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The Synthesis of Phosphonium Cascade Molecules[1,2]

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The synthesis of a series of cascade molecules (dendrimers) in which the core and branch points are phosphonium ion sites has been accomplished. The primary cores of these cascade molecules are either tridirectional or tetradirectional for the development of the generations of the cascade structure. Secondary branch points, also phosphonium ion sites, are all tridirectional for the development of further generations of the cascade structure.

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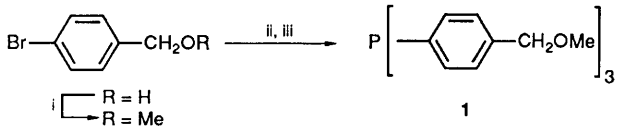
Cascade molecules are those which incorporate particular structural features, including a 'primary core' from which emanates two or more branches, each branch bearing reiterative structural components leading to further 'secondary cores'. As such, these cascade molecules (or dendrimers) represent three-dimensional molecular fractals. The fundamental geometry of this type of structure along with the synthesis of numerous examples has recently been reviewed.[3]

Although there has been a significant synthetic effort for the generation of new cascade molecules in recent years, no compounds have been prepared in which the primary and/or secondary cores are ionic sites. The construction of dendrimers in which are incorporated large numbers of symmetrically distributed charged sites is a problem of organic synthesis which in itself is challenging and generates materials of interesting and potentially useful characteristics. To this end we here report on the synthesis of cascade molecules in which the primary and secondary core sites are (cationic) phosphonium ion centres. Starting from a properly functionalized alkyltriaryl- or tetraaryl-phosphonium salt, cascade molecules have been constructed in the covalent structure of which are present up to 40 cationic sites.

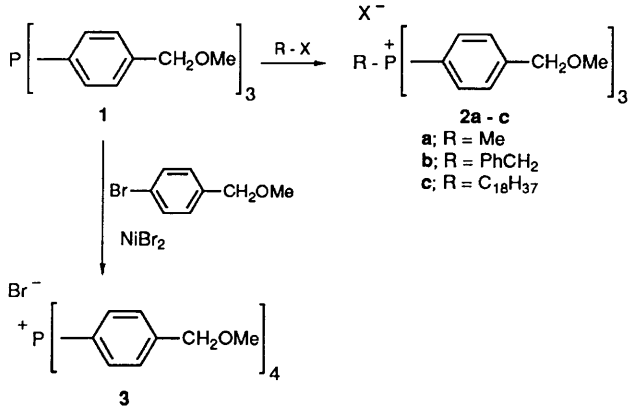
Results and Discussion

The approach toward the synthesis of dendrimers bearing numerous phosphonium sites within the covalent structure involves the design and preparation of a suitable reagent to serve as the reiterative structural component. This component must be capable of forming a phosphonium ion species in a facile manner, and contain, in addition, several symmetrically distributed masked sites, each of which upon activation is capable of reaction with additional units of the original reagent. To serve as the fundamental reiterative component of the phosphonium cascade species, the tertiary phosphine **1** has been prepared as shown in Scheme 1.



Scheme 1 *Reagents:* i, MeI, KOH; ii, Mg, tetrahydrofuran; iii, PCl_3

The completion of the construction of the primary phosphonium ion core is accomplished as illustrated in Scheme 2. The phosphine centre of **1** is quaternized either by reaction with an alkyl halide to generate the primary core for a tridirectional development of the cascade, or with *p*-methoxymethylbromobenzene in the presence of nickel bromide[4] to generate the primary core for a tetradirectional development of the cascade. Methyl, benzyl and octadecyl halides have been used for the generation of the tridirectional cascade core.



Scheme 2

For the construction of the first, and further generations of the cascade structure, the benzylic ether function in **2a–c** and **3** is efficiently cleaved using iodotrimethylsilane. This reaction of benzylic ethers is known to proceed readily and selectively at room temperature to yield the benzylic iodide in excellent yield.[5] Thus it is an ideal route for simultaneous deprotection and activation for the present synthetic aim. The approach for incorporation of successive generations of the cascade structure is illustrated in Scheme 3 for the system beginning with **2a–c**. (Structures for generations beyond the primary core are indicated using the generation number in parentheses along with the number of the primary core structure.)

The successive generations of cascade species were isolated from the reaction mixtures as dark semi-solid materials which were readily soluble in most solvents. These crude materials were purified by passage through an anion exchange column to yield high melting solids which exhibited spectra (^{1}H NMR, ^{31}P NMR, IR) and elemental analyses in accord with the proposed structures. The solubility characteristics of the purified materials were significantly different from those in the crude state. While still exhibiting significant solubility in a variety of solvents, the solubilities of the purified materials were notably lower than those of the crude materials. The higher generation cascade molecules maintained solubility in low molecular weight alcohols and acetonitrile, although the ready solubility in acetone, chloroform and dimethyl sulphoxide exhibited by the lower generation species had decreased with **2**(3)**b**. Although all species were significantly hygroscopic, water solubility decreased with the higher generation cascade species.

The solubility characteristics and analytical data for the tridirectional cascade materials synthesized are summarized in Table 1. With the third generation species **2**(3)**a** and **2**(3)**b** only

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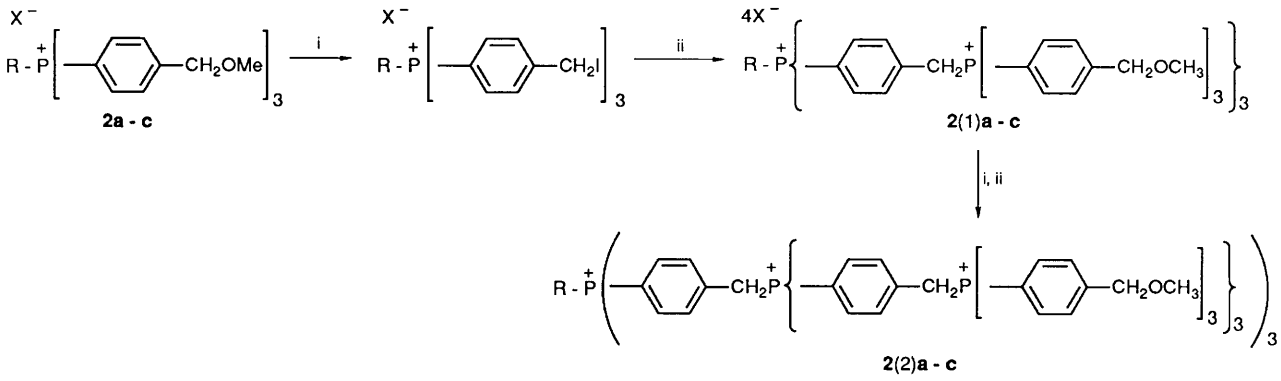

Scheme 3 *Reagents:* i, $ISi(Me)_3$; ii, **1**

Table 1 Analytical and solubility data for tridirectional cascade molecules

Compound	R	^{1}H NMR (60 MHz) (δ)	^{31}P NMR (δ)[b]	Formula	C/H Anal. Required (Found)	Solubility[c]
2a	Me	3.2 (3 H, d, *J* 24) 3.4 (9 H, s) 4.6 (6 H, s) 7.6–8.0 (12 H, m)	21.4	$C_{25}H_{30}IO_3P$	C: 55.98 (55.9) H: 5.64 (5.6)	sol. (a–g)
2b	$PhCH_2$	3.4 (9 H, s) 4.5 (8 H, br) 7.2–7.7 (17 H, m)	22.7	$C_{31}H_{34}BrO_3P$	C: 63.81 (64.05) H: 6.21 (6.3)	sol. (a–g)
2c	$C_{18}H_{37}$	0.9 (3 H, t, *J* 6) 1.3 (30 H, br) 2.3 (2 H, m) 3.4 (9 H, s) 3.6–4.2 (2 H, m) 4.6 (6 H, br) 7.6–8.0 (12 H, m)	41.0	$C_{42}H_{64}BrO_3P$	C: 69.30 (69.1) H: 8.79 (8.5)	sol. (a–g)
2(1)a	Me	3.2 (3 H, d, *J* 22) 3.4 (27 H, br) 4.5 (24 H, br) 7.3–7.9 (48 H, m)	21.8, 29.3	$C_{94}H_{102}I_4O_9P_4$	C: 56.24 (56.0) H: 5.12 (5.25)	sol. (b–g) sl.sol. (a)
2(1)b	$PhCH_2$	3.3 (27 H, s) 4.5 (26 H, br) 7.1–7.9 (53 H, m)	22.0, 28.0	$C_{100}H_{106}BrI_3O_9P_4$	C: 58.98 (59.0) H: 5.25 (5.3)	sol. (b–g) sl.sol. (a)
2(1)c	$C_{18}H_{37}$	0.9 (3 H, t, *J* 6) 1.3 (30 H, br) 2.3 (2 H, m) 3.4 (27 H, s) 3.6–4.2 (2 H, m) 4.6 (24 H, br) 7.6–8.0 (48 H, m)	41.0, 29.0	$C_{111}H_{136}I_4O_9P_4$	C: 59.36 (59.05) H: 6.10 (6.0)	sol. (b–g) sl.sol. (a)
2(2)a	Me	3.2 (3 H, d, *J* 21) 3.4 (81 H, s) 4.5 (78 H, br) 7.1–7.8 (156 H, m)	21.9, 29.6	$C_{301}H_{318}I_{13}O_{27}P_{13}$	C: 56.31 (56.2) H: 4.99 (5.3)	sol. (b–g) sl.sol. (a)
2(2)b	$PhCH_2$	3.5 (81 H, s) 4.6 (80 H, br) 7.1–7.9 (161 H, m)	23.0, 30.1	$C_{307}H_{322}I_{13}O_{27}P_{13}$	C: 56.60 (56.2) H: 4.94 (5.3)	sol. (b–g) sl.sol. (a)
2(2)c	$C_{18}H_{37}$	0.9 (3 H, t, *J* 6) 1.3 (32 H, s) 2.3 (2 H, m) 3.4 (81 H, s) 4.6 (78 H, br) 7.1–7.8 (156 H, m)	40.0, 28.5	$C_{318}H_{352}I_{13}O_{27}P_{13}$	C: 57.21 (56.95) H: 5.27 (5.4)	sol. (b–g) sl.sol. (a)
2(3)a	Me	3.2–3.5 (247 H, br) 4.5 (240 H, br) 7.1–7.9 (480 H, m)	29.0	$C_{922}H_{966}I_{40}O_{81}P_{40}$	C: 56.33 (56.3) H: 4.95 (4.7)	sol. (b–g) sl.sol. (a)
2(3)b	$C_6H_5CH_2$	3.5 (243 H, s) 4.5 (242 H, br) 7.2–7.8 (485 H, m)	30.0	$C_{928}H_{970}I_{40}O_{81}P_{40}$	C: 58.98 (58.6) H: 4.91 (5.1)	sol. (b,f,g) sl.sol. (c–e) insol. (a)

[a] Deuteriochloroform or deuterioacetonitrile solution, relative to Me_4Si, *J* in Hz. [b] Deuteriochloroform or deuterioacetonitrile solution, relative to 85% H_3PO_4, 81 MHz. [c] a = water, b = acetonitrile, c = chloroform, d = acetone, e = dimethylsulphoxide, f = ethanol and g = methanol.

one signal to phosphorus could be observed in the ^{31}P NMR spectrum. While in the ^{31}P NMR spectra of prior generation species separate signals could be observed for the core and peripheral phosphonium ion sites, the separation of the two

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Table 2 Analytical and solubility data for tetradirectional cascade molecules

Compound	^{1}H NMR (δ 60 MHz)[a]	^{31}P NMR (δ)[b]	Formula	C/H Anal. Required (Found)	Solubility[c]
3	3.5 (12 H, s) 4.6 (8 H, s) 7.6–7.9 (16 H, AA′BB′)	20.9	$C_{32}H_{36}BrO_4P$	C: 64.54 (64.2) H: 6.09 (6.3)	sol. (a–g)
3(1)	3.4 (36 H, s) 4.6 (32 H, br) 6.8–7.8 (64 H, m)	21.5, 28.0	$C_{124}H_{132}I_5O_{12}P_5$	C: 57.20 (56.95) H: 5.11 (5.3)	sol. (b–g) sl.sol. (a)
3(2)	3.4 (108 H, s) 4.5 (104 H, br) 6.8–7.8 (208 H, m)	21.0, 28.0	$C_{400}H_{420}I_{17}O_{36}P_{17}$	C: 56.59 (56.35) H: 4.98 (5.1)	sol. (b–g) sl.sol. (a)

[a] Deuteriochloroform or deuterioacetonitrile solution, relative to Me_4Si. [b] Deuteriochloroform or deuterioacetonitrile solution, relative to 85% H_3PO_4, 81 MHz. [c] a = water, b = acetonitrile, c = chloroform, d = acetone, e = dimethylsulphoxide, f = ethanol and g = methanol.

signals was insufficient in these two instances for the smaller core signal to be observed. The large signal for the peripheral phosphonium ion sites overlapped the region of the core signal.

The solubility characteristics and analytical data for the tetradirectional cascade materials synthesized are summarized in Table 2.

Experimental

General.—All chemicals were of commercial reagent quality and were used without further purification with the following exceptions: benzene and tetrahydrofuran (THF) were distilled over sodium hydride and stored over molecular sieves; chloroform was distilled over phosphorus pentoxide; acetonitrile was distilled and stored over molecular sieves; phosphorus trichloride was freshly distilled prior to use. Silica gel for preparative chromatography was from Baker (230–400 mesh). IR spectra were measured using a Perkin-Elmer 1600 FTIR. The ^{1}H NMR spectra were measured using either a Varian EM360 (60 MHz) or IBM-Bruker WP200SY (200 MHz) instrument. The ^{31}P NMR spectra were measured using the IBM-Bruker instrument operating at 81 MHz. *J* values are given in Hz. Ion exchange was performed using DOWEX 2-X8 (20–50 mesh) in the iodide form. Elemental analyses were performed by Desert Analytics, Tucson, Arizona, or Schwarzkopf Microanalytical Laboratory, Woodside, New York.

Preparation of p-(*Methoxymethyl*)*bromobenzene.*—To dimethyl sulphoxide (175 cm^3) was added powdered KOH (18.0 g, 321 mmol). After the mixture had been stirred for 5 min, *p*-bromobenzyl alcohol (15.0 g, 80.2 mmol) was added, followed immediately by iodomethane (22.8 g, 160 mmol). The resulting solution was stirred at room temperature for 30 min after which the mixture was poured into water (350 cm^3) and extracted with methylene dichloride (4 × 200 cm^3). The combined organic extracts were washed with water (5 × 100 cm^3), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the pure *p*-(methoxymethyl)bromobenzene (15.5 g, 96%) which exhibited NMR and IR spectra, and elemental analysis in accord with the proposed structure; δ_H(200 MHz; $CDCl_3$) 3.4 (3 H, s), 4.4 (2 H, s) and 7.1–7.5 (4 H, AA′BB′) (Found: C, 47.8; H, 4.45. C_8H_9BrO requires: C, 47.79; H, 4.51%).

Preparation of Tri(p-*methoxymethyl*)*phenylphosphine* **1**.—In a 1 dm^3 3-neck flask fitted with a paddle stirrer, dropping funnel and reflux condenser were placed magnesium turnings (3.02 g, 124 mmol) and dry THF (tetrahydrofuran) (25 cm^3). The flask was flushed continuously with nitrogen. A solution of *p*-(methoxymethyl)bromobenzene (25.0 g, 124 mmol) in dry THF (175 cm^3) was added dropwise to the mixture. After completion of addition, the reaction mixture was heated at reflux for 45 min using steam heat. After this the reaction mixture was cooled with ice and further THF (60 cm^3) was added. A solution of phosphorus trichloride (5.70 g, 41.6 mmol) in THF (25 cm^3) was then added dropwise over a period of 45 min with continuous stirring. After the addition, the mixture was stirred at room temperature for 30 min, and allowed to stand overnight. Hydrochloric acid (50 cm^3 concentrated, in 150 cm^3 water) was added slowly with cooling in an ice-bath and continuous stirring. The reaction mixture was concentrated under reduced pressure and the residual aqueous solution was extracted with ether (3 × 50 cm^3). The organic portions were combined, dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the pure tri(*p*-methoxymethyl)phenylphosphine **1** (10.1 g, 62% yield) as a semi-solid which exhibited ^{1}H and ^{31}P NMR, and IR spectra, and elemental analysis in accord with the proposed structure. ^{1}H NMR (60 MHz, $CDCl_3$), δ 3.4 (9 H, s), 4.5 (6 H, s) and 7.1–7.9 (12 H, AA′BB′). ^{31}P NMR (81 MHz, $CDCl_3$, relative to external H_3PO_4), δ_P −16 (Found: C, 72.95; H, 6.8. $C_{24}H_{27}O_3P$ requires: C, 73.08; H, 6.90%).

General Procedure for the Preparation of Alkyl(*triaryl*)-*phosphonium Halides* **2a–c**.—A solution of **1** (1.4–2.5 mmol) in dry solvent (**2a–b**, benzene; **2c**, *o*-xylene) (15 cm^3) was placed in a 100 cm^3 flask fitted with a reflux condenser and which was flushed continuously with dry nitrogen. A solution of the alkyl halide (1.4–2.5 mmol) in benzene (10 cm^3) was added to the reaction solution which was stirred for 24 h (**2a**, room temperature; **2b–c**, reflux). After cooling, the solvent was removed from the reaction mixture under reduced pressure and the residue were subjected to flash chromatography on silica gel (100 g) eluting with acetonitrile to yield the pure alkyl(trialyl)-phosphonium halides **2a–c** which exhibited spectra and elemental analysis in accord with their proposed structures (Table 1). Yields: **2a**, 96%; **2b**, 94%; **2c**, 17%.

General Procedure for the Preparation of First-generation Tridirectional Phosphonium Cascade Molecules **2**(1)**a–c**.—A solution of **2** (0.2–0.9 mmol) in dry aceonitrile (10–25 cm^3) was placed in a round-bottomed flask fitted with a reflux condenser and flushed continuously with dry nitrogen. A solution of iodotrimethylsilane (7 equiv.) in dry acetonitrile (10–25 cm^3) was added slowly with continuous stirring. The reaction mixture was refluxed for 16 h, and then cooled. The solvent was evaporated under reduced pressure to give the crude benzylic iodide, which was used without further purification. The crude benzylic iodide was dissolved in dry acetonitrile (10–50 cm^3) and placed in a round-bottomed flask fitted with reflux condenser and flushed continuously with dry nitrogen. A solution of **1** (3.1 equiv.) in dry acetonitrile (5–40 cm^3) was added slowly with continuous stirring. The solution was refluxed for 24 h and then cooled. The solvent was removed at reduced pressure to give the crude product. For **2**(1)**b** the pure

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product was isolated by washing with 30% aqueous ethanol and evaporating the solution. For **2**(1)**a** and **2**(1)**c** the pure product was isolated by passage through a DOWEX 2 column in the iodide form, eluting with 80% aqueous ethanol, and evaporation of the solvent. In this manner the pure **2**(1)**a–c** were isolated which exhibited spectra and analysis in accord with their proposed structures (Table 1). Yields: **2**(1)**a**, 54%; **2**(1)**b**, 22%; **2**(1)**c**, 92%.

General Procedure for the Preparation of Second-generation Tridirectional Phosphonium Cascade Molecules **2**(2)**a–c**.—A solution of **2**(1) (0.1–0.2 mmol) in dry acetonitrile (20–30 cm^3) was placed in a round-bottomed flask fitted with a reflux condenser and flushed continuously with dry nitrogen. There was then added slowly with continuous stirring a solution of iodotrimethylsilane (10 equiv.) in dry acetonitrile (5–30 cm^3). The solution was heated at reflux for 16 h. After this time the solution was cooled and the solvent evaporated under reduced pressure to give the crude benzylic iodide which was used without further purification. The crude benzylic iodide was dissolved in acetonitrile (20–40 cm^3) and the solution placed in a round-bottomed flask fitted with a reflux condenser and continuously flushed with nitrogen. A solution of **1** (10 equiv.) in acetonitrile (10–40 cm^3) was added slowly with continuous stirring and the solution was refluxed for 30 h. After this time the solution was cooled and the solvent evaporated under reduced pressure to give the crude product. The crude material was purified by passage through a DOWEX 2 column in the iodide form, eluting with 30% aqueous ethanol. The eluents were evaporated under reduced pressure to give the pure **2**(2)**a–c** which exhibited spectra and analysis in accord with the proposed structures (Table 1). Yields **2**(2)**a**, 55%; **2**(2)**b**, 64%; **2**(2)**c**, 68%.

General Procedure for the Preparation of Third-generation Tridirectional Phosphonium Cascade Molecules **2**(3)**a–b**.—A solution of **2**(2) (0.1–0.2 mmol) in dry acetonitrile (20–40 cm^3) was placed in a round-bottomed flask fitted with a reflux condenser and flushed continuously with dry nitrogen. There was then added slowly with continuous stirring a solution of iodotrimethylsilane (35 equiv.) in dry acetonitrile (50–100 cm^3), and the mixture was heated at reflux for 24 h. After this time the solution was cooled and the solvent evaporated under reduced pressure to give the crude benzylic iodide. The crude benzylic iodide was dissolved in dry acetonitrile (10–20 cm^3) and placed in a round-bottomed flask fitted with a reflux condenser and flushed continuously with dry nitrogen. There was added a solution of **1** (40 equiv.) in acetonitrile (20–50 cm^3) and the reaction mixture was heated at reflux for 4 d. After cooling, diethyl ether (100 cm^3) was added to the reaction mixture and the target material precipitated from solution and was collected by filtration and dried. In this manner pure **2**(3)**a–b** could be isolated which exhibited spectra and analysis in accord with the proposed structure (Table 1). Yields: **2**(3)**a**, 15%; **2**(3)**b**, 21%.

Preparation of Tetra(p-*methoxymethyl*)*phenylphosphonium Bromide* **3**.—A solution of **1** (0.500 g, 1.26 mmol) in dry methanol (5 cm^3) was placed in a pressure tube with a Teflon needle valve along with *p*-(methoxymethyl)bromobenzene (0.255 g, 1.26 mmol) and anhydrous nickel(II) bromide (0.007 g, 0.032 mmol). The tube was flushed with dry nitrogen and closed. The closed tube was kept in an oil bath maintained at 180 °C for 48 h. After cooling to room temperature, the solvent was evaporated under reduced pressure to give the crude product, which was purified by flash chromatography on silica gel (50 g) using 1:1 acetonitrile–ethanol as eluent. In this manner was isolated pure **3** (0.050 g, 7%) which exhibited spectra and analysis in accord with the proposed structure (Table 2).

Preparation of the First-generation Tetradirectional Cascade Molecules **3**(1).—A solution of **3** (0.040 g, 0.067 mmol) in dry acetonitrile (15 cm^3) was placed in a 100 cm^3 round-bottomed flask fitted with a reflux condenser and flushed continuously with dry nitrogen. To it was added slowly with continuous stirring a solution of iodotrimethylsilane (0.110 g, 0.538 mmol) in dry acetonitrile (5 cm^3). The reaction mixture was refluxed for 16 h, and then cooled to room temperature. The solvent was removed at reduced pressure to give the crude benzylic iodide. The crude benzylic iodide so obtained was dissolved in dry acetonitrile (25 cm^3) and placed in a 100 cm^3 round-bottomed flask fitted with a reflux condenser and flushed continuously with dry nitrogen. To it was added slowly with continuous stirring a solution of **1** (0.15 g, 0.38 mmol) in dry acetonitrile (10 cm^3). The solution was refluxed for 24 h and then cooled to room temperature. The solvent was evaporated under reduced pressure to give the crude product which was passed through a DOWEX 2 column in the iodide form using 30% aqueous ethanol as eluent. The material isolated from this treatment was further purified by flash chromatography on silica gel (40 g) eluting with a 1:1 mixture of acetonitrile–ethanol. Evaporation of the eluents gave the pure **3**(1) (0.040 g, 23%) which exhibited spectra and analysis in accord with the proposed structure (Table 2).

Preparation of the Second-generation Tetradirectional Cascade Molecule **3**(2).—A solution of **3**(1) (0.030 g, 0.012 mmol) in dry acetonitrile (15 cm^3) was placed in a 100 cm^3 round-bottomed flask fitted with a reflux condenser and flushed continuously with dry nitrogen. To it was added slowly, with continuous stirring, a solution of iodotrimethylsilane (0.056 g, 0.27 mmol) in dry acetonitrile (5 cm^3). The mixture was refluxed for 16 h and then cooled to room temperature. The solvent was evaporated under reduced pressure to give the crude benzylic iodide. The crude benzylic iodide thus obtained was dissolved in dry acetonitrile (25 cm^3) and placed in a 100 cm^3 round-bottomed flask fitted with a reflux condenser and flushed continuously with dry nitrogen. There was added to it a solution of **1** (0.110 g, 0.290 mmol) in dry acetonitrile (10 cm^3) and the reaction mixture was heated at reflux for 24 h. After this time the solvent was evaporated under reduced pressure to give the crude product, which was purified by first passing through a DOWEX 2 column in the iodide form and then subjected to flash chromatography on silica gel (40 g) eluting with a 1:1 mixture of acetonitrile–ethanol. Upon evaporation of the eluent there could be isolated pure **3**(2) (0.078 g, 93%) which exhibited spectra and analysis in accord with the proposed structure (Table 2).

Acknowledgements

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