ARTICLE

OBC
www.rsc.org/obc

The facile preparation of primary and secondary amines *via* an improved Fukuyama–Mitsunobu procedure. Application to the synthesis of a lung-targeted gene delivery agent

Cristina Guisado,[a] Jodie E. Waterhouse,[a] Wayne S. Price,[a] Michael R. Jorgensen*[b] and Andrew D. Miller*[a]

[a] *Imperial College Genetic Therapies Centre, Department of Chemistry, Flowers Building, Armstrong Road, Imperial College London, London, UK SW7 2AZ. E-mail: a.miller@imperial.ac.uk*

[b] *IC-Vec Ltd., Flowers Building, Armstrong Road, London, UK SW7 2AZ. E-mail: m.jorgensen@imperial.ac.uk*

Received 2nd December 2004, Accepted 25th January 2005
First published as an Advance Article on the web 15th February 2005

An efficient modification of the Fukuyama–Mitsunobu procedure has been developed whereby primary or secondary amines can be synthesized from alkyl alcohols and the corresponding nosyl-protected/activated amine. Most importantly, the use of the DTBAD and diphenylpyridinylphosphine, as Mitsunobu reagents, generates reaction by-products that can be easily removed, providing a remarkably clean product mixture. This improved technique was implemented in the synthesis of a complex lipopeptide designed to target $\alpha_9\beta_1$-integrin proteins predominant on upper airway epithelial cells.

Introduction

With the ever increasing amount of biologically relevant nitrogenous molecules, the preparation of the amine functional group is probably one of the most significant aspects in organic chemistry today. Furthermore, polymethylene polyamines have been shown to be involved in many important biological functions and are promising antiparasitic agents, antimalarials, antidiarrhoeals, anti-HIV agents and metal chelators.[1] Another important application of the polyamines is their recent exploitation as gene delivery agents, especially when they are conjugated to lipid moieties such as cholesterol. In this case the polyamine has the dual purpose of binding and condensing nucleic acids, as well as structurally providing the hydrophilic end of the ambiphilic lipid important in the formation of liposomes and micelles.[2]

The efficiency of polyamine synthesis generally relies on the effectiveness of the transformation steps of primary alcohols to primary amines and, subsequently, primary amines to secondary amines. Although the investigation into new methods for the synthesis of amines is recognised as an important area of organic chemistry, there are few efficient installations of nitrogen onto functionalised organic molecules. Furthermore, the manipulation, handling and purification difficulties relating to nitrogenous containing compounds are well accepted by organic chemists.

The installation of primary amines[3] can be achieved *via* Gabriel synthesis[4] or by transformation of an alkyl halide to an azide[5] followed by reduction to the primary amine.[6] The alkylation of *p*-toluensulfonamide[7] or *N*-Boc-*p*-toluensulfonamide[8] under Mitsunobu conditions are also useful methods, although they require relatively harsh deprotection conditions.

The synthesis of secondary amines from the corresponding primary amines can also be achieved by several methods:[9] *N*-Alkylation with alkyl halides or sulfonates, reductive alkylations with aldehydes or ketones and reduction of *N*-alkylamides. The method of Weinreb and coworkers for the alkylation of *N*-methyl-*p*-toluenesulfonamide[8] with various primary and secondary alcohols under Mitsunobu conditions has led to the development of many different Mitsunobu modifications over the past 15 years.

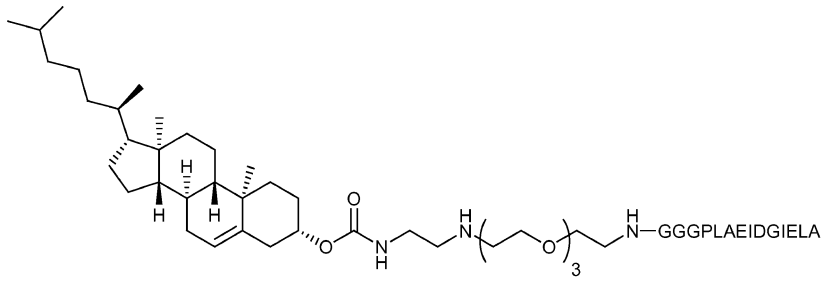
For the synthesis of amines from alcohols using the Mitsunobu reaction, the amines must be activated/protected as the acidic component ($pK_a < 11$) of the reaction in the form of *N*-alkylsulfonamides,[8] amides,[10] phthalimides[11] or *N*-trifluoroacetamides.[12] Perhaps the most useful activating group is the 2-nitrobenzenesulfonamide (Ns- or nosyl group), developed by Fukuyama and Kan,[13] which also functions as a protecting group that can be efficiently removed with soft nucleophiles *via* Meisenheimer complexes.[13,14] Both primary and secondary amines can be synthesized under standard Mitsunobu conditions[15] from alkyl alcohols using the corresponding nosylamide or *N*-alkylnosylamide, respectively.

Numerous reagents have been developed to improve on the versatility of the original DEAD and TPP combination *e.g.* 1,1′-(azodicarbonyl)dipiperidine (ADDP),[16] *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD)[12] and cyanomethylenetributyl-phosphorane (CMBP),[17] with modified phosphines such as tributylphosphines (TBP),[18] trimethylphosphine (TMP),[18] 4-(dipenylphosphinyl)benzoic acid 2-(trimethylsilyl)ethyl ester (DPPBE)[19] and 1,2-bis[diphenylphosphino] ethane.[20] None of these aforementioned reagents has appeared to have gained widely accepted use in the literature.

However, as previously noted, one major problem with the Mitsunobu reaction is the isolation and purification of the desired product from the complex reaction mixtures; in particular, from reagent by-products such as triphenylphosphine oxide and dicarboethoxyhydrazine derived from TPP and DEAD, respectively. This problematic aspect has led to the development of some Mitsunobu reagents that can be removed from the reaction mixtures by simple post-reaction procedures.[21] For example, fluorous analogues of DEAD can be removed by fluorous extraction techniques[21b,c] and chemically-tagged reagents (and resultant by-products) can be selectively removed by post-reaction sequestations.[21a,f] Polymer-bound PPh_3 and the resultant post-reaction polymer-bound triphenylphosphine oxide are eliminated from the reaction mixture by simple filtration.[21e,f]

During the synthesis of lung-targeting gene delivery agent **1** (Fig. 1) significant synthetic problems were experienced when we attempted to install the secondary amine;[22,23] the methods attempted often leading to the elimination of cholesterol or production of other by-products. Furthermore, due to their inherent ambiphilic nature the purification of lipids can be an extremely difficult task, especially when dealing with complex mixtures of product, by-products and reactants. As a result an

DOI: 10.1039/b418168a



1, JW001

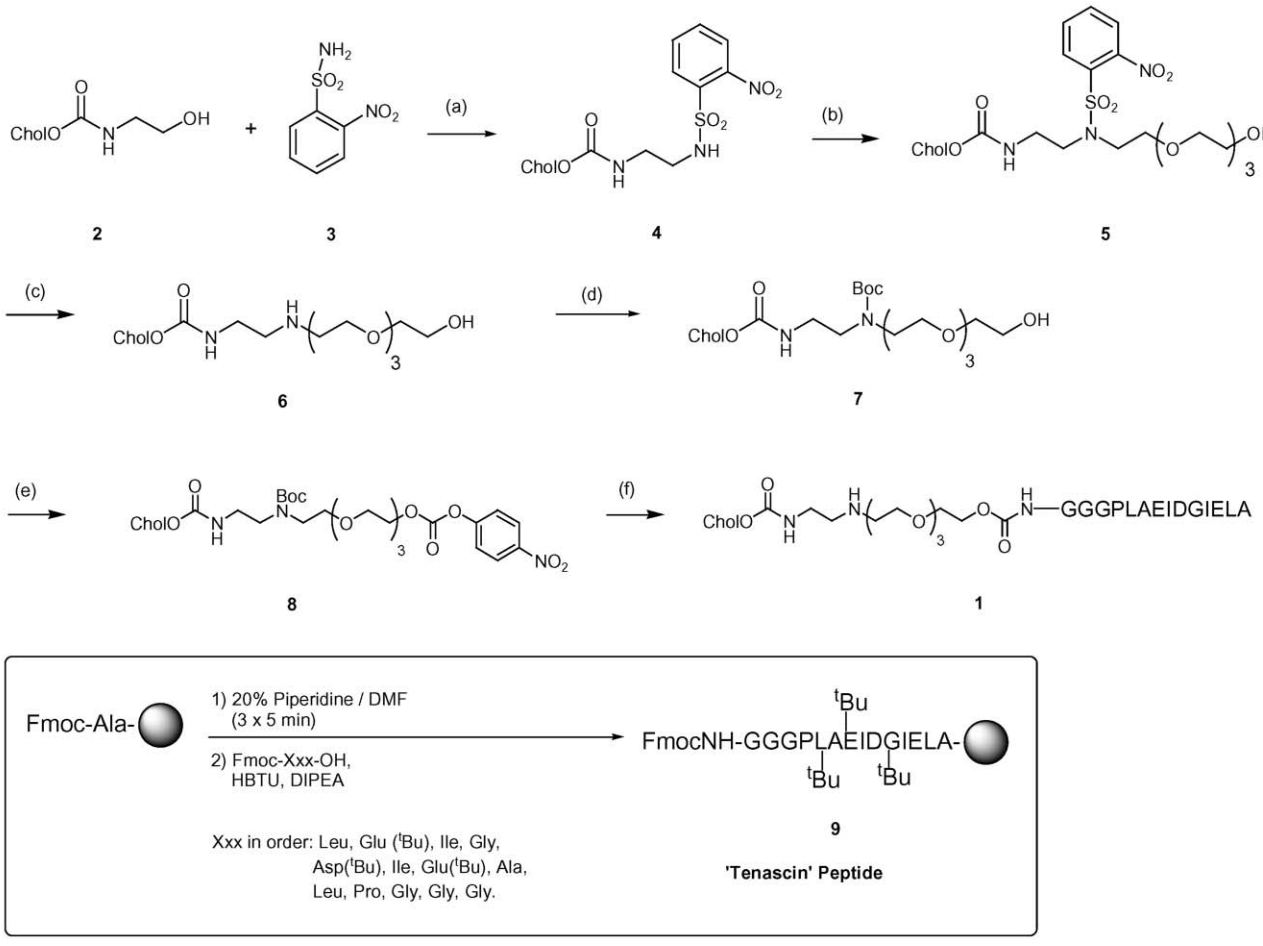
Fig. 1 Lung-targeting gene delivery agent JW001 **1**.

efficient modification of the Fukuyama–Mitsunobu reaction for generation of primary and secondary amines from primary or secondary alcohols was established (Scheme 1).[22]

The modified lipid **1** incorporates an integrin-mediated targeting ligand, based upon the protein tenascin C, that can target the α9β1-integrin commonly found in lung epithelial cells (Fig. 1).[22] Such an agent could be important for the delivery of suitable therapeutic DNA to the lung for treatment of the devastating respiratory disease cystic fibrosis.

Results and discussion

A large laboratory stock of cholesterol-derived alcohol **2**[22,23] was deemed to be a good starting point for the synthesis of tenascin lipopeptide **1** (Scheme 1). Initially our synthetic route for the conversion of **2** to the desired amine **4** was achieved by a combination of several cumbersome, often low yielding, functional group interconversion steps.[23] These proceeded *via* the conversion of the alcohol to the corresponding mesylate, nucleophilic substitution by an azide anion and subsequent reduction of the azide (adaptation of the Staudinger reaction) to the primary amine giving the desired product in 45% overall yield.[23] The seemingly simple *N*-alkylation of the amine (to give the desired secondary amine) frequently results in the production of undesired by-products, including polyalkylated amine products. Despite the ease with which this reaction proceeds, the inherent lack of control results in complex mixtures and low isolated yields. In an effort to improve on this strategy we employed an adapted and optimised version of the Fukuyama–Mitsunobu procedure.[24] Using this method it is



2 **3** **4** **5** **6** **7** **8** **1** **9**

Scheme 1 The synthesis of lung-targeting gene delivery agent JW001 **1**. Reaction conditions: (a) DTBAD, Ph_2PyP, CH_2Cl_2, rt, 90%; (b) 3,6,9-trioxa-11-benzyloxyundecan1-ol, DTBAD, Ph_2PyP, CH_2Cl_2, rt, 71%; (c) sodium naphthalenide, THF, −30 °C, 74%; (d) $(Boc)_2O$, Et_3N, DCM, 84%; (e) *p*-nitrophenyl chloroformate, DMAP, DCM, 92%; (f) i. **9**, piperidine, DMF; ii. **8**, Et_3N, DMF, 18 h; iii. Resin cleavage: 5% H_2O in TFA, 1.5 h, 10%.

possible to convert a primary alcohol to a protected primary amine in one step. This primary amine can also be easily converted to a secondary amine under analogous conditions. This procedure bypasses some of the caveats of previous protocols for synthesis of linear polyamines; it affords better yields of the primary amines and also asserts more chemoselective control over their subsequent alkylation.

Initially we utilised the standard Fukuyama–Mitsunobu procedure[24] whereby cholesteryl-alcohol **2** was reacted with 2-nitrobenzenesulfonamide **3** under standard DEAD–PPh_3 conditions (Scheme 1). However, poor conversion of **2** to 2-nosyl amine occurred and **4** was obtained in only 43% yield. Furthermore, purification of **4** from the reaction by-products was problematic. In an effort to simply the purification of the mixtures resulting from standard Mitsunobu conversions[15], Kiankarimi *et al.*[25] introduced a procedure whereby they substituted DEAD for di-*tert*-butylazodicaboxylate (DTBAD). By adding an additional post-reaction acid quench step, the unreacted DTBAD and dicarbo-*tert*-butyloxyhydrazine would decompose to isobutene, nitrogen (or hydrazine) and carbon dioxide, thereby considerably cleaning-up the reaction mixture. Furthermore, the substitution of PPh_3 for diphenyl-2-pyridylphosphine allowed removal of all unreacted phosphine and its oxide by-product by means of an acidic extractive work up. Employing these conditions, together with slow addition (*ca.* 40 min) of the DTBAD reagent in anhydrous dichloromethane, we generated **4** cleanly in much improved yield (90%). It was later noted that, by using 2 eq. each of DTBAD and diphenyl-2-pyridylphosphine, respectively, the slow addition step could be omitted. Similarly, nosyl-protected secondary amine **5** was synthesized in 71% yield from **4** and monobenzyl-protected tetraethylene glycol.[26]

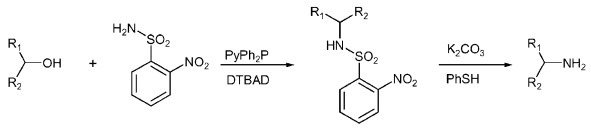
Deprotection of both the nosyl and benzyl protecting groups in **5** was achieved in one step with sodium naphthalenide affording **6** in 74% yield. Boc-protection of the secondary amine and subsequent activation of the primary alcohol as the *p*-nitrophenol carbonate gave **8** in 77% yield for the two steps. The lipidic carbonate **8** allows for facile conjugation of an alcohol to a primary amine through formation of a carbamate linkage. Thus **8** was now activated for solid phase synthetic coupling to the fully protected, resin bound tenascin peptide **9**.

The tenascin peptide[22a] (amino acid sequence: NH_2–GGGPLAEIDGIELA–CO_2H) was synthesized on acid labile Wang resin (Novabiochem, C Biosciences, UK) according to a standard Fmoc peptide synthesis protocol[22b] affording the corresponding fully protected and resin-bound tenascin **9** (Scheme 1). After removal of the *N*-terminal Fmoc-protecting group, the liberated amine was reacted with carbonate **8** giving the fully-protected tenascin lipopeptide on resin. Finally, the resin cleavage (and concomitant removal of all protecting groups) with trifluoroacetic acid (TFA) gave the desired tenascin product **1** in 10% yield after purification by semi-preparative reverse phase HPLC.

Thus, having developed an extremely facile procedure for producing primary and secondary amines on cholesterol-based lipids, previously a problematic synthetic step in our laboratories,[23] we were interested to investigate its versatility further. 2-Nitrobenzenesulfonamide **3** was treated with a variety of primary (entries 1–11) and secondary alcohols (entries 12–13) under the new DTBAD (2 eq.)–diphenyl-2-pyridylphosphine (2 eq.) conditions, thereby obtaining the respective nosyl-protected amines **10** (Table 1). Deprotection of the nosyl group was achieved by treating **10** with thiophenol and potassium carbonate in acetonitrile at 50 °C overnight, giving the amines **11** (Table 1). Both nosylamine **10** and deprotected **11** were obtained in good to excellent yields, from both primary and secondary alcohols. An exception to this trend was the reaction with *p*-nitrobenzylalcohol (entry 6) which gave the corresponding sulfonamide **10f** in a poor 30% yield.

The Fukuyama–Mitsunobu reaction of *N*-nosyl-*N*′-alkylamines with primary and secondary alcohols has been extensively studied in the literature.[8,13] Under our conditions, treatment of nosyl-protected phenylethylamine **10a** with primary alcohols *n*-pentanol (entry 14) and phenylethylamine (entry 15) gave sulfonamides **12a** and **12b** respectively in good yields (Table 2). However, reaction of **10a** with secondary alcohols hexan-2-ol (entry 16) and 1-phenylpropan-2-ol (entry 17) gave only average yields of the corresponding sulfonamides **12c** and **12d**. It should be noted however, that no further attempts were made to optimise this procedure for the synthesis of secondary amines. Nonetheless, the ease of purification would still make this modification an attractive alternative to standard Mitsunobu procedures.

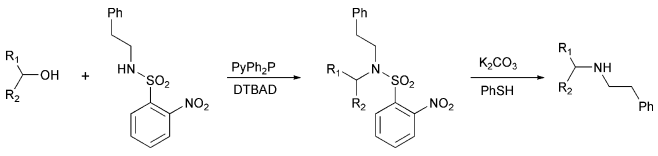
Table 1 Conversion of primary and secondary alcohols to primary amines



3 10 11

Entry	R_1	R_2	Sulfonamide	Amine
1	$PhCH_2$	H	**10a** (97%)	**11a** (89%)
2	*p*-$MeOC_6H_4CH_2$	H	**10b** (90%)	**11b** (95%)
3	*p*-$NO_2C_6H_4CH_2$	H	**10c** (89%)	**11c** (91%)
4	Ph	H	**10d** (96%)	**11d** (92%)
5	*p*-$MeOC_6H_4$	H	**10e** (95%)	**11e** (93%)
6	*p*-$NO_2C_6H_4$	H	**10f** (30%)	**11f** (80%)
7	PhCH=CH	H	**10g** (90%)	**11g** (86%)
8	$CH_3CH_2CH_2CH_2$	H	**10h** (96%)	**11h** (90%)
9	$CH_3(CH_2)_2(CH_3)CH$	H	**10i** (75%)	**11i** (100%)
10	$CH_3CH_2C{\equiv}C$	H	**10j** (92%)	**11j** (91%)
11	$CH_3CH_2CH{=}CH$	H	**10k** (84%)	**11k** (80%)
12	$CH_3CH_2CH_2CH_2$	CH_3	**10l** (70%)	**11l** (80%)
13	$PhCH_2$	CH_3	**10m** (85%)	**11m** (84%)

Table 2 Conversion of primary and secondary alcohols to secondary amines



10a 12 13

Entry	R_1	R_2	Sulfonamide	Amine
14	$CH_3CH_2CH_2CH_2$	H	**12a** (74%)	**13a** (90%)
15	$PhCH_2$	H	**12b** (64%)	**13b** (96%)
16	$CH_3CH_2CH_2CH_2$	CH_3	**12c** (50%)	**13c** (96%)
17	Ph CH_2	CH_3	**12d** (40%)	**13d** (94%)

In conclusion, we have developed an improved Fukuyama–Mitsunobu procedure for the high yielding synthesis of primary and secondary amines. The combination of nosyl-chemistry and "cleaner" Mitsunobu reagents described here is applicable to the sysnthesis of amines in both natural product and medicinal chemistry. Lastly, this method has permitted the synthesis of the lung-targeted gene delivery agent **1** which is currently undergoing biological evaluation.

Experimental section

General

Dried dichloromethane was distilled with phosphorus pentoxide, other solvents were purchased predried as required. All the

reactions were performed under nitrogen using dry solvents unless otherwise stated. Thin layer chromatography (tlc) was performed on pre-coated Merck-Kieselgel 60 F254 aluminium backed plated and revealed with ultraviolet light, iodine, acidic ammonium molybdate(IV), acidic ethanolic vanillin, iodine, bromocresol green, Dragendorff's reagent, ninhydrin, chloranil or other agents. Flash column chromatography was accomplished on Merck-Kieselgel 60 (230–400 mesh). ^{1}H- and ^{13}C-NMR were recorded on either Bruker DRX_{300}, Jeol GX-270Q, or Bruker $Advance_{400}$ Ultrashield TM machine using residual isotopic solvent as an internal reference (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, br = broad singlet). FAB mass spectra were recorded using VG-7070B, Jeol SX-102 instruments and ESI mass spectrometry was carried out using a Bruker Daltronics ESI 6000 spectrometer. Infrared spectra were recorded using Jasco 620 FTIR spectrometer. Where appropriate a Pharmacia LKB–Ultrospec III (deuterium lamp at 300 nm) was used to read the UV absorbance. All chemicals were purchased from Sigma Aldrich or Lancaster if not otherwise stated.

Peptide synthesis: materials and methods

The FastMocTM reagent HBTU was obtained from Advanced Chemtech Europe (Cambridge, UK) and CN Bioscience (Nottingham, UK). The solvents, DMF and acetonitrile, were purchased from Rathburn (Walker-Burn, Scotland). All the reagents used in the syntheses were of the highest purity. The following amino acids and resins were obtained from Nova Biochem: Fmoc–Leu–OH, Fmoc–Glu(OtBu)–OH, Fmoc–Ile–OH, Fmoc–Gly–OH, Fmoc–Asp(OtBu)–OH, Fmoc–Ala–OH, Fmoc–Pro–OH, Fmoc–Gly_3–OH, Gly–(OtBu)·HCl and Fmoc–Ala-Wang (100–200) preloaded resin.

Peptides and lipopeptides were synthesised using two different reaction vessels. The first used the Isolute SPE Filtration Columns and their appropriate accessories (caps and stoppers) combined with a VacMaster-10 sample processing station for removing solvents, all purchased from Jones Chromatography (Mid Glamorgan, UK). The second was using a glass reaction vessel treated overnight with a solution of 50 mL toluene–dichlorodimethylsilane 20%. The vessel was then washed with methanol (2 × 30 mL), DMF (2 × 30 mL) and dichloromethane (1 × 30 mL) before drying.

The preloaded resin derivatised with the first Fmoc-protected amino acid was added to either reaction vessel. It was washed with MeOH (4 × 2 min with 30 mL) and DMF (4 × 2 min with 30 mL). To allow the resin to swell, DMF (10–20 mL) was added to the resin for 30 min to 1 h. After the first deprotection of Fmoc, the loading of the resin was calculated. For it, the collected solutions from Fmoc-deprotection were filled up to 250 mL with MeOH in a volumetric flask, diluted 1 : 25 and the absorbance at 300 nm was measured by a UV spectrometer. The loading on the resin was calculated by the following equation:

$$n = \frac{\mathrm{A} \cdot \mathrm{d} \cdot \mathrm{v} \cdot 1 \times 10^{-3}}{\varepsilon \cdot 1},$$

where

$\varepsilon_{300} = 7800\,\mathrm{mol^{-1}\,cm^{-1}}$ d = 25 (dilution) v = 250 mL
$A_{(\lambda\,300\,\mathrm{nm})}$ = absorbance n = mol × 10^{-3} 1 = 1 cm

N^1-Cholesteryloxycarbonyl-1-amino-2-hydroxyethane 2

Ethanolamine (15 mL, 246.0 mmol) was dissolved in dichloromethane (35 mL) and was cooled to 0 °C using an ice bath. A solution of cholesteryl chloroformate (50 g, 112.0 mmol) in dichloromethane (300 mL) was added dropwise over 1 h; during that time a white precipitate formed. The reaction warmed to rt and continued stirring for 18 h. The precipitate was removed by filtration and the solution was washed with saturated $NaHCO_3$ (2 × 75 mL), water (2 × 75 mL), dried ($MgSO_4$) and the solvent removed under a reduced pressure to give **2** (44 g, 87%) as a colourless oil; υ_{max}(film)/cm^{-1} 3339, 2922, 1671, 1472 and 1376; δ_H(300 MHz, $CDCl_3$) 0.67 (3H, s), 0.87 (6H, d, *J* 6.5), 0.91 (3H, d, *J* 6.5), 1.00 (3H, s), 1.62 − 1.03 (21H, m), 1.70–2.06 (5H, m), 2.23–2.36 (2H, m), 3.33 (2H, t, *J* 4.5), 3.72 (2H, t, *J* 5.0), 4.50 (1H, m), 5.00 (1H, br), 5.37 (1H, m); *m/z* (FAB) 496 (M + Na)$^+$, 474 (M + H)$^+$, 369 (chol)$^+$. Found: (M + H)$^+$ 474.3654, $C_{30}H_{52}NO_3$ requires (M + H)$^+$ 474.3947.

N^1-Cholesteryloxycarbonyl-1-amino-2″-nitrobenzenesulfonamidoethane 4

A mixture of 2-nitrobenzylsulfonamide **3** (0.202 g, 1 mmol), diphenyl-2-pyridylphosphine (0.263 g, 1 mmol) and **2** (0.237 g, 0.5 mmol) was dissolved in anhydrous dichloromethane (10 mL) under a nitrogen atmosphere. To this stirred mixture di-*tert*-butylazadicarboxylate (0.230 g, 1 mmol) was added in one portion. After stirring for 2 h, HCl in dioxane (4 M, 5 mL) was added and the mixture left to stir for 1 h. The mixture was then concentrated *in vacuo*, dissolved in dichloromethane (20 mL) and washed with aq. HCl (4 M, 3 × 15 mL). The organic phase was collected, dried with magnesium sulfate and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (hexane–EtOAc 2 : 1), to yield **4** (0.304 g, 90%) as an off white solid, mp 185 °C; υ_{max}(film)/cm^{-1} 3347, 2946, 2868, 2253, 1770, 1696, 1540, 1440, 1364, 1254, 1167, 908 and 733; δ_H(400 MHz, $CDCl_3$) 0.67 (3H, s), 0.85 (3H, d, *J* 6.4), 0.86 (3H, d, *J* 6.4), 0.90 (3H, d, *J* 6.8), 0.99 (3H, s), 1.02–1.63 (21H, m), 1.77–2.06 (5H, m), 2.22–2.32 (2H, m), 4.42–4.46 (1H, m,), 4.98 (1H, br), 5.33 (1H, m), 5.77 (1H, br), 7.71–7.76 (2H, m), 7.84–7.88 (1H, m), 8.11–8.15 (1H, m); δ_C(100 MHz, $CDCl_3$) 11.8, 18.7, 19.3, 21.0, 22.5, 22.8, 23.8, 24.3, 28.0, 28.1, 28.2, 31.8, 31.9, 35.8, 36.2, 36.5, 36.9, 38.4, 39.5, 39.7, 40.7, 42.3, 43.7, 50.0, 56.1, 56.7, 74.8, 122.6, 125.4, 131.0, 132.8, 133.5, 133.6, 139.7, 148.0, 156.4; *m/z* (ESI) 655.9 (M − H)$^-$, $C_{36}H_{54}N_3O_6S$ requires (M − H)$^-$ 656.4.

N^1-Cholesteryloxycarbonyl-3-aza-N^3-2″-nitrobenzenesulfonyl-6,9,12-trioxa-15-benzyloxy-1-amino-tetradecane 5

A solution of diphenyl 2-pyridylphosphine (0.028 g, 0.11 mmol) and DTBAD (0.024 g, 0.11 mmol) in dry dichloromethane (5 mL) was transferred under nitrogen into a solution of 3,6,9-trioxa-11-benzyloxyundecan-1-ol (0.020 g, 0.07 mmol) in dry dichloromethane (2.5 mL). A solution of sulfonamide **4** (0.050 g, 0.07 mmol) in dry dichloromethane (2.5 mL) was also added to the reaction mixture and left stirring overnight. The solvent was removed under a reduced pressure and the resultant residue was purified by column chromatography (hexane–EtOAc 2 : 3) to produce **5** (0.048 g, 71%) as a colourless viscous oil; υ_{max}(film)/cm^{-1} 3345, 3045, 2945, 2873, 1711, 1455, 1123 and 1010; δ_H(400 MHz, $CDCl_3$) 0.68 (3H, s), 0.85 (6H, d, *J* 6.5), 0.90 (3H, d, *J* 6.5), 0.99 (3H, s), 1.00–1.62 (21H, m), 1.78–2.09 (5H, m), 2.15–2.38 (2H, m), 3.38 (2H, m), 3.45 (m, 2H), 3.52 (2H, t, *J* 4.8), 3.58 (2H, m), 3.59 (12H, m), 4.47 (1H, m), 4.58 (2H, s), 5.38 (1H, m), 5.55 (1H, br), 7.27–7.37 (5H, m), 7.71–7.76 (2H, m), 7.84–7.88 (1H, m), 8.11–8.15 (1H, m); δ_C(100 MHz, $CDCl_3$) 11.8, 18.7, 19.3, 21.0, 22.5, 22.7, 23.8, 24.3, 28.0, 28.2, 29.7, 31.9, 35.8, 36.2, 36.6, 37.0, 39.5, 39.8, 42.3, 48.3, 49.6, 50.1, 56.2, 56.7, 69.5, 69.8, 70.3, 70.4, 70.5, 70.6, 70.7, 73.2, 76.6, 119.5, 122.5, 126.3, 127.6, 128.3, 130.6, 132.7, 135.3, 138.0, 139.6, 148.0, 148.1, 155.9; *m/z* (FAB) 969 (M + H)$^+$, 369 (chol)$^+$.

N^1-Cholesteryloxycarbonyl-3-aza-6,9,12-trioxa-1-amino-15-hydroxytetradecane 6

A dry round bottomed flask was charged with naphthalene (4.5 g, 34.7 mmol) and sodium metal (0.8 g, 34.7 mmol) under nitrogen. Dry THF (100 mL) was added to the flask and vigorously stirred for 1 h. The solution was cooled to −30 °C using dry ice and acetone. A solution of **5** (1.6 g, 1.7 mmol) in

dry THF (10 mL) was added to the flask over 5 min, and stirred for 45 min maintaining −30 °C. Once the reaction had gone to completion, a solution of 2,6-di-*tert*-butyl-4-methyl phenol (7.48 g, 34.7 mmol) in THF (2 mL) was slowly added and allowed to warm to rt. The solvent was removed under a reduced pressure and the resultant residue was dry loaded onto a silica flash column (DCM–MeOH–NH_3 97 : 2.5 : 0.5) giving **6** (0.83 g, 74%) as a viscous white solid; ν_{max}(film)/cm^{-1} 3610, 3345, 2936, 2863, 1698, 1456 and 1260; δ_H(400 MHz, $CDCl_3$) 0.67 (3H, s), 0.85 (6H, d, *J* 6.5), 0.90 (3H, d, *J* 6.5), 0.99 (3H, s), 1.01–1.65 (21H, m), 1.76–2.08 (5H, m), 2.17–2.41 (2H, m), 2.74 (4H, m), 2.98 (1H, br), 3.30 (2H, m), 3.58–3.79 (14H, m), 4.50 (1H, m), 5.36 (1H, m), 5.72 (1H, br); δ_C(100 MHz, $CDCl_3$) 11.8, 18.7, 19.3, 21.0, 22.5, 22.8, 23.8, 24.2, 28.0, 28.2, 29.6, 31.8, 35.7, 36.0, 36.5, 36.9, 38.6, 39.5, 39.7, 40.3, 42.2, 48.4, 48.7, 49.9, 56.1, 56.6, 61.3, 69.7, 70.1, 70.3, 70.5, 73.0, 74.1, 122.4, 139.9, 156.3; *m/z* (FAB) 649 $(M + H)^+$, 369 $(chol)^+$. Found: $(M + H)^+$ 649.5144, $C_{38}H_{68}N_2O_6$ requires $(M + H)^+$ 649.5156.

N^1-Cholesteryloxycarbonyl-3-aza-N^3-^{t}butoxycarbonyl-6,9,12-trioxa-1-amino-15-hydroxytetradecane 7

To a solution of **6** (0.030 g, 0.046 mmol) in dry dichloromethane (1 mL), di-*tert*-butyldicarbonate (0.010 g, 0.046 mmol) and triethylamine (4.1 mL, 0.05 mmol) were added under nitrogen. The reaction was stirred for 10 h until the reaction had gone to completion. The solvent was removed *in vacuo* and the residue was dry loaded onto a silica flash column (hexane–EtOAc 1 : 1) affording **7** (0.028 g, 84%) as a white viscous solid; ν_{max}(film)/cm^{-1} 3611, 2947, 2871, 1698, 1652, 1456 and 1265; δ_H(400 MHz, $CDCl_3$) 0.69 (3H, s), 0.88 (6H, d, *J* 6.5), 0.93 (3H, d, *J* 6.5), 1.02 (3H, s), 1.03–1.72 (21H, m), 1.47 (9H, s), 1.76–2.10 (5H, m), 2.22–2.48 (2H, m), 3.14 (1H, br), 3.26–3.48 (6H, m), 3.52–3.85 (14H, m), 4.49 (1H, m), 5.35 (1H, m), 5.65 (1H, br); δ_C(100 MHz, $CDCl_3$) 11.5, 18.4, 19.0, 20.7, 22.3, 22.5, 23.5, 24.0, 27.7, 27.9, 28.1, 31.5, 35.5, 36.2, 36.7, 38.3, 39.3, 39.4, 39.5, 39.7, 42.0, 47.9, 48.2, 49.7, 55.9, 56.3, 61.2, 69.5, 70.0, 70.1, 72.3, 73.7, 79.5, 122.1, 139.5, 155.9; *m/z* (FAB) 771 $(M + Na)^+$, 749 $(M + H)^+$, 649 $(M\text{-Boc} + H)^+$, 369 $(chol)^+$. Found: $(M + H)^+$ 749.5708, $C_{43}H_{76}N_2O_8$ requires $(M + H)^+$ 749.5680.

N^1-Cholesteryloxycarbonyl-3-aza-N^3-^{t}butoxycarbonyl-6,9,12-trioxa-1-amino-15-O^{15}-4″-nitrophenyloxycarbonyltetradecane 8

To a solution of **7** (0.050 g, 0.067 mmol) in dry dichloromethane (3.5 mL) was added DMAP (0.016 g, 0.13 mmol), triethylamine (19 mL, 0.13 mmol) and *p*-nitrophenyl chloroformate (0.041 g, 0.2 mmol) under nitrogen. The reaction was stirred for 10 h, the solvent removed under a reduced pressure and purified by column chromatography (hexane–EtOAc 2 : 3) giving **8** (0.056 g, 92%) as a viscous white solid; ν_{max}(film)/cm^{-1} 3348, 2942, 1770, 1696, 1616 and 1593; δ_H(400 MHz, $CDCl_3$) 0.69 (3H, s), 0.87 (6H, d, *J* 6.5), 0.91 (3H, d, *J* 6.5), 1.00 (3H, s), 1.01–1.72 (21H, m), 1.46 (9H, s), 1.78–2.14 (5H, m), 2.21–2.44 (2H, m), 3.26–3.52 (6H, m), 3.56–3.78 (10H, m), 3.80 (2H, m), 4.42–4.54 (3H, m), 5.35 (1H, m), 5.63 (1H, br), 7.38 (2H, m), 8.27 (2H, m); δ_C(100 MHz, $CDCl_3$) 11.5, 18.4, 19.0, 20.7, 22.3, 22.5, 23.5, 24.0, 27.7, 27.9, 28.1, 31.5, 35.5, 36.2, 36.7, 38.3, 39.2, 39.4, 39.5, 39.7, 42.1, 48.0, 48.2, 49.7, 55.8, 56.3, 69.3, 69.9, 70.2, 70.4, 73.9, 79.3, 122.2, 124.9, 125.7, 139.6, 145.0, 152.1, 156.5, 163.0; *m/z* (FAB) 936 $(M + Na)^+$, 914 $(M + H)^+$, 814 $(M\text{–Boc} + H)^+$, 369 $(chol)^+$. Found: $(M + H)^+$ 914.5772, $C_{50}H_{79}N_3O_{12}$ requires $(M + H)^+$ 914.5742.

Tenascin peptide 9

This peptide was synthesised using preloaded Fmoc–Ala-Wang resin (0.4 g, 0.2 mmol, 0.5 mmol g^{-1}). Once the resin was swollen the peptide sequence was built up by alternating coupling and Fmoc deprotection steps. Fmoc deprotection was achieved by cleaving with a solution of 25% piperidine in DMF (2 × 5 min) followed by washing with DMF (5 × 2 min). After each Fmoc deprotection step, the collected cleavage and washing solutions were diluted and the absorbance was determined as for the initial loading calculations in order to check the completeness of the Fmoc cleavage. A Kaiser test was performed; if it was negative the deprotection step was repeated. Once the Fmoc groups were removed a solution of Fmoc protected amino acid (3 eq.), HBTU (3 eq.) and DIPEA (5 eq.) in DMF (5 to 10 mL) was added to the resin and shaken for 45 min. The resin was washed with DMF (5 × 2 min) and another Kaiser test performed, again if a negative result was not obtained the coupling was repeated. This process was repeated until the correct amino acid sequence was obtained, where it was then washed with dichloromethane (2 × 5 mL, 2 min) and MeOH (2 × 5 mL, 2 min). Batches of 50 mg were deprotected and cleaved for characterisation. The crude peptide was purified by reversed-phase HPLC (Vydac C4 column at a flow rate of 1 mL min^{-1}, 214 nm), using a gradient 30–100% acetonitrile over 40 min (water as the second solvent). G_3PLAEIDGIELA (0.010 g, 27%) eluting at $R_t = 6.24$ min, 99% purity; *m/z* (ESI) 1311 $(M + H)^+$, $C_{57}H_{95}N_{14}O_{21}$ requires $(M + H)^+$ 1311.

Lipopeptide 1

The tenascin peptidoresin **9** (0.050 g, 0.03 mmol) was swelled with DMF (7 mL, 30 min), the terminal Fmoc was deprotected using 25% piperidine in DMF (2 × 5 min, 5 mL) and washed with DMF (5 × 2 min, 5 mL). A Kaiser test was performed and produced a positive result. Dry DMF (1.5 mL) and triethylamine (11 mL, 0.075 mmol) were transferred to the resin and shaken for 5 min. A premixed solution containing carbonate **8** (0.054 g, 0.06 mmol) and triethylamine (11 mL, 0.075 mmol) in dry DMF (1 mL) was also transferred into the reaction vessel under argon (including 2 mL of washings) and shaken for 18 h. The resin was washed with DMF (5 × 2 min, 10 mL) and a Kaiser test performed. The colourless beads produced a negative result indicating that the lipid had been successfully coupled. The resin was washed further with MeOH (3 × 2 min, 5 mL) and dichloromethane (3 × 5 mL, 2 min). The resin was air-dried then cleaved for 1.5 h using 95% TFA–water (2 mL). The crude lipopeptide was precipitated in ice cold MTBE (10 mL), centrifuged (3600 rpm, 4 °C, 2 × 5 min) and freeze dried to produce a white powder. The crude lipopeptide was purified by reversed-phase HPLC (Vydac C4 colum at a flow rate of 1 mL min^{-1}, 214 nm), using a gradient 30–100% acetonitrile over 40 min (water as the second solvent). Lipopeptide **1** (0.0058 g, 9.7%) was eluted at $R_t = 32.6$ min, 99% purity; *m/z* (ESI-MS) 1985.8 $(M + H)^+$, 1574.8 $(M\text{–CholOCO})^+$, 1311.7 (tenascin + $H)^+$. $C_{96}H_{162}N_{16}O_{28}$ requires $(M + H)^+$ 1986.

General procedure for Mitsunobu reaction of primary and secondary alcohols with 2-nitrobenzenesulfonamide

A mixture of 2-nitrobenzenesulfonamide **3** (0.202 g, 1.0 mmol), diphenyl-2-pyridylphosphine (0.263 g, 1.0 mmol) and the alcohol (0.5 mmol) was dissolved in anhydrous dichloromethane (10 mL) under an atmosphere of nitrogen. To this solution di-*tert*-butylazodicarboxylate (0.230 g, 1.0 mmol) was added in one portion and the resulting mixture was stirred at rt for 2 h. HCl in dioxane (5 mL, 4 M) was added to the mixture and, after stirring for 1 h, the excess solvent was evaporated. The residue was dissolved in dichloromethane and washed with 4 M HCl twice. The organic layer was dried with anhydrous magnesium sulfate and the solvent evaporated. Flash column chromatography gave the desired sulfonamide.

2-Nitro-*N*-phenethyl-benzenesulfonamide 10a[14,18,27]

Flash column chromatography (hexane–EtOAc 4 : 1) gave **10a** (97%) as a white waxy oil; δ_H(400 MHz, $CDCl_3$) 2.76 (2H, t, *J* 6.8), 3.32 (2H, q, *J* 6.8), 5.24 (1H, t, *J* 5.6), 7.00–7.02 (2H, m), 7.10–7.18 (3H, m), 7.63–7.65 (2H, m), 7.73–7.76 (1H, m),

8.01–8.03 (1H, m); δ_C(100 MHz, $CDCl_3$) 36.0, 45.0, 125.4, 126.9, 128.7, 128.8, 131.0, 132.8, 133.5, 133.9, 137.4, 147.9; *m/z* (ESI) 328.9 $(M + Na)^+$, $C_{14}H_{14}N_2O_4SNa$ requires $(M + Na)^+$ 329.06.

_N_-[2-(4-Methoxy-phenyl)-ethyl]-2-nitro-benzenesulfonamide 10b

Flash column chromatography (hexane–EtOAc 4 : 1) gave **10b** (90%) as a white solid, mp 151 °C; δ_H(400 MHz, $CDCl_3$) 2.77 (2H, t, *J* 6.8), 3.35 (2H, q, *J* 6.8), 3.77 (3H, s), 5.29 (1H, t, *J* 4.8), 6.76 (2H, d, *J* 8.4), 6.99 (2H, d, *J* 8.4), 7.71 (2H, dd, *J* 5.6, *J* 3.2), 7.83 (1H, dd, *J* 6.0, *J* 3.2), 8.08 (1H, dd, *J* 6.0, *J* 3.2); δ_C(100 MHz, $CDCl_3$) 35.1, 45.3, 55.3, 114.2, 125.4, 129.3, 129.7, 131.0, 132.8, 133.4, 134.0, 158.5; *m/z* (ESI) 358.9 $(M + Na)^+$, $C_{15}H_{16}N_2O_5SNa$ requires $(M + Na)^+$ 359.07.

2-Nitro-_N_-[2-(4-nitro-phenyl)-ethyl]-benzenesulfonamide 10c

Flash column chromatography (hexane–EtOAc 4 : 1) gave **10c** (89%) as a yellow solid, mp 115 °C; δ_H(400 MHz, $CDCl_3$) 2.98 (2H, t, *J* 6.8), 3.45 (2H, q, *J* 6.8), 5.36 (1H, t, *J* 6.0), 7.31 (2H, d, *J* 8.4), 7.70–7.73 (2H, m), 7.83–7.85 (1H, m), 8.05–8.07 (1H, m), 8.09 (2H, d, *J* 8.8); δ_C(100 MHz, $CDCl_3$) 36.2, 44.5, 123.9, 125.5, 129.7, 130.8, 132.9, 133.7, 133.8, 145.3, 147.1; *m/z* (ESI) 349.9 $(M - H)^-$, $C_{14}H_{12}N_3O_6S$ requires $(M - H)^-$ 350.1.

_N_-Benzyl-2-nitro-benzenesulfonamide 10d[27,28]

Flash column chromatography (hexane–EtOAc 4 : 1) gave **10d** (96%) as a pale oil; δ_H(400 MHz, $CDCl_3$) 4.32 (2H, d, *J* 6.0), 5.72 (1H, t, *J* 6.0), 7.22 (5H, br), 7.63 (1H, td, *J* 7.6, *J* 1.6), 7.67 (1H, td, *J* 7.6, *J* 1.6), 7.81 (1H, dd, *J* 7.6, *J* 1.6), 8.00 (1H, dd, *J* 7.6, *J* 1.6); δ_C(100 MHz, $CDCl_3$) 47.9, 125.3, 127.9, 128.1, 128.7, 131.0, 132.8, 133.4, 134.0, 135.7, 147.9; *m/z* (FAB) 293 $(M + H)^+$, 91 $(PhCH_2)^+$. Found: $(M + H)^+$ 293.0600, $C_{13}H_{13}N_2O_4S$ requires $(M + H)^+$ 293.0596.

_N_-(4-Methoxy-benzyl)-2-nitro-benzenesulfonamide 10e[29]

Flash column chromatography (hexane–EtOAc 4 : 1) gave **10e** (95%) as a pale solid; δ_H(400 MHz, $CDCl_3$) 3.75 (3H, s), 4.25 (2H, d, *J* 6.0), 5.62 (1H, t, *J* 6.0), 6.75 (2H, d, *J* 8.8), 7.12 (2H, d, *J* 8.8), 7.64 (1H, td, *J* 7.6, *J* 1.6), 7.68 (1H, td, *J* 7.6, *J* 1.6), 7.82 (1H, dd, *J* 8.0, *J* 1.6), 8.01 (1H, dd, *J* 7.6, *J* 1.6); δ_C(100 MHz, $CDCl_3$) 47.5, 55.3, 114.1, 125.3, 127.7, 129.3, 131.1, 132.7, 133.3, 134.1, 147.9, 159.4; *m/z* (FAB) 323 $(M + H)^+$, 290 $(M - OMe)^+$.

2-Nitro-_N_-(4-nitro-benzyl)-benzenesulfonamide 10f

Flash column chromatography (hexane–EtOAc 4 : 1) gave **10f** (30%) as a yellow solid, mp 132 °C; δ_H(400 MHz, $CDCl_3$) 4.44 (2H, d, *J* 6.4), 5.89 (1H, t, *J* 6.4), 7.46 (2H, d, *J* 8.8), 7.68 (1H, td, *J* 7.6, *J* 1.6), 7.74 (1H, td, *J* 7.6, *J* 1.6), 7.87 (1H, dd, *J* 7.6, *J* 1.2), 8.03 (1H, dd, *J* 7.6, *J* 1.6), 8.13 (2H, d, *J* 8.8); *m/z* (ESI) 335.9 $(M - H)^-$, $C_{13}H_{10}N_3O_6S$ requires $(M - H)^-$ 336.0.

2-Nitro-_N_-(3-phenyl-allyl)-benzenesulfonamide 10g

Flash column chromatography (hexane–EtOAc 4 : 1) gave **10g** (90%) as a yellow solid; δ_H(400 MHz, $CDCl_3$) 3.85 (2H, td, *J* 6.4, *J* 1.2), 5.43 (1H, t, *J* 6.0), 5.94 (2H, dt, *J* 15.6, *J* 6.4), 6.42 (1H, d, *J* 15.6), 7.12–7.21 (5H, m), 7.58–7.60 (2H, m), 7.74–7.77 (1H, m), 8.04–8.06 (1H, m); δ_C(100 MHz, $CDCl_3$) 46.1, 123.5, 125.4, 126.5, 128.1, 128.6, 131.2, 132.8, 133.6, 133.7, 134.2, 135.9, 148.0; *m/z* (ESI) 340.9 $(M + Na)^+$, $C_{15}H_{14}N_2O_4SNa$ requires $(M + Na)^+$ 341.06.

2-Nitro-_N_-pentyl-benzenesulfonamide 10h[30]

Flash column chromatography (hexane–EtOAc 4 : 1) gave **10h** (96%) as a colourless oil; δ_H(400 MHz, $CDCl_3$) 0.81 (3H, t, *J* 7.2), 1.21–1.26 (4H, m), 1.46–1.53 (2H, m), 3.07 (2H, q, *J* 6.8), 5.28 (1H, t, *J* 6.0), 7.72–7.74 (2H, m), 7.81–7.84 (1H, m), 8.09–8.11 (1H, m); δ_C(100 MHz, $CDCl_3$) 13.8, 22.1, 28.6, 29.1, 43.9, 125.4, 131.1, 132.8, 133.5, 148.1; *m/z* (FAB) 273 $(M + H)^+$, 186 $(Ns)^+$. Found: $(M + H)^+$ 273.0901, $C_{11}H_{17}N_2O_4S$ requires $(M + H)^+$ 273.0909.

_N_-(2-Methyl-pentyl)-2-nitro-benzenesulfonamide 10i

Flash column chromatography (hexane–EtOAc 7 : 1) gave **10i** (75%) as a colourless oil; δ_H(400 MHz, $CDCl_3$) 0.81 (3H, t, *J* 7.2), 0.86 (3H, d, *J* 6.4), 1.03–1.30 (4H, m), 1.58–1.66 (1H, m), 2.86 (1H, dt, *J* 12.8, *J* 6.4), 2.98 (1H, dt, *J* 12.4, *J* 6.4), 5.30 (1H, t, *J* 6.4), 7.72–7.74 (2H, m), 7.81–7.84 (1H, m), 8.08–8.10 (1H, m); δ_C(100 MHz, $CDCl_3$) 14.0, 17.4, 19.8, 32.9, 36.1, 49.7, 125.3, 131.0, 132.8, 133.6, 148.1; *m/z* (ESI) 308.9 $(M + Na)^+$, $C_{12}H_{18}N_2O_4SNa$ requires $(M + Na)^+$ 309.1.

2-Nitro-_N_-pent-2-ynyl-benzenesulfonamide 10j

Flash column chromatography (hexane–EtOAc 6 : 1) gave **10j** (92%) as a colourless oil; δ_H(400 MHz, $CDCl_3$) 0.81 (3H, t, *J* 7.6), 1.82 (2H, qt, *J* 7.2, *J* 2.4), 3.95 (2H, dt, *J* 6.0, *J* 2.4), 5.60 (1H, t, *J* 6.0), 7.73–7.77 (2H, m), 7.89–7.92 (1H, m), 8.18–8.20 (1H, m); δ_C(100 MHz, $CDCl_3$) 12.0, 13.4, 34.0, 73.0, 87.3, 125.4, 131.7, 132.9, 133.6, 134.4, 148.0; *m/z* (FAB) 269 $(M + H)^+$. Found: $(M + H)^+$ 269.0597, $C_{11}H_{13}N_2O_4S$ requires $(M + H)^+$ 269.0596.

2-Nitro-_N_-pent-2-enyl-benzenesulfonamide 10k

Flash column chromatography (hexane–EtOAc 7 : 1) gave **10k** (84%) as a colourless oil; δ_H(400 MHz, $CDCl_3$) 0.92 (3H, t, *J* 7.6), 1.95–2.03 (2H, m), 3.77 (2H, t, *J* 6.8), 5.21–5.29 (2H, m), 5.45–5.52 (1H, m), 7.72–7.76 (2H, m), 7.85–7.87 (1H, m), 8.12–8.14 (1H, m); δ_C(100 MHz, $CDCl_3$) 13.9, 20.7, 40.7, 122.7, 125.4, 131.2, 132.8, 133.6, 134.0, 136.7, 148.1; *m/z* (FAB) 271 $(M + H)^+$, 186 $(M - Ns)^+$. Found: $(M + H)^+$ 271.0766, $C_{11}H_{15}N_2O_4S$ requires $(M + H)^+$ 271.0753.

_N_-(1-Methyl-pentyl)-2-nitro-benzenesulfonamide 10l

Flash column chromatography (hexane–EtOAc 6 : 1) gave **10l** (70%) as a colourless oil; δ_H(400 MHz, $CDCl_3$) 0.77 (3H, t, *J* 7.2), 1.08 (3H, d, *J* 6.8), 1.14–1.26 (4H, m), 1.40–1.45 (2H, m), 3.45–3.55 (1H, m), 5.11 (1H, d, *J* 8.0), 7.71–7.74 (2H, m), 7.82–7.85 (1H, m), 8.13–8.15 (1H, m); δ_C(100 MHz, $CDCl_3$) 13.9, 21.8, 22.2, 27.6, 27.8, 37.0, 51.2, 125.3, 130.6, 132.9, 133.4, 135.1, 147.8; *m/z* (ESI) 308.9 $(M + Na)^+$, $C_{12}H_{18}N_2O_4SNa$ requires $(M + Na)^+$ 309.1.

_N_-(1-Methyl-2-phenyl-ethyl)-2-nitro-benzenesulfonamide 10m

Flash column chromatography (hexane–EtOAc 4 : 1) gave **10m** (85%) as a pale solid, mp 138 °C; δ_H(400 MHz, $CDCl_3$) 1.22 (3H, d, *J* 6.4), 2.68–2.81 (2H, m), 3.74–3.81 (1H, m), 5.30 (1H, d, *J* 7.2), 7.00–7.03 (2H, m), 7.07–7.10 (3H, m), 7.64–7.66 (2H, m), 7.74–7.77 (1H, m), 8.00–8.02 (1H, m); δ_C(100 MHz, $CDCl_3$) 22.2, 43.5, 52.8, 125.5, 126.8, 128.4, 129.2, 130.5, 132.9, 133.2, 134.6, 137.0, 147.4; *m/z* (ESI) 318.9 $(M - H)^-$, $C_{15}H_{15}N_2O_4S$ requires $(M - H)^-$ 319.1.

General procedure for Mitsunobu reaction for primary and secondary alcohols and Nosyl-protected primary amines

A mixture of 2-nitro-*N*-phenethyl-benzenesulfonamide (0.306 g, 1.0 mmol), diphenyl-2-pyridylphosphine (0.263 g, 1.0 mmol) and the primary alcohol (0.5 mmol) was dissolved in anhydrous dichloromethane (10 mL) under an atmosphere of nitrogen. To this solution di-*tert*-butylazodicarboxylate (0.230 g, 1.0 mmol) was added slowly (syringe pump, 30–45 min) and the resulting mixture was stirred at rt for 2 h. HCl in dioxane (5 mL, 4 M) was added to the mixture and, after stirring for 1 h, the excess solvent was evaporated. The residue was dissolved in dichloromethane and washed twice with 4 M HCl. The organic layer was dried with anhydrous magnesium sulfate and the solvent evaporated. Flash column chromatography gave the desired sulfonamide.

2-Nitro-*N*-pentyl-*N*-phenethyl-benzenesulfonamide 12a

Flash column chromatography (hexane–EtOAc 4 : 1) gave **12a** (74%) as a pale solid; δ_H(400 MHz, $CDCl_3$) 0.77 (3H, t, *J* 6.8), 1.10–1.25 (4H, m), 1.43–1.50 (2H, m), 2.77 (2H, t, *J* 8.4), 3.24 (2H, t, *J* 8.0), 3.42 (2H, dd, *J* 10.0, *J* 8.0), 7.06–7.19 (5H, m), 7.49 (1H, dd, *J* 7.2, *J* 2.0), 7.54 (1H, td, *J* 7.2, *J* 2.0), 7.57 (1H, td, *J* 7.6, *J* 1.6), 7.85 (1H, dd, *J* 7.6, *J* 1.6); δ_C(100 MHz, $CDCl_3$) 14.0, 22.3, 27.8, 28.7, 35.2, 47.8, 48.8, 124.2, 126.7, 128.6, 128.8, 130.6, 131.7, 133.5, 133.7, 138.2, 148.1; *m/z* (FAB) 377 (M + H)$^+$. Found: (M + H)$^+$ 377.1543, $C_{19}H_{25}N_2O_4S$ requires (M + H)$^+$ 377.1535.

2-Nitro-*N*,*N*-diphenethyl-benzenesulfonamide 12b

Flash column chromatography (hexane–EtOAc 6 : 1) gave **12b** (64%) as a pale oil; δ_H(400 MHz, $CDCl_3$) 2.76 (4H, t, *J* 8.4), 3.47 (4H, dd, *J* 9.2, *J* 7.6), 7.05–7.19 (10H, m), 7.46–7.57 (3H, m),7.85 (1H, dd, *J* 7.6, *J* 1.6); δ_C(100 MHz, $CDCl_3$) 35.2, 49.3, 124.3, 126.8, 128.7, 128.8, 130.6, 131.7, 133.5, 138.1, 148.1; *m/z* (ESI) 432.9 (M + Na)$^+$, $C_{22}H_{22}N_2O_4SNa$ requires (M + Na)$^+$ 433.1.

***N*-(1-Methyl-pentyl)-2-nitro-*N*-phenethyl-benzenesulfonamide 12c**

Flash column chromatography (hexane–EtOAc 6 : 1) gave **12c** (50%) as a pale oil; δ_H(400 MHz, $CDCl_3$) 0.77 (3H, t, *J* 7.2), 1.08 (3H, d, *J* 6.8), 1.14–1.26 (4H, m), 1.40–1.45 (2H, m), 2.66 (2H, t, *J* 8.4), 3.43 (2H, dd, *J* 9.2, *J* 7.6), 3.45–3.55 (1H, m), 7.71–7.74 (2H, m), 7.82–7.85 (1H, m), 8.13–8.15 (1H, m); δ_C(100 MHz, $CDCl_3$) 13.9, 21.8, 22.2, 27.6, 27.8, 37.0, 45.0, 51.2, 125.4, 126.9, 128.7, 128.8, 131.0, 132.8, 133.5, 133.9, 137.4, 147.9; *m/z* (ESI) 412.9 (M + Na)$^+$, $C_{20}H_{26}N_2O_4SNa$ requires (M + Na)$^+$ 413.2.

***N*-(1-Methyl-2-phenyl-ethyl)-2-nitro-*N*-phenethyl-benzenesulfonamide 12d**

Flash column chromatography (hexane–EtOAc 7 : 1) gave **12d** (40%) as a pale oil; δ_H(400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 6.4), 2.68 (1H, dd, *J* 12.8, *J* 9.6), 2.98–3.03 (3H, m), 3.47–3.58 (2H, m), 4.20–4.25 (1H, m), 7.12–7.14 (2H, m), 7.15–7.27 (6H, m), 7.32–7.35 (2H, m), 7.57–7.67 (3H, m), 7.96 (1H, dd, *J* 7.6, *J* 1.6); δ_C(100 MHz, $CDCl_3$) 18.7, 28.2, 38.4, 42.5, 45.7, 56.2, 124.2, 126.7, 128.6, 128.7, 128.8, 129.2, 130.9, 131.6, 133.4, 134.0, 138.0, 138.6, 148.1; *m/z* (ESI) 446.9 (M + Na)$^+$, $C_{23}H_{24}N_2O_4SNa$ requires (M + Na)$^+$ 447.1.

General procedure for deprotection reaction

A mixture of the sulfonamide **10** or **12** (0.6 mmol), thiophenol (0.195 g, 1.8 mmol) and potassium carbonate (0.326 g, 2.4 mmol) in acetonitrile (10 mL) was stirred at 50 °C for 5–12 h. Once tlc indicated that the reaction had gone to completion, the reaction mixture was directly purified by flash chromatography on silica gel to give the correspondent amine **11** or **13**.

Phenethylamine 11a[31]

Flash column chromatography (CH_2Cl_2–MeOH–NH_3 92 : 7 : 1) gave **11a** (89%) as a yellow oil; δ_H(400 MHz, $CDCl_3$) 2.76 (2H, t, *J* 6.8), 2.98 (2H, t, *J* 6.8), 7.22–7.25 (3H, m), 7.31–7.34 (2H, m); δ_C(100 MHz, $CDCl_3$) 40.2, 43.7, 126.1, 128.5, 128.7, 139.9; *m/z* (EI) 121 (M)$^+$, 92 ($PhCH_2$)$^+$, 77 (Ph). Found: (M)$^+$ 121.0897, $C_8H_{11}N$ requires (M)$^+$ 121.0891.

2-(4-Methoxy-phenyl)-ethylamine 11b[32]

Flash column chromatography (CH_2Cl_2–MeOH–NH_3 92 : 7 : 1) gave **11b** (95%) as a yellow solid; δ_H(400 MHz, $CDCl_3$) 2.68 (2H, t, *J* 6.8), 2.92 (2H, t, *J* 6.8), 3.78 (3H, s), 6.84 (2H, d, *J* 8.8), 7.11 (2H, d, *J* 8.8); δ_C(100 MHz, $CDCl_3$) 39.2, 43.7, 55.3, 113.9, 129.8, 131.9, 158.1; *m/z* (ESI) 151.9 (M + H)$^+$, $C_9H_{14}NO$ requires (M + H)$^+$ 152.1.

2-(4-Nitro-phenyl)-ethylamine 11c[33]

Flash column chromatography (CH_2Cl_2–MeOH–NH_3 92 : 7 : 1) gave **11c** (91%) as a yellow solid; δ_H(400 MHz, $CDCl_3$) 2.86 (2H, t, *J* 6.8), 3.02 (2H, t, *J* 6.8), 7.36 (2H, d, *J* 8.8), 8.16 (2H, d, *J* 8.8); δ_C(100 MHz, $CDCl_3$) 39.9, 43.1, 123.7, 129.6, 146.7, 147.9; *m/z* (ESI) 166.9 (M + H)$^+$, $C_8H_{18}N_2O_2$ requires (M + H)$^+$ 167.1.

Benzylamine 11d[34]

Flash column chromatography (CH_2Cl_2–MeOH–NH_3 92 : 7 : 1) gave **11d** (92%) as a yellow liquid; δ_H(400 MHz, $CDCl_3$) 3.81 (2H, s), 7.16–7.20 (2H, m), 7.24–7.30 (3H, m); δ_C(100 MHz, $CDCl_3$) 46.6, 126.8, 127.1, 128.6, 143.4; *m/z* (EI) 107 (M)$^+$. Found: (M)$^+$ 107.0727, C_7H_9N requires (M)$^+$ 107.0735.

4-Methoxy-benzylamine 11e[35]

Flash column chromatography (CH_2Cl_2–MeOH–NH_3 92 : 7 : 1) gave **11e** (93%) as a yellow oil; δ_H(400 MHz, $CDCl_3$) 3.79–3.81 (2H, m), 3.80 (3H, s), 6.87 (2H, d, *J* 8.8), 7.23 (2H, d, *J* 8.8); δ_C(100 MHz, $CDCl_3$) 46.0, 55.3, 114.0, 128.3, 135.6, 158.6; *m/z* (EI) 255 (dimer–NH_3)$^+$, 136 (M)$^+$, 77 (Ph)$^+$. Found: (M)$^+$ 137.0810, $C_8H_{11}NO$ requires (M)$^+$ 137.0841.

4-Nitro-benzylamine 11f[36]

Flash column chromatography (CH_2Cl_2–MeOH–NH_3 92 : 7 : 1) gave **11f** (80%) as a yellow oil; δ_H(400 MHz, $CDCl_3$) 4.03 (2H, s), 7.52 (2H, d, *J* 8.8), 8.21 (2H, d, *J* 8.4); *m/z* (ESI) 176.6 (M + Na)$^+$, $C_8H_{18}N_2O_2Na$ requires (M + Na)$^+$ 175.1.

3-Phenyl-allylamine 11g[37]

Flash column chromatography (CH_2Cl_2–MeOH–NH_3 92 : 7 : 1) gave **11g** (86%) as a slightly yellow liquid; δ_H(400 MHz, $CDCl_3$) 3.48 (2H, d, *J* 4.8), 6.32 (2H, dt, *J* 15.6, *J* 5.6), 6.50 (1H, d, *J* 16.0), 7.20–7.38 (5H, m); δ_C(100 MHz, $CDCl_3$) 44.3, 126.2, 127.3, 128.5, 128.8, 129.6, 131.0, 131.4, 137.1; *m/z* (EI) 133 (M)$^+$, 77 (Ph)$^+$. Found: (M)$^+$ 133.0885, $C_9H_{11}N$ requires (M)$^+$ 133.0891.

Pentylamine 11h[38]

Due to the low boiling point of the amine **11h**, the reaction was carried out in CD_3CN (0.6 mL) in a NMR tube and the yield (90%) was determinated by ^{1}H-NMR spectrum, using benzylamine as internal standard; δ_H(400 MHz, CD_3CN) 0.89 (3H, t, *J* 4.8), 1.26–1.39 (6H, m), 2.57 (2H, t, *J* 6.8); δ_C(100 MHz, CD_3CN) 13.1, 22.0, 28.6, 33.1, 41.6; *m/z* (ESI) 88.2 (M + H)$^+$, $C_5H_{14}N$ requires (M + H)$^+$ 88.2.

2-Methyl-pentylamine 11i[39]

Due to the low boiling point of the amine **11i**, the reaction was carried out in CD_3CN (0.6 mL) in a NMR tube and the yield (100%) was determinated by ^{1}H-NMR spectrum, using benzylamine as internal standard; δ_H(400 MHz, CD_3CN) 0.85 (3H, d, *J* 6.4), 0.89 (3H, t, *J* 7.2), 1.01–1.08 (1H, m), 1.24–1.42 (4H, m), 2.37 (1H, dd, *J* 12.4, *J* 6.8), 2.51 (1H, dd, *J* 12.4, *J* 5.6); δ_C(100 MHz, CD_3CN) 13.4, 16.5, 19.6, 35.7, 36.1, 47.9; *m/z* (ESI) 102.2 (M + H)$^+$, $C_5H_{16}N$ requires (M + H)$^+$ 102.1.

Pent-2-ynylamine 11j[40]

Due to the low boiling point of the amine **11j**, the reaction was carried out in CD_3CN (0.6 mL) in a NMR tube and the yield (91%) was determinated by ^{1}H-NMR spectrum, using benzylamine as internal standard; δ_H(400 MHz, CD_3CN) 1.08

(3H, t, *J* 7.6), 2.13–2.16 (2H, m), 3.28 (2H, t, *J* 2.0); δ_C(100 MHz, CD_3CN) 11.5, 13.2, 30.7, 80.4, 82.6; *m/z* (ESI) 84.2 $(M + H)^+$, $C_5H_{10}N$ requires $(M + H)^+$ 84.7.

Pent-2-enylamine 11k[41]

Due to the low boiling point of the amine **11k**, the reaction was carried out in CD_3CN (0.6 mL) in a NMR tube and the yield (80%) was determinated by ^{1}H-NMR spectrum, using benzylamine as internal standard; δ_H(400 MHz, CD_3CN) 0.95 (3H, t, *J* 7.6), 2.01–2.06 (2H, m), 3.20–3.22 (2H, m), 5.33–5.44 (2H, m); δ_C(100 MHz, CD_3CN) 13.4, 19.9, 38.1, 125.3, 126.0; *m/z* (ESI) 86.2 $(M + H)^+$, $C_5H_{11}N$ requires $(M + H)^+$ 86.1.

1-Methyl-pentylamine 11l[42]

Due to the low boiling point of the amine **11l**, the reaction was carried out in CD_3CN (0.6 mL) in a NMR tube and the yield (80%) was determinated by ^{1}H-NMR spectrum, using benzylamine as internal standard; δ_H(400 MHz, CD_3CN) 0.92 (3H, t, *J* 6.8), 1.00 (3H, d, *J* 6.0), 1.27–1.34 (6H, m), 2.75–2.83 (1H, m); δ_C(100 MHz, CD_3CN) 13.1, 22.3, 23.2, 28.1, 35.9, 46.4; *m/z* (ESI) 102.1 $(M + H)^+$, $C_6H_{16}N$ requires $(M + H)^+$ 102.1.

1-Methyl-2-phenyl-ethylamine 11m[43]

Flash column chromatography (CH_2Cl_2–MeOH–NH_3 92 : 7 : 1) gave **11m** (84%) as a yellow solid; δ_H(400 MHz, $CDCl_3$) 1.06 (3H, d, *J* 6.0), 2.48 (1H, dd, *J* 13.2, *J* 8.0), 2.64 (1H, dd, *J* 13.2, *J* 5.2), 3.07–3.15 (1H, m), 7.10–7.24 (5H, m); δ_C(100 MHz, $CDCl_3$) 23.4, 46.5, 48.6, 126.2, 128.4, 129.3, 139.6; *m/z* (ESI) 135.9 $(M + H)^+$, $C_9H_{14}N$ requires $(M + H)^+$ 136.1.

Pentyl-phenethyl-amine 13a[44]

Flash column chromatography (CH_2Cl_2–MeOH–NH_3 96 : 3.5 : 0.5) gave **13a** (90%) as a yellow oil; δ_H(400 MHz, $CDCl_3$) 0.92 (3H, t, *J* 6.8), 1.27–1.40 (4H, m), 1.49–1.57 (2H, m), 2.66 (2H, t, *J* 7.2), 2.85–2.95 (4H, m), 7.22–7.26 (3H, m), 7.30–7.36 (2H, m); δ_C(100 MHz, $CDCl_3$) 14.0, 22.6, 29.6, 29.6, 36.3, 49.9, 51.2, 126.2, 128.5, 128.7, 140.1; *m/z* (ESI) 191.9 $(M + H)^+$, $C_{13}H_{22}N$ requires $(M + H)^+$ 192.2.

Diphenethyl-amine 13b[45]

Flash column chromatography (CH_2Cl_2–MeOH–NH_3 96 : 3.5 : 0.5) gave **13b** (96%) as a yellow oil; δ_H(400 MHz, $CDCl_3$) 2.71 (4H, t, *J* 7.2), 2.82 (4H, t, *J* 7.2), 7.08–7.13 (6H, m), 7.17–7.21 (4H, m); δ_C(100 MHz, $CDCl_3$) 36.4, 51.1, 126.2, 128.5, 128.7, 140.0; *m/z* (ESI) 225.9 $(M + H)^+$, $C_{16}H_{20}N$ requires $(M + H)^+$ 226.2.

(1-Methyl-pentyl)-phenethyl-amine 13c

Flash column chromatography (CH_2Cl_2–MeOH–NH_3 96 : 3.5 : 0.5) gave **13c** (96%) as a yellow oil; δ_H(400 MHz, $CDCl_3$) 0.80 (3H, t, *J* 7.2), 0.97 (3H, d, *J* 6.4), 1.10–1.25 (5H, m), 1.34–1.42 (1H, m), 2.52–2.60 (1H, m), 2.72–2.88 (4H, m), 7.10–7.15 (3H, m), 7.18–7.24 (2H, m); δ_C(100 MHz, $CDCl_3$) 14.1, 20.2, 22.9, 28.2, 36.5, 36.6, 48.5, 53.2, 126.2, 128.5, 128.7, 140.1; *m/z* (ESI) 205.9 $(M + H)^+$, $C_{14}H_{24}N$ requires $(M + H)^+$ 206.2.

(1-Methyl-2-phenyl-ethyl)-phenethyl-amine 13d[46]

Flash column chromatography (CH_2Cl_2–MeOH–NH_3 96 : 3.5 : 0.5) gave **13d** (94%) as a yellow oil; δ_H(400 MHz, $CDCl_3$) 1.00 (3H, d, *J* 6.4), 2.53 (1H, dd, *J* 13.6, *J* 6.8), 2.64–2.79 (4H, m), 2.82–2.93 (2H, m), 7.04–7.27 (8H, m), 7.41–7.44 (2H, m); δ_C(100 MHz, $CDCl_3$) 20.0, 36.2, 43.4, 48.5, 54.6, 126.1, 126.2, 127.2, 127.6, 128.4, 128.5, 128.7, 129.1, 129.3, 137.1, 139.2, 139.8; *m/z* (ESI) 239.9 $(M + H)^+$, $C_{17}H_{22}N$ requires $(M + H)^+$ 240.2.

Acknowledgements

We would like to thank IC-Vec Ltd. for funding this research and Mitsubishi Chemical Corporation for supporting the Imperial College Genetic Therapies Centre. Mass spectral analysis was kindly performed by Mr John Barton (Imperial College) and additional experimentation by Dr Arnaud Cheguillaume (IC-Vec Ltd.).

References

1 G. Karigiannis and D. Papaioannou, *Eur. J. Org. Chem.*, 2000, 1841–1863.
2 A. D. Miller, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 1768.
3 (*a*) R. Sandler and W. Karo, in *Organic Functional Group Preparations*, ed. H. H. Wasserman, Academic Press, New York, 2nd edn., 1983, ch. 13, pp. 378–429; (*b*) C. M. Marson and A. D. Hobson, *Comprehensive Organic Functional Group Transformations*, ed. A. Katrinsky, O. Meth-Cohn and C. W. Rees, Permagon Press, Oxford, 1995, vol. 2, p. 297.
4 M. S. Gibson and R. W. Bradshaw, *Angew. Chem., Int. Ed. Engl.*, 1968, **7**, 919.
5 F. Rolla, *J. Org. Chem.*, 1982, **47**, 4327.
6 H. Suzuki and K. Takaoka, *Chem. Lett.*, 1984, 1733.
7 T. Tsunoda, H. Yamamoto, K. Goda and S. Itô, *Tetrahedron Lett.*, 1996, **37**, 2457.
8 J. R. Henry, L. R. Marcint, M. C. McIntosh, P. M. Scola, G. D. Harris and S. M. Weinreb, *Tetrahedron Lett.*, 1989, **30**, 5709.
9 R. N. Salvatore, C. H. Yoon and K. W. Jung, *Tetrahedron*, 2001, **57**, 7785.
10 D. L. Comins and J. Gao, *Tetrahedron Lett.*, 1994, **35**, 2819.
11 M. A. Walker, *J. Org. Chem.*, 1995, **60**, 5352.
12 T. Tsunoda, J. Otsuka, Y. Yamamiya and S. Itô, *Chem. Lett.*, 1994, 539.
13 T. Kan and T. Fukuyama, *Chem. Commun.*, 2004, 353.
14 K. Nihei, M. J. Kato, T. Yamane, M. S. Palma and K. Konno, *Synlett*, 2001, 1167.
15 O. Mitsunobu, *Synthesis*, 1981, 1.
16 T. Tsunoda, Y. Yamamiya and S. Itô, *Tetrahedron Lett.*, 1993, **34**, 1639.
17 T. Tsunoda, F. Ozaki and S. Itô, *Tetrahedron Lett.*, 1994, **35**, 5081.
18 C. A. Olsen, M. R. Jørgensen, M. Witt, I. R. Mellor, P. N. R. Usherwood, J. W. Jaroszewski and H. Franzyk, *Eur. J. Org. Chem.*, 2003, 3288.
19 C. Yoakim, I. Guse, J. A. O'Meara and B. Thavonekham, *Synlett*, 2003, **4**, 473.
20 I. A. O'Neill, S. Thompson, C. L. Murray and S. B. Kalindjian, *Tetrahedron Lett.*, 1998, **39**, 7787.
21 (*a*) G. W. Starkey, J. J. Parlow and D. L. Flynn, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2385; (*b*) S. Dandapani and D. P. Curran, *Tetrahedron*, 2002, **58**, 3855; (*c*) A. P. Dobbs and C. McGregor-Johnson, *Tetrahedron Lett.*, 2002, **43**, 2807; (*d*) R. A. Amos, R. W. Emblidge and N. Havens, *J. Org. Chem.*, 1983, **48**, 3598; (*e*) A. Tunoori, D. Dutta and G. Georg, *Tetrahedron Lett.*, 1998, **39**, 8751; (*f*) A. G. M. Barrett, R. S. Roberts and J. Schröder, *Org. Lett.*, 2000, **2**, 2999; (*g*) S. Mukherjee, K. W. C. Poon, D. L. Flynn and P. R. Hanson, *Tetrahedron Lett.*, 2003, **44**, 7187.
22 (*a*) R. G. Cooper, R. P. Harbottle, H. Schneider, C. Coutelle and A. D. Miller, *Angew. Chem., Int. Ed.*, 1999, **38**, 1949; (*b*) M. Keller, R. P. Harbottle, E. Perouzel, M. Colin and L. Shah, *ChemBioChem*, 2003, **4**, 286.
23 R. G. Cooper, C. J. Etheridge, L. Stewart, J. Marshall, S. Rudginsky, S. H. Cheng and A. D. Miller, *Chem. Eur. J.*, 1998, **4**, 137.
24 T. Fukuyama, C.-K. Jow and M. Cheung, *Tetrahedron Lett.*, 1995, **36**, 6373.
25 M. Kiankarimi, R. Lowe, J. R. McCarthy and J. P. Whitten, *Tetrahedron Lett.*, 1999, **40**, 4497.
26 A. Bouzide and G. Sauve, *Tetrahedron Lett.*, 1997, **38**, 5945.
27 T. Fukuyama, M. Cheung and T. Kan, *Synlett*, 1999, **8**, 1301.
28 P. A. Evans, J. E. Robinson and J. D. Nelson, *J. Am. Chem. Soc.*, 1999, **121**, 6761.
29 S. Barret, P. O'Brien, H. C. Steffens, T. D. Towers and M. Voith, *Tetrahedron*, 2000, **56**, 9633.
30 J. H. Freeman and E. C. Wagner, *J. Org. Chem.*, 1951, **16**, 815.
31 R. L. Lichter and J. D. Roberts, *J. Am. Chem. Soc.*, 1972, **94**, 2495.
32 E. F. Kiefer, *J. Med. Chem.*, 1972, **15**, 214.
33 N. Umino, T. Iwakuma and N. Itoh, *Tetrahedron Lett.*, 1976, **33**, 2875.
34 (*a*) H. Suhr, *J. Mol. Struct.*, 1968, **1**, 295; (*b*) K. Adam and E. Haver, FR146 8354, 1967.

35 A. A. Siddiqui, N. H. Khan, M. Ali and A. R. Kidwai, *Synth. Commun.*, 1977, **7**, 71.
36 H. Feuer and D. M. Braunstein, *J. Org. Chem.*, 1969, **34**, 1817.
37 E. J. Corey, K. C. Nicolaou, R. D. Balanson and Y. Machida, *Synthesis*, 1975, **9**, 590.
38 M. Olomucki and P. Hebrard, *Tetrahedron Lett.*, 1969, **1**, 13.
39 H. C. Brown, K. W. Kim, M. Srebnik and B. Singaram, *Tetrahedron*, 1987, **43**, 4071.
40 (*a*) A. Marszak-Fleury, *Bull. Soc. Chim. Fr.*, 1958, 480; (*b*) A. Marszak-Fleury, *Ann. Chim.*, 1958, **3**, 656.
41 B. Piugin and L. M. Venanzi, *J. Am. Chem. Soc.*, 1983, **105**, 6877.
42 S. H. Jung and H. Kohn, *Tetrahedron Lett.*, 1984, **25**, 399.
43 (*a*) K. Kotera, T. Okada and S. Miyazaki, *Tetrahedron*, 1968, **24**, 5677; (*b*) G. A. Neville, R. Deslauriers, B. J. Blackburn and I. C. P. Smith, *J. Med. Chem.*, 1971, **14**, 717.
44 A. I. Meyers and G. E. Jagdmann, Jr., *J. Am. Chem. Soc.*, 1982, **104**, 877.
45 (*a*) H. Rupe and K. Glenz, *Helv. Chim. Acta*, 1922, **5**, 937; (*b*) S. Caddick, A. K. K. Haynes, D. B. Judd and M. R. Williams, *Tetrahedron Lett.*, 2000, **41**, 3513.
46 R. A. Glennon, J. D. Smith, A. M. Ismaiel, M. El-Ashmawy, G. Battaglia and J. B. Fisher, *J. Med. Chem.*, 1991, **34**, 1094.