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Synthesis of 3-Arylpropenyl, 3-Arylpropynyl and 3-Arylpropyl 2-Azetidinones as Cholesterol Absorption Inhibitors: Application of the Palladium-Catalyzed Arylation of Alkenes and Alkynes

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Abstract—A series of 3-(3′-arylpropenyl)-2-azetidinones **8a**–**8k** and 3-(3′-arylpropynyl)-2-azetidinones **16m**–**16p** were prepared by the palladium-catalyzed arylation of 3-(3′-propenyl)-2-azetidinone **7**, or by arylation of 4-pentenoic acid, or via ethyl 4-pentynoate followed by 2-azetidinone ring construction. The unsaturated 2-azetidinones were transformed to their saturated analogs **9a**–**9p** by catalytic hydrogenation. Azetidinones **8a**–**8k**, **9a**–**9p**, and **16m**–**16p** were evaluated for their biological activity as cholesterol absorption inhibitors in hamsters.

Introduction

SCH 48461 (**1a**), a 3-(3′-phenylpropyl)-2-azetidinone has been reported by Burnett[1] et al., as a potent cholesterol absorption inhibitor (CAI) in vivo. Subsequently, an extensive structure-activity (SAR) effort in our laboratory culminated with the discovery of SCH 58235 (**1b**),[2] a remarkably potent (CAI ED_{50}=0.04 mg/Kg in a 7-day cholesterol-fed hamster model) orally active cholesterol absorption inhibitor that is currently undergoing clinical investigation for the treatment of hypercholesterolemia. During an early phase of the SAR exploration, unsaturated analogs **2** and **3** were prepared in order to determine the effect of conformationally restricted C3-side chains on CAI activity. Reported herein is the synthesis, spectral characterization and the CAI activity of these compounds.

We considered two synthetic approaches for the preparation of compounds **2** and **3** containing variations of the pendent C3-side chain aromatic residue. One route involved the

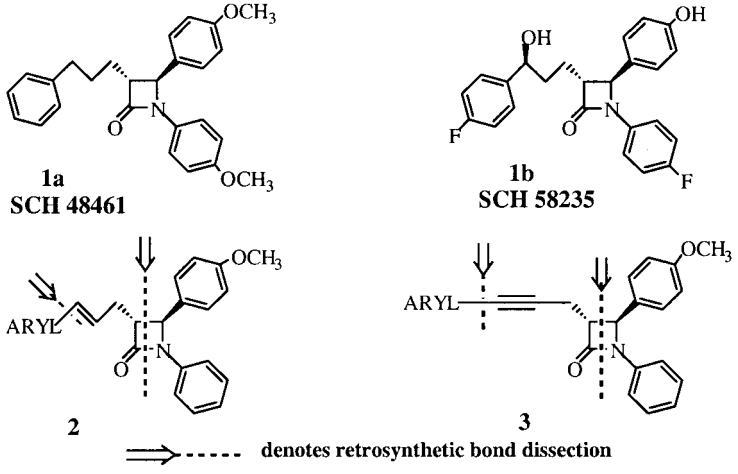

Figure 1.

Keywords: arylpropenyl; azetidinones; hydrogenation.
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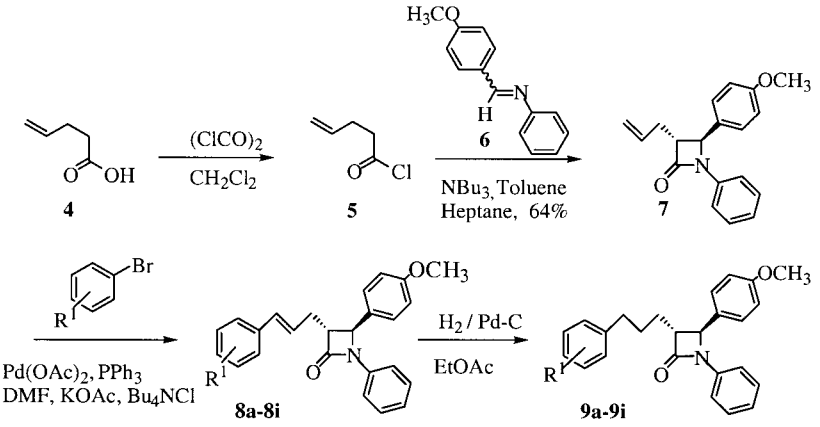


Scheme 1. R^1=(**a**) 2-OH; (**b**) 4-OMOM; (**c**) 2-CH_2OH; (**d**) 4-CH_2OH; (**e**) 4-CF_3; (**f**) 4-CO_2H; (**g**) R^1-Ph=3-pyridyl; (**h**) R^1-Ph=5-indolyl; (**i**) R^1-Ph=3,5-pyrimidyl.

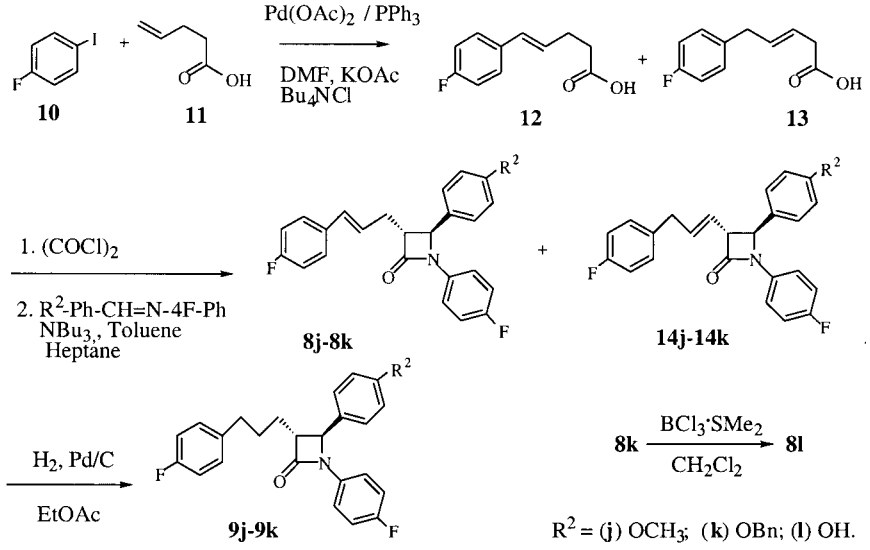
Table 1. Palladium catalyzed coupling of **7** with aryl bromides ($Pd(OAc)_2$ (10–15 mol%), PPh_3 (10–15 mol%), KOAc (500 mol%), *n*-Bu_4NCl (140 mol%), DMF; yields of purified materials)

Entry no.	R^1	Temp. (time)	Yield (%)
8a	2-OH	80°C, 16 h	10
8b	4-OMOM	80°C, 18 h	45
8c	2-CH_2OH	80°C, 18 h	31
8d	4-CH_2OH	80°C, 18 h	45
8e	4-CF_3	80°C, 18 h	51
8f	4-CO_2H	80°C, 16 h	16
8g	R^1-Ph=3-Pyridinyl	80°C, 18 h	24
8h	R^1-Ph=5-Indolyl	80°C, 24 h	35
8i	R^1-Ph=3,5-Pyrimidyl	80°C, 4 h	38

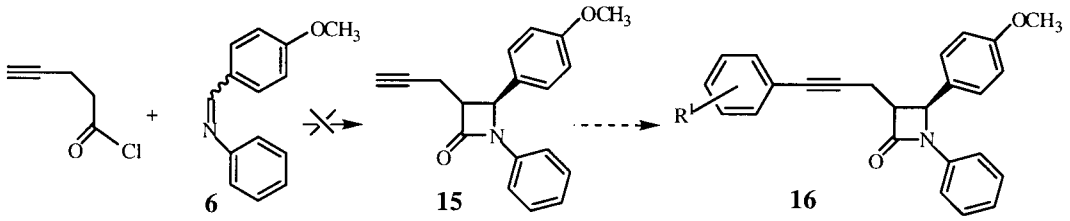
direct arylation of a late stage C3-propenyl/propynyl-2-azetidinone intermediate, and an alternative route utilized acyclic 3-aryl-propenoate/propynoates, as shown in the retrosynthetic fashion in Fig. 1. Palladium catalyzed arylation of olefinic azetidinones have not been reported in the literature.

Chemistry

The synthesis of 3-(3′-arylpropenyl)-2-azetidinones **8a–8i** is summarized in Scheme 1. 4-Pentenoyl chloride (**5**), prepared from carboxylic acid **4**, was treated with imine **6** under *trans*-selective Staudinger reaction conditions[3] to afford **7** (64%). Compound **7** was then utilized as the olefinic intermediate for introduction of various aryl groups at the 3′ position of the C3-propenyl group. A variety of experimental conditions for the palladium-catalyzed arylation of alkenes and alkynes have been reported.[4] Investigation of the relative efficiency of these reaction conditions as applied for the arylation of **7** concluded that the use of $PdOAc_2/PPh_3$ was equivalent to $PdCl_2(PPh_3)_4$ but superior to $Pd(PPh_3)_4$ as the palladium catalyst. Furthermore, addition of a tetraalkylammonium salt and an alkali metal acetate (e.g. KOAc) was preferred for the conversion of **7** to compounds **8a–8i**. Although the yields for arylation of **7** were modest (Table 1), this methodology was convenient from a SAR exploration perspective. The attempted arylations of **7** with 4-bromopyrazole, 3-bromofuran, and fluoro-4-iodobenzene were unsuccessful.[5]



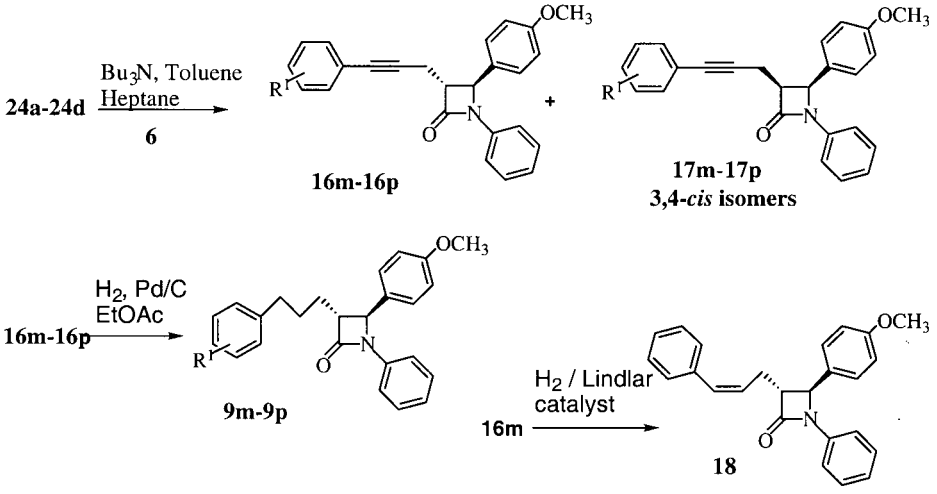
Scheme 2.



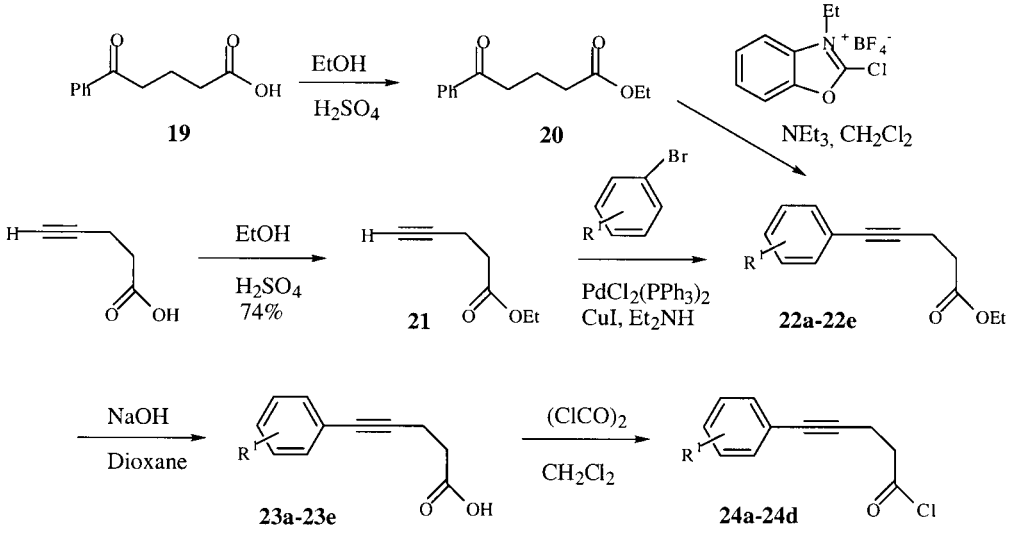
Scheme 3.

The *p*-fluorophenyl analogs **8j–l** were important for our SAR studies from a pharmacokinetic perspective;[6] and therefore failure to obtain **8j** by arylation of **7** prompted us to investigate the alternative ketene-imine approach (Scheme 2). Arylation of 4-pentenoic acid **11** with fluoro-4-iodobenzene (**10**) using the protocol above ($PdOAc_2$, PPh_3, KOAc, Bu_4NCl), afforded a 1:1 mixture of 4-*E*-pentenoic acid **12** and 3-*E*-pentenoic acid **13**. The isomeric product mixture of **12** and **13** can be partially purified by recrystallization, but preferably was converted as a mixture to chromatographically separable azetidinones **8j**,**k** and **14j**,**k**. The observed olefin migration is in contrast to the arylation of **7**, which afforded only 2-*E*-propenyl derivatives.

Selective *O*-debenzylation of **8k** was accomplished with boron trichloride-dimethyl sulfide complex[7] to afford phenol **8l** in 68% yield. Reduction of **8j**,**k** or **14j**,**k** with hydrogen over palladium on carbon afforded the saturated fluorinated analogs **9j**,**k**.



Scheme 4. R^1=(**m**) H; (**n**) 4-Ph; (**o**) 4-*n*-butyl; (**p**) 3,5-di-F.



Scheme 5. R^1=(**a**) H; (**b**) 4-Ph; (**c**) 4-*n*-butyl; (**d**) 3,5-di-F; (**e**) R^1-Ph=3-pyridinyl

Table 2. Preparation of ethylpentynoates **21a–e** and propynyl 2-azetidinones **16m–p**

Entry no	R^1	Method[a]	Yield (%)	Entry no	R^1	Method[a]	Yield(%)
22a	4-H	1	49	**16m**	4-H	3	20
22b	4-Ph	2	60	**16n**	4-Ph	3	38
22c	4-*n*-Butyl	2	37	**16o**	4-*n*-Butyl	3	23
22d	3,5-F	2	75	**16p**	3,5-F	3	41
22e	3-Pyridyl[b]	2	49	**16q**	3-Pyridyl[b]	3	<5

[a] Methods: 1=2-Chloro-3-ethyl-benzoxazolium tetrafluoroborate; 2=ArBr, $PdCl_2(PPh_3)_2$, CuI, Et_2NH; 3=Tributylamine, 1:1 toluene:heptane, reflux.
[b] R^1-Ph=3-Pyridyl.

In an analogous late stage arylation approach to **8a–i** above, we envisaged the preparation of the C3-arylpropynyl series **16** via **15** (Scheme 3). Slow addition of 4-pentynoyl chloride to imine **7** and $(n\text{-Bu})_3N$ at reflux (efficient condenser, 100°C, 12 h, 1:1 toluene:heptane) afforded only trace amounts of **15**. Reaction of 4-pentynoyl chloride with triethylamine in methylene chloride under preformed ketene conditions (−78°C, 1 h), followed by addition of **6** and warming to −10°C over 4 h, afforded a complex mixture of products, with no detectable **15**.

Alternatively, reaction of 5-arylpentynoyl chlorides **24a–d** with imine **6** in the presence of $(n\text{-Bu})_3N$ using the *trans*-selective Staudinger reaction conditions,[3] afforded the desired 3-(3′-aryl-2′-propynyl)-2-azetidinones **16m–p** and **17m–p** in moderate yields (Scheme 4). The *trans*:*cis* azetidinone selectivity in this reaction was >25:1. Hydrogenation of **16m–16p** over palladium on carbon afforded the saturated analogs **9m–9p**, while hydrogenation of **16m** over Lindlar catalyst afforded 2′-Z-olefinic analog **18** in 50% yield.

Preparation of the required 5-arylpentynoyl chlorides **24a–d** is outlined in Scheme 5. Ethyl 5-phenyl-3-propynoate (**22a**) was synthesized by esterification of benzoylbutyric acid (**19**), followed by treatment with 2-chloro-3-ethyl-benzoxazolium tetrafluoroborate.[8] Alkynyl-esters **22b–e** were prepared from terminal-alkyne **21** by Pd-mediated coupling with an appropriately substituted aryl bromide in moderate yields (Table 2). The addition of an inorganic salt such as copper iodide plus an amine (Et_2NH) was optimal for arylation of alkyne **21** in contrast to the arylation of **7**, where addition of a tetraalkylammonium salt and an alkali metal acetate was preferred. The alkynyl acid chlorides **24a–d** were obtained in high yield by base hydrolysis of esters **22a–e**, followed by treatment with oxalyl chloride.

Biology

The CAI activity of series **8**, **9**, and **16** is summarized in Table 3. The low CAI activity of **7** (<10% reduction of CE @ 10 mpK) confirms previous observations that a carbon spacer with a pendant phenyl residue is required for CAI activity.[9] The CAI activity of **8a–f** favored small lipophilic substitution on the pendant C3-aromatic residue (i.e. H>4-F∼4-CF_3⩾4-CO_2H).

The CAI activity of C3-side chain unsaturated analogs **8** and **16** was similar to their corresponding saturated analog **9**. First-order calculations using MM2 indicate a high energy penalty for rotation of either the C3-1′ or 1′-2′ bonds that orient the C3-side chain over the 2-azetidinone ring. The current work suggests that the active binding conformation is close to a fully extended side chain conformation. We would also like to suggest that side chain restricted analogs which explore similar conformation space as **9** will not show significantly enhanced CAI activity.

Table 3. CAI Activity of 2-Azetidinones **8**, **9**, and **16**

Entry no	Aryl substitution	Series	CAI activity[a]	Entry no	Series	CAI activity[a]
8a	2-OH	3-Alkene	−66 @ 10 mpK	**9a**	Saturated	−51 @ 10 mpK
8b	4-OMOM	3-Alkene	−95 @ 10 mpK	**9b**	Saturated	−62 @ 10 mpK
8c	2-CH_2OH	3-Alkene	−54 @ 10 mpK	**9c**	Saturated	−49 @ 10 mpK
8d	4-CH_2OH	3-Alkene	0 @ 10 mpK	**9d**	Saturated	−24 @ 10 mpK
8e	4-CF_3	3-Alkene	−64 @ 10 mpK	**9e**	Saturated	0.7 mpK
8f	4-CO_2H	3-Alkene	−17 @ 10 mpK	**9f**	Saturated	0 @ 10 mpK
8g	R^1-Ph=3-Pyridyl	3-Alkene	−13 @ 10 mpK	**9g**	Saturated	−13 @ 10 mpK
8h	R^1-Ph=5-Indolyl	3-Alkene	−49 @ 10 mpK	**9h**	Saturated	−55 @ 10 mpK
8i	R^1-Ph=3,5-Pyrimidyl	3-Alkene	−23 @ 10 mpK	**9i**	Saturated	−23 @ 10 mpK
8j	OCH_3	3-Alkene	1.3 mpK	**9j**	Saturated	2 mpK
8k	OBn	3-Alkene	−60 @ 3 mpK	**9k**	Saturated	2 mpK
8l	OH	3-Alkene	∼2 mpK	**9l**	Saturated	2 mpK
16m	4-H	3-Alkyne	−64 @ 10 mpK	**9m**[b]	Saturated	0.5 mpK
16n	4-Ph	3-Alkyne	0 @ 10 mpK	**9n**	Saturated	0 @ 10 mpK
16o	4-*n*-Butyl	3-Alkyne	0 @ 10 mpK	**9o**	Saturated	0 @ 10 mpK
16p	3,5-F	3-Alkyne	−37@ 10 mpK	**9p**	Saturated	−49 @ 10 mpK
8m	H	3-Alkene	0.6 mpK	**1a**	Saturated	2.2 mpK
7	R^1-Ph=H	3-Alkene	<10 @ 10 mpK	**1b**	Saturated	0.04 mpK

[a] Activity is expressed at ED_{50} (mg/Kg/day) or percent reduction in liver cholesterol esters (LCE) in a 7-day cholesterol-fed hamsters model as detailed in Ref. 2.
[b] Data taken from Ref. 9.

Even though the activity of 4-fluoro substituted congener **9j** was slightly weaker than the unsubstituted analog **9m**, we felt that potential metabolic aromatic hydroxylation could be minimized, and thus subsequent SAR studies focused on congeners of **9j**. Compounds **2** and **3** have additionally been transformed into a series of side chain hydroxylated analogs, the activity of which will be reported elsewhere.[10]

Conclusion

Two complementary synthetic routes, both based on the palladium-catalyzed coupling of substituted arylhalides with functionalized unsaturated partners, have been utilized for the synthesis of unsaturated 2-azetidinones of general structures **2** and **3**.

Experimental

All reactions were performed under argon with magnetic stirring unless otherwise stated. Air and moisture sensitive reagents were transferred with disposable all-polypropylene syringes available from Aldrich Chemical Company. All commercially available compounds were used without further purification unless otherwise noted. Analytical TLC was performed using Analtech glass-coated plates with fluorescent indicator (Silica Gel GF, 250 micron) and visualization was accomplished with a UV lamp (254 nm). Preparative flash chromatography utilized Selecto Scientific flash silica gel (32–63 micron) under medium pressure with compound to silica weight ratios of 1:10–30. Analytical HPLC was performed on a Rainin HPXL pump system using either Rainin Dynamax 60A Columns with UV detection (254 nm). ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in deuterated chloroform unless otherwise noted on a Varian Gemini 300 spectrometer. Chemical shifts are reported in ppm (δ) relative to TMS and coupling constants (J) are reported in Hz. Chemical Ionization (CI, CH_4 carrier) and Electron Ionization (EI, ~70 eV) mass spectra were recorded on a Hewlett Packard 5989A spectrometer.

4-(4-Methoxyphenyl)-1-phenyl-3-(2-propenyl)-2-azetidinone (7). A solution of 4-methoxybenzylidene-*N*-phenylanisidine **6** (19.34 g, 0.09 mol) in heptane (40 mL) and tributylamine (43.6 mL, 0.18 mol) was heated to 45°C under argon. A solution of acid chloride **5** (11.75 g, 0.09 mol) in toluene (20 mL) was added dropwise over 0.5 h. The solution was stirred at 45°C for 16 h and then at 80°C for 5 h. The solution was cooled and quenched with 1 N HCl, and diluted with ethyl acetate. The solution was washed with 1 N HCl (2×), H_2O, dried with $MgSO_4$ and concentrated in vacuo. The crude product mixture was purified by flash chromatography, eluting with hexane–ethyl acetate (9:1) to yield **7** (19.0 g, 64%); ^{1}H NMR δ 2.64 (m, 1H, H_1'), 2.77 (m, 1H, H_1'), 3.25 (m, 1H, H_3), 3.86 (s, 3H, OCH_3), 4.72 (d, 1H, J=2.2 Hz, H_4), 5.20 (m, 2H, C=CH_2), 5.92 (m, 1H, C=CH), 6.92–7.35 (m, 9H, Ar). Anal. calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.68; H, 6.59; N, 4.62.

3-(3-Aryl-2-propenyl)-2-azetidinones 8a–8i. A solution of the appropriate arylbromide (11.0 mmol), palladium acetate (0.34 g, 1.52 mmol), triphenylphosphine (0.43 g, 1.63 mmol), potassium acetate (oven dried, 4.31 g, 44.0 mmol), anhydrous tetrabutyl-ammonium chloride (3.05 g, 11.0 mmol) and **7** (8.0 mmol) in DMF (50 mL) was heated to 80°C for 18 h. The solution was cooled, diluted with ethyl acetate, washed with H_2O (3×), dried and concentrated in vacuo. The crude product mixture was purified by flash chromatography, eluting with hexane–ethyl acetate (9:1). The product was further purified by HPLC (2.1×20 cm^2 column, 10% hexane–ethyl acetate). **8a** ^{1}H NMR δ 2.85 (p, J=8.7, 16.0 Hz), 2.98 (p, J=6.1, 15.0 Hz), 3.35 (ddd, J=2.3, 6.4, 8.7 Hz), 3.88 (s, 3H, OCH_3), 4.82 (d, 2.3 Hz), 5.58 (s br, 1H, OH), 6.28 (sx, J=6.9, 15.9 Hz, H_2'), 6.80 (d, J=15.7 Hz, H_3'), 6.89–7.39 (13H, Ar); HRMS (FAB) calcd for $C_{25}H_{24}NO_3$; 386.1756, found 386.1763; IR (C=O) 1743.66 cm^{-1}; **8b** ^{1}H NMR δ 2.78 (p, J=8.7, 15.7 Hz), 2.96 (sx, J=5.5, 15.1 Hz), 3.34 (ddd, J=2.1, 5.1, 9.4 Hz), 3.58 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.80 (d, J=2.2 Hz), 5.28 (s, 2H), 6.22 (sx, J=6.6, 15.9 Hz, H_2'), 6.54 (d, J=16.0 Hz, H_3'), 6.95–7.40 (13H, Ar); MS (CI) m/z 430 (M+H); **8c** ^{1}H NMR δ 2.88 (p, J=7.9, 15.3 Hz), 2.99 (p, J=6.1, 13.8 Hz), 3.40 (ddd, J=2.3, 6.2, 8.4 Hz), 3.90 (s, 3H, OCH_3), 4.81 (s, 2H, CH_2OH), 4.84 (d, J=2.3 Hz), 6.28 (sx, J=6.8, 15.7 Hz, H_2'), 6.98 (d, J=16.4 Hz, H_3'), 6.99–7.52 (13H, Ar); MS (CI) m/z 400 (M+H); HRMS (FAB) calcd for $C_{26}H_{26}NO_3$ 400.1913. found 400.1908. **8d** ^{1}H NMR δ 2.81 (p, J=8.4, 15.9 Hz) 2.98 (p, J=5.2, 16.0 Hz), 3.36 (ddd, J=2.3, 5.3, 9.5 Hz), 3.90 (s, 3H, OCH_3), 4.77 (s, 2H, CH_2OH), 4.79 (d, J=2.2 Hz), 6.35 (sx, J=6.8, 15.9 Hz, H_2'), 6.60 (d, J=15.9 Hz, H_3'), 6.96–7.43 (13H, Ar); MS (CI) m/z 400 (M+H); **8e** ^{1}H NMR δ 2.86 (p, J=8.0, 15.7 Hz), 2.98 (sx, J=5.7, 15.4 Hz), 3.40 (ddd, J=2.4, 4.7, 8.8 Hz), 3.91 (s, 3H, OCH_3), 4.81 (s, 2H), 6.48 (sx, J=6.5, 15.9 Hz, H_2') 6.64 (d, J=16.0 Hz) 6.99–7.68 (14H, Ar); HRMS (FAB) calcd for $C_{26}H_{22}NO_2F_3$ 437.1603, found 437.1603. **8f** ^{1}H NMR δ 2.90 (p, 8.8, 16.0 Hz), 3.07 (sx, J=5.9, 15.3 Hz), 3.43 (ddd, J=2.3, 6.0, 8.6 Hz), 3.94 (s, 3H, OCH_3), 4.84 (d, J=2.2 Hz), 6.56 (sx, J=6.4, 16.3 Hz, H_2'), 6.69 (d, J=15.9 Hz, H_3'), 7.02–8.18 (13H, Ar); HRMS (FAB) calcd for $C_{26}H_{23}NO_4$ 413.1627, found: 413.1605. **8g** ^{1}H NMR δ 2.83 (ddd, J=7.0, 9.0, 15.8 Hz), 2.98 (sx, J=5.7, 15.4 Hz), 3.35 (ddd, J=2.3, 5.6, 8.0 Hz), 3.86 (s, 3H, OCH_3), 4.76 (d, J=2.4 Hz), 6.46 (sx, J=6.3, 15.9 Hz, H_2'), 6.56 (d, J=15.9 Hz, H_3'), 6.94–8.61 (13H, Ar); HRMS (FAB) calcd for $C_{24}H_{22}N_2O_2$ 370.1660, found 370.1660. **8h** ^{1}H NMR δ 2.75 (sx, J=8.6, 16.1 Hz), 2.94 (p, J=5.2, 16.0 Hz), 3.30 (ddd, J=2.2, 5.0, 9.6 Hz), 3.83 (s, 3H, OCH_3), 4.82 (d, J=2.2 Hz), 6.25 (sx, J=6.7, 15.4 Hz, H_2'), 6.65 (d, J=15.9 Hz, H_3'), 6.57 and 6.9–8.25 (15H, Ar); HRMS (FAB) calcd for $C_{27}H_{24}N_2O_2$ 408.1838, found 408.1847. **8i** ^{1}H NMR δ 2.91 (ddd, J=5.0, 9.0, 14.5 Hz), 3.06 (sx, J=5.5, 15.3 Hz), 3.41 (ddd, J=2.4, 5.8, 8.6 Hz), 3.92 (s, 3H, OCH_3), 4.81 (d, J=2.3 Hz), 6.56 (m, 2H), 7.00–9.20 (12H, Ar); Anal. calcd for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70; N, 11.33. Found: C, 73.88; H, 5.58; N, 10.89.

1-(4-Fluorophenyl)-3-(3-(4-fluorophenyl)-2/1-*E*-propenyl)-4-(4-methoxyphenyl)-2-azetidinones 8j, 14j. A solution of 4-methoxybenzylidene-*N*-4-fluorophenyl anisidine (2.18 g, 9.5 mmol) in heptane (10 mL) and tributylamine (4.5 mL, 19 mmol) was heated to 80°C under

argon. A solution of acid chlorides derived from **12** and **13** (Oxalyl chloride, CH_2Cl_2, 1 h, 22°C, 11.3 mmol) in toluene (50 mL) was added dropwise over 0.5 h. The solution was stirred at 80°C for 18 h. The solution was cooled and quenched with 1 N HCl, and diluted with ethyl acetate. The solution was washed with 1 N HCl (2×), H_2O, dried with $MgSO_4$ and concentrated in vacuo. The crude product mixture was purified by flash chromatography, eluting with hexane–ethyl acetate (9:1) to yield **8j** (65%) ^{1}H NMR δ 2.82 (p, J=8.3, 15.9 Hz), 2.99 (sx, J=5.0, 15.3 Hz), 3.39 (d, J=2.3, 5.4, 9.3 Hz), 3.93 (s, 3H, OCH_3), 4.79 (d, J=2.3 Hz), 6.27 (sx, J=6.7, 15.7 Hz, H_2'), 6.58 (d, J=15.9 Hz, H_3'), 7.00–7.42 (12H, Ar); MS (CI) m/z 406 (M+H). Anal. calcd for $C_{25}H_{21}F_2NO_2$: C, 74.02; H, 5.22; N, 3.45. Found: C, 73.69; H, 5.36; N, 3.46; and **14j** (~2%) ^{1}H NMR δ 3.45 (d, J=6.1 Hz, 2H), 3.76 (dd, 1H), 3.86 (s, 3H, OCH_3), 5.71 (dd, 1H), 5.99 (sx, J=8.0, 15.3 Hz), 6.9–7.4 (12H, Ar); HRMS (FAB) calcd for $C_{25}H_{21}N0_2F_2$ 405.1540, found 405.1533.

1-(4-Fluorophenyl)-3-(3-(4-fluorophenyl)-2/1-*E*-propenyl)-4-(4-benzyloxyphenyl)-2-azetidinones 8k, 14k. Using the method above, **8k** and **14k** were prepared from 4-benzyloxybenzylidene-*N*-(4-fluoro)phenylanisidine and the mixture of **12** and **13**. The crude product mixture was purified by flash chromatography to afford **8k** ^{1}H NMR δ 2.80 (sx), 2.94 (p), 3.36 (m), 4.74 (d, J=2.2 Hz), 5.14 (s, 2H), 6.23 (sx, J=7.5, 15.0 Hz, H_2'), 6.54 (d, J=15.0 Hz, H_3'), 7.00–7.53 (17H, Ar); and **14k** ^{1}H NMR δ 3.45 (d, J=7.5 Hz, 2H, H_3'), 3.78 (d, J=7.5 Hz), 4.76 (d, J=2.3 Hz), 5.13 (s, 2H, CH_2), 5.73 (dd, J=7.5, 15.0 Hz), 5.98 (sx, J=7.5, 15.0 Hz, H_2'), 6.98–7.48 (17H, Ar); MS (CI) m/z 482 (M+H).

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-2-*E*-propenyl]-4-(4-hydroxyphenyl)-2-azetidinone (8l). A solution of **8k** (34.3 mg, 0.07 mmol), boron trichloride-dimethyl sulfide complex (127.7 mg, 0.71 mmol) and CH_2Cl_2 (2 mL) was stirred at room temperature for 18 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with ethyl acetate. The organic phase was dried with $MgSO_4$ and concentrated in vacuo to yield **8l** (18.9 mg, 68%). ^{1}H NMR δ 2.80 (p), 2.97 (sx), 3.36 (m), 4.75 (d, J=2.2 Hz), 5.15 (s br, 1H, 0H), 6.25 (sx, J=7.5, 15.0 Hz, H_2'), 6.55 (d, J=15.8 Hz, H_3'), 6.90–7.39 (12H, Ar); MS (CI) m/z 392 (M+H).

3-(3-Arylpropyl)-2-azetidinones 9a–9p. General procedure

A flask was charged with either **8a**–**8l**, **14j**–**14k** or **16m**–**16p** (0.72 mmol), 10% palladium on carbon (33 mg) and ethyl acetate (10 mL) were added. The heterogeneous mixture was stirred under 1 atm of hydrogen gas (balloon) for 2 h. The reaction mixture was filtered through celite and concentrated in vacuo. The crude product mixture was purified by flash chromatography, eluting with hexane–ethyl acetate (4:1). **9a** ^{1}H NMR δ 1.89–2.15 (m), 2.80 (m), 3.25 (t), 3.90 (s, 3H, OCH_3), 4.73 (1H, d, J=2.2 Hz), 6.1 (br s, 1H, OH) 6.9–7.5 (13H, Ar); MS (CI) m/z 388 (M+H). **9b** ^{1}H NMR δ 1.87–2.10 (m), 2.71 (t), 3.20 (t), 3.58 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.70 (d, J=2.2 Hz), 5.25 (s, 2H, CH_2), 6.99–7.39 (13H, Ar); HRMS (FAB) calcd for $C_{27}H_{29}NO_4$ 431.2097, found 431.2097. **9c** ^{1}H NMR δ 1.91–2.10 (m), 2.77 (t), 3.20 (t), 3.83 (s, 3H, OCH_3), 4.71 (d, J=2.2 Hz), 4.78 (s, 2H, CH_2OH), 7.00–7.50 (13H, Ar). HRMS (FAB) calcd for $C_{26}H_{27}NO_3$ 401.1991, found 401.1984. **9d** ^{1}H NMR δ 1.90–2.10 (m), 2.75 (t), 3.20 (t), 3.90 (s, 3H, OCH_3), 4.71 (d, J=2.2 Hz), 4.80 (s, 2H, CH_2OH), 7.00–7.50 (13H, Ar). HRMS (FAB) calcd for $C_{26}H_{27}NO_3$ 401.1991, found 401.1985. **9e** ^{1}H NMR δ 1.90–2.08 (m), 2.80 (t), 3.19 (t), 3.89 (s, 3H, OCH_3), 4.68 (d, 2.3 Hz), 6.95–7.64 (13H, Ar). HRMS (FAB) calcd for $C_{26}H_{22}NO_2F_3$ 439.1759, found 439.1760. **9f** ^{1}H NMR δ 1.9–2.05 (m), 2.80 (t), 3.15 (t), 3.88 (s, 3H, OCH_3), 4.67 (d, J=2.0 Hz), 6.9–8.1 (13H, Ar). Anal. calcd for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.06; N, 3.37. Found: C, 74.75; H, 6.06; N, 3.42. **9g** ^{1}H NMR δ 1.86–2.05 (m), 2.70 (t), 3.14 (t), 3.86 (s, 3H, OCH_3), 4.64 (d, J=2.2 Hz), 6.93–8.48 (13H, Ar); HRMS (FAB) calcd for $C_{24}H_{24}N_2O_2$ 372.1838, found: 372.1842. **9h** ^{1}H NMR δ 1.9–2.09 (m), 2.82 (t), 3.19 (t), 3.87 (s, 3H, OCH_3), 4.68 (d, J=2.3 Hz), 6.55–8.34 (15H, Ar). HRMS (FAB) calcd for $C_{27}H_{26}N_2O_2$ 410.1994, found 410.1986. **9i** ^{1}H NMR δ 1.80–2.09 (m), 2.72 (t), 3.17 (t), 3.85 (s, 3H, OCH_3), 4.68 (d, J=2.2 Hz), 6.96–9.14 (12H, Ar); Anal. calcd for $C_{23}H_{25}N_3O_2$: C, 73.97; H, 6.21; N, 11.25. Found: C, 73.45; H, 6.24; N, 10.95. **9j** ^{1}H NMR δ 1.75–2.10 (m), 2.72 (t), 3.15 (t), 3.85 (s, 3H, OCH_3), 4.7 (d, J=2.2 Hz), 6.90–7.5 (12H, Ar); MS (CI) m/z 408 (M+H). **9k** ^{1}H NMR δ 1.76–2.12 (m), 2.72 (t), 3.2 (t), 4.7 (d, J=2.2 Hz), 4.9 (s, 2H, CH_2), 6.96–7.7 (17H, Ar). MS (CI) m/z 484 (M+H). **9l** ^{1}H NMR δ 1.80–2.09 (m), 2.72 (t), 3.17 (t), 4.68 (d, J=2.2 Hz), 5. 3 (br s, 1H, OH), 6.96–7.4 (12H, Ar). MS (CI) m/z 394 (M+H). **9n** ^{1}H NMR δ 1.95–2.20 (m), 2.82 (t), 3.23 (t), 3.92 (s, 3H, OCH_3), 4.74 (d, J= 2.2 Hz), 7.00–7.45 (13H, Ar). MS (CI) m/z 448 (M+H). **9o** ^{1}H NMR δ 1.01 (t, 3H, CH_3), 1.45 (sx, 2H, CH_2), 1.68 (q, 2H, CH_2), 1.88–2.10 (m), 2.62–2.71 (m, 2H, CH_2), 3.19 (t), 3.88 (s, 3H, OCH_3), 4.69 (d, J=2.2 Hz), 6.94–7.38 (13H, Ar). HRMS (FAB) calcd for $C_{29}H_{36}NO_2$ 428.2582, found 428.2590. **9p** ^{1}H NMR δ 1.85–2.12 (m), 2.73 (t), 3.21 (t), 3.92 (s, 3H, OCH_3), 4.68 (d, J=2.2 Hz), 6.80–7.39 (12H, Ar); MS (CI) m/z 408 (M+H); Anal. calcd for $C_{25}H_{23}F_2NO_2$: C, 73.69; H, 5.69; N, 3.44. Found: C, 73.45; H, 5.73; N, 3.70.

5-(4-Fluorophenyl)-4-pentenoic acid (12). A solution of 4-pentenoic acid **11** (5.0 g, 50 mmol), 4-fluoroiodobenzene **10** (8.7 mL, 75.4 mmol), palladium acetate (2.25 g, 10.0 mmol), triphenylphosphine (2.62 g, 10.0 mmol), potassium acetate (oven dried, 15.0 g, 153 mmol), anhydrous tetrabutylammonium chloride (20.8 g, 74.8 mmol) and DMF (40 mL) was heated to 80°C for 18 h. The solution was cooled, poured into a solution of 3 N NaOH (40 mL) and extracted with ethyl acetate. The organic phase was washed with 3 N NaOH (2×). The combined aqueous phases were acidified with 3 N HCl to pH 2, and extracted with ethyl acetate. The product was recrystallized partially with hexane yielding **12** (1.69 g, 17%) plus the mother liquors which were further processed below. Total yield: **12** (5.38 g, 56%); ^{1}H NMR δ 2.70 (m, 4H, CH_2), 6.25 (m, 1H, C=CH), 6.55 (d, J=15.9 Hz, 1H, C=CH–Ar), 7.09–7.44 (m, 4H, Ar).

5-(4-Fluorophenyl)-3-pentenoic acid (13). The mother liquors from **12** prepared above contained a mixture of both **12** and **13** (7.86 g, 1:1 mixture). Further purification

by HPLC afforded additional **12** (see above) and **13** (4.16 g, 43%); ^{1}H NMR δ 2.90 (m, 1H), 3.23 (d, 1H), 3.44 (m, 2H), 5.68–5.90 (m, 2H, HC═CH), 7.00–7.45 (m, 4H, Ar).

3-(3-Aryl-2-propynyl)-2-azetidinones 16m–16p. General procedure

A solution of 4-methoxybenzylidene-*N*-phenylanisidine (**6**, prepared from 4-methoxybenzaldhyde and aniline) (0.94 g, 4.44 mmol) in heptane (5 mL) and tributylamine (2.11 mL, 8.90 mmol) was heated to 50°C under argon. A solution of the appropriate acid chloride **24a**–**24d** (4.85 mmol) in toluene (10 mL) was added dropwise to the reaction solution over 0.5 h. The solution was stirred at 90°C for 18 h. Ethyl acetate was added and the solution washed successively with 1 N HCl (3×), H_2O, saturated NH_4Cl, dried with $MgSO_4$ and concentrated in vacuo. The crude product mixture was purified by flash chromatography, eluting with hexane–ethyl acetate (9:1). **16m** ^{1}H NMR δ 3.03 (dd, J=8.3, 17.4 Hz), 3.12 (dd, J=5.2, 18.4 Hz), 3.40 (ddd, J=2.1, 5.0, 7.7 Hz), 3.88 (s, 3H, OCH_3), 5.06 (d, J=2.2 Hz), 7.00–7.45 (14H); MS (CI) m/z 368; IR 1746 cm^{-1}. **16n** ^{1}H NMR δ 3.05 (dd, J=8.1, 17.2 Hz), 3.14 (dd, J=5.1, 17.4 Hz), 3.43 (ddd, J=2.4, 5.1, 7.8 Hz), 3.91 (s, 3H, OCH_3), 5.08 (d, J=2.2 Hz), 7.00–7.70 (18H, Ar); HRMS (FAB) calcd for $C_{31}H_{26}NO_2$ 444.1964, found 444.1963. **16o** ^{1}H NMR δ 0.98 (t, 3H, CH_3), 1.39 (sx, 2H, CH_2), 1.64 (q, 2H, CH_2), 2.64 (t, 2H, CH_2), 2.97 (dd, J=8.3, 17.3 Hz), 3.07 (dd, J=5.1, 17.4 Hz), 3.36 (ddd, J=2.3, 5.1, 7.8 Hz), 3.88 (s, 3H, OCH_3), 5.03 (d, J=2.2 Hz), 6.96–7.42 (13H, Ar); IR 1744 cm^{-1}. **16p** ^{1}H NMR δ 2.85 (dd, J=9.2, 16.9 Hz), 2.93 (dd, J=5.3, 17.5 Hz), 3.22 (ddd, J=2.3, 5.1, 7.7 Hz), 3.73 (s, 3H, OCH_3), 4.82 (d, J=2.2 Hz), 6.63–7.29 (12H); MS (EI) m/z 403.15; IR 1748 cm^{-1}. **17m** ^{1}H NMR δ 2.40 (dd, J=9, 12 Hz), 2.80 (dd, J=6, 12 Hz), 3.90 (s, 3H, OCH_3), 3.95 (dd, J=5.6, 9 Hz), 5.4 (d, J=5.6 Hz), 7–7.7 (14H, Ar); **18** ^{1}H NMR δ 2.96 (ddd, J=2.3, 9, 15 Hz), 3.1 (ddd, J=2.3, 6, 15 Hz), 3.27 (ddd, J=2.3, 5.8, 8.6 Hz), 3.89 (s, 3H, OCH_3), 4.76 (d, J=2.3 Hz), 5.80 (sx, J=7.1, 7.2, 12 Hz), 6.71 (d, J=11.6 Hz), 6.95–7.5 (14H, Ar).

Carboxylic esters 20, 21. General Procedure

To a mixture of the carboxylic acid (135 mmol) in anhydrous ethanol (150 mL) was added H_2SO_4 (18.1 M, 0.4 mL, 7.24 mmol) and the reaction heated at 50°C overnight. The solution was cooled and concentrated in vacuo to an oil. The residue was dissolved in ethyl acetate (75 mL), washed with 1 N $NaHCO_3$ (3×), dried with $MgSO_4$ and concentrated to afford product. **21** (74%); ^{1}H NMR δ 1.39 (t, 3H, CH_3), 2.06 (s, 1H), 2.60 (m, 4H, CH_2), 4.28 (q, 2H, CH_2).

Ethyl 5-phenyl-4-pentynoate (22a). To a solution of **20** (3.46 g, 15.7 mmol) in CH_2Cl_2 (20 mL) at 4°C was added 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (4.24 g, 15.7 mmol) followed by dropwise addition of triethylamine (16.5 mL, 118 mmol) over 1.5 h. The solution was then allowed to warm to rt and stirred for 16 h. The reaction was quenched with saturated NaCl and extracted with ethyl acetate (3×). The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo. The crude product mixture was purified by flash chromatography, eluting with hexane–ethyl acetate (10:1) to yield **22a** (1.22 g, 38%). ^{1}H NMR δ 1.38 (t, 3H, CH_3), 2.72 (m, 2H, H_3), 2.82 (m, 2H, H_2), 4.28 (q, 2H, CH_2), 7.37–7.50 (5H, Ar).

5-Arylpropynyl esters 22b–e. General procedure

A mixture of the appropriate aryl bromide (5.28 mmol), ester **21** (0.82 g, 6.48 mmol), bis (triphenylphosphine)palladium dichloride (74.3 mg, 0.10 mmol), cuprous iodide (23.0 mg, 0.12 mmol) and diethylamine (40 mL) was heated to 65°C under argon for 18 h. The excess diethylamine was removed in vacuo and the residue dissolved in diethyl ether. The insoluble material was removed by filtration. The filtrate was washed with 1 N HCl, H_2O (2×), dried with $MgSO_4$ and concentrated in vacuo. The crude product mixture was purified by flash chromatography, eluting with hexane–ethyl acetate (9:1). **22b** ^{1}H NMR δ 1.38 (t, 3H, CH_3), 2.72 (m, 2H, H_3), 2.85 (m, 2H, H_2), 4.28 (q, 2H, CH_2), 7.40–7.70 (9H, Ar). **22c** ^{1}H NMR δ 0.93 (t, 3H, CH_3), 1.30 (t, 3H, CH_3), 1.35 (p, 2H, CH_2), 1.56 (m, 2H, CH_2), 2.61 (m, 2H, CH_2), 2.50–2.75 (m, 4H), 4.15 (q, 2H, CH_2), 7.05–7.40 (4H, Ar). **22d** ^{1}H NMR δ 1.30 (t, 3H, CH_3), 2.63 (m, 2H, H_3), 2.75 (m, 2H, H_2), 4.17 (q, 2H, CH_2), 6.73–7.12 (3H, Ar). **22e** ^{1}H NMR δ 1.39 (t, 3H, CH_3), 2.75 (m, 2H, H_3), 2.87 (m, 2H, H_2), 4.30 (q, 2H, CH_2), 7.30–8.73 (4H, Ar).

5-Arylpentynyl acids 23a–e. General procedure

A solution of the carboxylic ester (5.0 mmol), dioxane (20 mL) and sodium hydroxide (3 M, 10 mL) was stirred at room temperature for 3 h. Ethyl acetate was added, the solution acidified with 1 N HCl, the organic layer separated and washed with H_2O. The organic phase was dried with $MgSO_4$ and concentrated in vacuo. **23a** ^{1}H NMR δ 2.81 (m, 4H, CH_2), 7.34–7.50 (5H, Ar). **23b** ^{1}H NMR δ 2.85 (m, 4H, CH_2), 7.40–7.69 (9H, Ar). **23c** ^{1}H NMR δ 1.00 (t, 3H, CH_3), 1.40 (p, 2H, CH_2), 1.64 (m, 2H, CH_2), 2.66 (m, 2H, CH_2), 2.78 (m, 4H, CH_2), 7.15–7.40 (4H, Ar). **23d** ^{1}H NMR δ 2.79 (m, 4H, CH_2), 6.78–6.97 (3H, Ar). **23e** ^{1}H NMR δ 2.70 (m, 4H, CH_2), 7.45–8.61 (3H, Ar).

Acid chlorides 5, 24a–d. General procedure

A solution of the carboxylic acid (0.10 mol) in CH_2Cl_2 (50 mL) was stirred under argon at room temperature and oxalyl chloride (9.51 mL, 0.11 mol) added dropwise over 15 min. The solution was either heated to 40°C for 2 h or stirred at room temperature (for volatile acid chlorides e.g. **5**) for 4 h. The reaction mixture was concentrated in vacuo, additional CH_2Cl_2 (10 mL) added and re-concentrated to an oil. Assessment of the product purity was made by ^{1}H NMR. **5** (99% yield); ^{1}H NMR δ 2.61 (t, 2H, CH_2), 3.15 (t, 2H, CH_2), 5.12 (m, 2H, C═CH_2), 5.94 (m, 1H, C═CH). **24a** ^{1}H NMR δ 2.94 (t, J=7.1 Hz), 2H), 3.33 (t, J=7.0 Hz), 2H), 7.38–7.58 (5H, Ar). **24b** ^{1}H NMR δ 3.31 (t, J=7.1 Hz, 2H), 2.90 (t, J=7.2 Hz, 2H), 7.42–7.78 (9H, Ar). **24c** ^{1}H NMR δ 1.00 (t, 3H, CH_3), 1.41 (p, 2H, CH_2), 1.65 (m, 2H, CH_2), 2.60 (t, J=7.2 Hz), 2H, CH2), 2.66 (m, 2H, CH2); 3.28 (t,

2H, J=7.1 Hz, CH2), 7.19–7.40 (4H, Ar). **24d** ^{1}H NMR δ 2.87 (t, 2H, J=7.0 Hz), 3.30 (t, 2H, J=7.1 Hz), 6.80–7.00 (3H, Ar).

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