_{16}H_{18}N_2$ requires: 238.1470.

7-Amino-1-benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (7d): Prepared according to the procedure for **7a** using benzyl magnesium chloride (1 M solution in tetrahydrofuran). The title compound (**7d**) was isolated in 70% yield; ν_{max}/cm^{-1} (CH_2Cl_2) 3660 and 3430; δ_H [250 M Hz, $CDCl_3$] 2.51 (3H, s), 2.54–2.61 (1H, m), 2.69–2.90 (3H, m), 3.10–3.26 (2H, m), 3.41 (2H, br.s), 3.70 (1H, t, $J = 6$ Hz), 6.03 (1H, d, $J = 2$ Hz), 6.47 (1H, dd, $J = 8$ and 2 Hz), 6.86 (1H, d, $J = 8$ Hz), 7.12–7.54 (5H, m); Found: 252.1626. $C_{17}H_{20}N_2$ requires: 252.1627.

7-Amino-1-isobutyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (7e): Prepared according to the procedure for **7a** using isobutyl magnesium chloride (2 M solution). The title compound (**7e**) was isolated in 53% yield; ν_{max}/cm^{-1} (CH_2Cl_2) 3615 and 3403; δ_H [250 M Hz, $CDCl_3$] 0.97 (6H, overlap.t, $J = 7$ Hz), 1.32–1.52 (1H, m), 1.71–1.98 (2H, m), 2.50 (3H, s), 2.42–2.64 (1H, m), 2.77–2.96 (2H, m), 3.20–3.38 (1H, m), 3.53 (1H, br. t, $J = 7$ Hz), 3.56 (2H, br s), 6.38 (1H, d, $J = 2$ Hz), 6.53 (1H, dd, $J = 8$ and 2 Hz), 6.88 (1H, d, $J = 8$ Hz); Found: 218.1784. $C_{14}H_{22}N_2$ requires: 218.1783.

1-Allyl-7-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline (7f): Prepared according to the procedure for preparation of **7a** using allyl magnesium chloride (2 M solution in tetrahydrofuran). The title compound (**7f**) was isolated in 54% yield; ν_{max}/cm^{-1} (CH_2Cl_2) 3630 and 3397; δ_H [250 MHz, $CDCl_3$] 2.48 (3H, s), 2.52–2.83 (5H, m), 3.09–3.21 (1H, m), 3.54 (1H, br.t, $J = 6$ Hz), 3.87 (2H, br.s), 5.01–5.11 (2H, m), 5.72–5.88 (1H, m), 6.44 (1H, d, $J = 2$ Hz), 6.50 (1H, d, $J = 2$ Hz), 6.88 (1H, d, $J = 8$ Hz); Found: 202.1472. $C_{13}H_{18}N_2$ requires: 202.1470.

1-Methyl-7-nitro-3,4-dihydroisoquinoline (9): A solution of 1-methyl-3,4-dihydroisoquinoline (2.57 g, 17.7 mmol) in concentrated sulfuric acid (10 mL) was added dropwise to a stirred mixture of potassium nitrate (1.93 g, 19.1 mmol) in concentrated sulfuric acid (10 mL) at –5°C. The mixture was allowed to warm to room temperature over 2 h before heating at 60°C for 4 h. Then the reaction mixture was poured into ice-water (100 mL) and basified (pH 9) with potassium hydroxide pellets. Extraction into dichloromethane, dried and solvent removal under reduced pressure yielded the crude product. Chromatographic purification using a dichloromethane solution of ammonia in methanol (0.5% c. ammonia : 4.5% methanol : 95% dichloromethane) yielded 1-methyl-7-nitro-3,4-dihydroisoquinoline (**9**) as a dark brown oil (1.92 g, 57%); ν_{max}/cm^{-1} (CH_2Cl_2) 1633, 1528, 1345 and 1266; δ_H [250 MHz, $CDCl_3$] 2.48 (3H, s), 2.82 (2H, t, $J = 8$ Hz), 3.75 (2H, dt, $J = 8$ and 2 Hz), 7.38 (1H, d, $J = 8$ Hz), 8.24 (1H, dd, $J = 8$ and 2 Hz), 8.33 (1H, d, $J = 2$ Hz); Found: 190.0740. $C_{10}H_{10}N_2O_2$ requires: 190.0742.

7-Amino-1-methyl-3,4-dihydroisoquinoline (10): Prepared according to the procedure for **5** using 1-methyl-7-nitro-3,4-dihydroisoquinoline (**9**) (2 g, 10.5 mmol). 1-Methyl-7-amino-3,4-dihydroisoquinoline (**10**) was isolated as a dark brown oil in 55% yield; ν_{max}/cm^{-1} (CH_2Cl_2) 3684, 3466, 3383, and 1618; δ_H [250 MHz, $CDCl_3$] 2.35 (3H, s), 2.59 (2H, t, $J = 7$ Hz), 3.62 (2H, t, $J = 7$ Hz), 3.40-3.75 (2H, br.s), 6.71 (1H, dd, $J = 8$ and 2 Hz), 6.83 (1H, d, $J = 2$ Hz), 6.98 (1H, d, $J = 8$ Hz); Found: 160.1002. $C_{10}H_{12}N_2$ requires: 160.1001.

7-Amino-1,1,2-trimethyl-1,2,3,4-tetrahydroisoquinoline (12): 7-Amino-1,2-dimethyl-3,4-dihydroisoquinolinium iodide (**11**) was prepared according to the procedure for preparation of **6** using 7-amino-1-methyl-3,4-dihydroisoquinoline (**10**) (0.9 g, 5.6 mmol). The iminium salt (**11**) was isolated as an orange powder (1.44 g, 85%); *m/z* (API) 175 (M^+, 100%). 7-Amino-1,2-dimethyl-3,4-dihydroisoquinolinium iodide (**11**) (1.44 g, 4.8 mmol) was suspended in tetrahydrofuran (200 mL) and cooled to −78°C under an argon atmosphere. The cooled solution was treated with methyl magnesium chloride (10 mL of a 3 M solution in tetrahydrofuran), added as a single portion. The reaction was stirred at room temperature for 18 h and then poured into water (200 mL). The organic solvent was removed and the resultant oily residue was extracted into dichloromethane. Evaporation under reduced pressure and chromatography, eluting with a dichloromethane solution of ammonia in methanol (0.5% c. ammonia : 4.5% methanol : 95% dichloromethane) yielded 7-amino-1,1,2-trimethyl-1,2,3,4-tetrahydroisoquinoline (**12**) as a light yellow oil (0.07 g, 8%). For ease of handling, the product was converted into the mono hydrochloride by the addition of 1 molar equivalent of ethereal hydrogen chloride followed by solvent evaporation under reduced pressure; ν_{max}/cm^{-1} (CH_2Cl_2) 3634, and 3410; δ_H [250 MHz,

$CDCl_3$, hydrochloride salt] 1.45 (6H, s), 2.48 (3H, s), 2.80 (2H, t, $J = 6$ Hz), 2.96 (2H, t, $J = 6$ Hz), 6.51 (1H, dd, $J = 8$ and 2 Hz), 6.57 (1H, d, $J = 2$ Hz), 6.86 (1H, d, $J = 8$ Hz); Found: 190.1472. $C_{12}H_{18}N_2$ requires: 190.1470.

7-Nitro-1,2,4,4-tetramethyl-1,2,3,4-tetrahydroisoquinoline (16): 7-Nitro-2,4,4-trimethyl-3,4-dihydroisoquinolinium iodide (**15**) (1.5 g, 4.3 mmol) was suspended in tetrahydrofuran (50 mL) under an argon atmosphere at 0°C. To this suspension was added dimethyl zinc (3.3 mL of a 2 M solution in toluene) with rapid stirring. The reaction was allowed to warm to room temperature over 1 h and saturated ammonium chloride solution (10 mL) was added. The organic solvent was removed and the resultant residue partitioned between dichloromethane (100 mL) and water (100 mL). The dichloromethane layer was separated, dried and evaporation under reduced pressure gave the title compound (**16**) (0.91 g, 90%); $\nu_{max/}cm^{-1}$ (CH_2Cl_2) 1508, 1451, 1425 and 1271; δ_H [250 MHz, $CDCl_3$] 1.30 (3H, s), 1.35 (3H, s), 1.40 (3H, d, $J = 6$ Hz), 2.37 (1H, d, $J = 12$ Hz), 2.47 (3H, s), 2.66 (1H, d, $J = 12$ Hz), 3.63 (1H, q, $J = 6$ Hz), 7.41–7.46 (1H, m), 7.97–8.03 (2H, m); Found: 234.1368. $C_{13}H_{18}N_2O_2$ requires: 234.1368.

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