Synthesis and evaluation of photolabile sulfonamides as potential reagents for rapid photorelease of neuroactive amines

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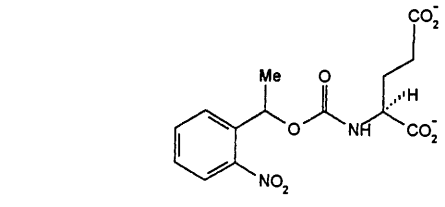
The synthesis is described of photolabile sulfonamide derivatives of amino acids, most of which incorporate a monophosphate ester to promote water solubility. Points of particular synthetic interest include observations on the reduction of diaryl ketones and diarylmethanols, *e.g.* compounds 7 and 9, with $NaBH_4$–TFA, and a convenient, effective sequence for conversion of bromoarenes into arenesulfonyl halides, *e.g.* 10 ⟶ 13. Photolysis of the glycine derivative 18a in aqueous solution released free glycine in poor yield, except in the presence of a very large excess of ascorbate as a reducing agent. The likely cause is discussed in terms of a decarboxylation side-reaction occurring during the overall progress of the photocleavage.

Rapid release of biologically active compounds, for example adenosine triphosphate, inositol trisphosphate, glucose or calcium ions by photolysis of protected derivatives is an established technique for investigation of fast biological processes such as muscle contraction or ion channel activation.[1–3] The reagents used in these experiments have become known amongst biological researchers as caged compounds[4] and are based almost exclusively on the photolabile 2-nitrobenzyl group and substituted variants thereof, which remain attached to the biomolecule and mask its effect until cleaved from it by a pulse of near-UV light.

The process of synaptic transmission, by which nerve cells pass electrical excitation from one cell to another, is mediated by chemical neurotransmitters which are released from one cell and diffuse across the synaptic cleft to stimulate the connecting cell. In mammalian brain, L-glutamate and γ-aminobutyrate (GABA) are the principal excitatory and inhibitory neurotransmitters respectively. Photorelease from caged neurotransmitters would be a valuable tool in studies of synaptic transmission but such experiments have been hindered by a lack of suitable compounds, which must satisfy a number of criteria, including solubility and stability in aqueous media, fast and efficient photolysis at neutral pH upon brief (ns–ms) irradiation with light of wavelength > 300 nm, and biological inertness prior to photolysis.

We have previously described the *N*-carbamoylglutamate **1** as a caged glutamate reagent but were able to achieve sufficiently rapid glutamate release only because the particular biological system used (the giant synapse of the squid) is able to tolerate low pH, which accelerates the rate-determining step of the sequence of dark reactions subsequent to the light-induced event.[5] Hess and co-workers[6–8] have described a number of compounds including caged forms of carbamoylcholine,[7] glycine[8a] and glutamate[8b] and have investigated biological responses. Gee *et al.*[9] have made a number of photolabile benzoin esters but described no biology. Our own results with related benzoin esters[1] suggest that these latter compounds are too prone to hydrolysis to be useful in aqueous solution.

Despite further considerable effort, in the course of which we have made numerous 2-nitrobenzyl derivatives of glutamate (esters, carbamates, *N*-alkyl),[1] we have not succeeded in devising further useful reagents. We have therefore been interested to examine alternative photolabile groups. The single electron transfer (SET) photochemistry of arylsulfonamides **2** (Scheme 1) developed by Yonemitsu and co-workers[10] appeared particularly attractive, since the reagents would be stable to hydrolysis, while the absence of the positive charge



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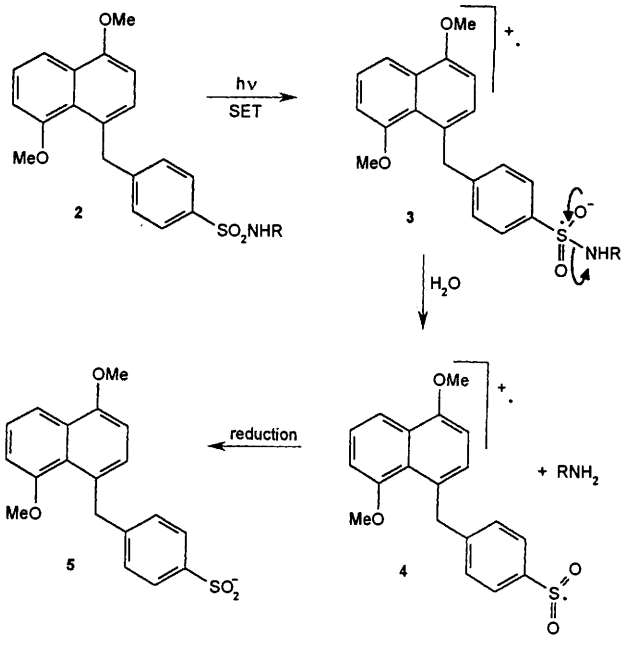


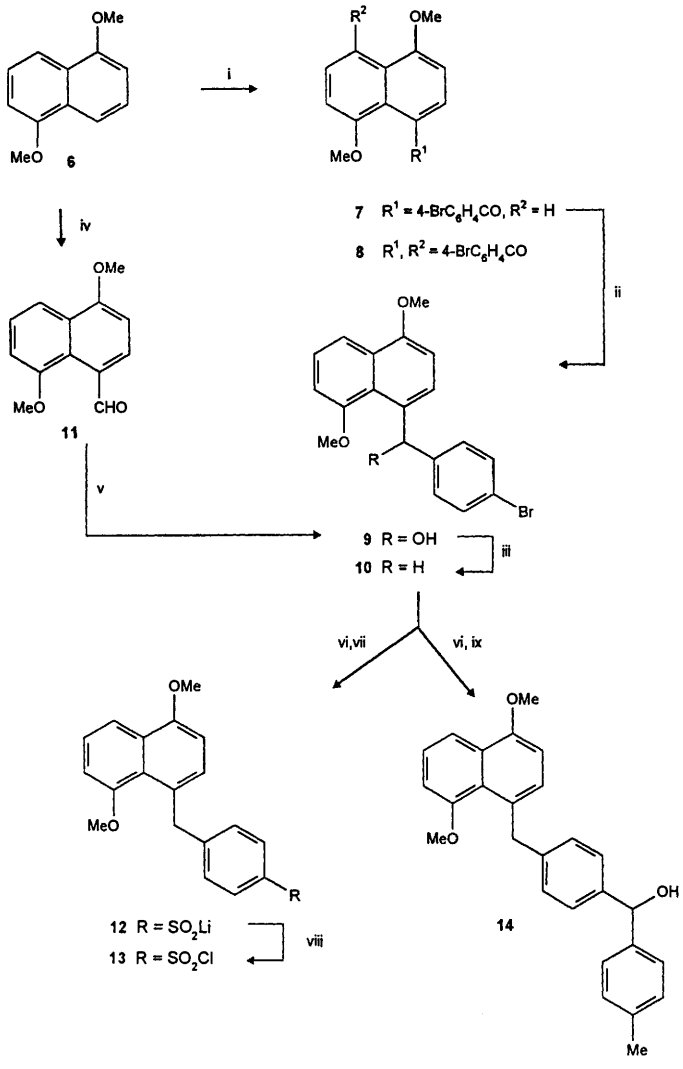
Scheme 1 Proposed[10] reaction mechanism for photochemical cleavage of arenesulfonamide **2**. Reducing agents which have been used include $NaBH_4$, $BH_3{\cdot}NH_3$, hydrazine and ascorbic acid.

normally present on an amine at neutral pH could be expected to eliminate neurotransmitter activity of the derivatised amines. The original intermolecular version of the sulfonamide photocleavage[10a] utilised a separate electron donor such as 1,4-dimethoxybenzene or 1,5-dimethoxynaphthalene, and has been successfully applied in a variety of synthetic routes.[11] The 2-naphthoxide anion has been investigated as an alternative electron donor.[12] However, the intramolecular version[10b] of the reaction shown in Scheme 1 has not yet been applied and

indeed full synthetic details for preparation of the necessary reagents have not been published. Furthermore the kinetics of amine release are unknown, although the initial electron transfer occurs on the nanosecond time scale. The present paper describes in full the synthesis of these compounds and related, more water-soluble analogues and also gives the results of photochemical studies. The efficiency of photorelease of amino acids has been found to be unexpectedly low, apparently because of a decarboxylative side reaction during photolysis, and a hypothesis to account for this is described, together with indications for possible future directions.

Results and discussion

Our first objective was to prepare the bromide **10** (Scheme 2),



Scheme 2 *Reagents:* i, $4\text{-}BrC_6H_4COCl\text{–}AlCl_3$; ii, $NaBH_4$–EtOH–THF; iii, $NaBH_4$–HOAc–TFA; iv, DMF–$POCl_3$; v, $4\text{-}BrC_6H_4Li$–TMEDA–Et_2O; vi, BuLi–TMEDA–Et_2O; vii, SO_2; viii, *N*-chlorosuccinimide; ix, $4\text{-}MeC_6H_4CHO$

which was the missing compound in the chemistry described by Yonemitsu and co-workers.[10] 1,5-Dimethoxynaphthalene **6** readily underwent Friedel–Crafts acylation with one equivalent of 4-bromobenzoyl chloride in nitrobenzene[13] to give the ketone **7**. If an excess of 4-bromobenzoyl chloride was present, a second acylation took place to give the symmetrical diketone **8**. Although diaryl ketones have been reported[14] to undergo almost quantitative reduction with sodium boranuide (sodium borohydride) in trifluoroacetic acid (TFA), reduction of ketone **7** to the diarylmethane **10** was unexpectedly difficult. Addition of the ketone to $NaBH_4$–TFA instantly gave a deep red solution which remained stable for days despite repeated additions of sodium boranuide. Evidently the protonated ketone (*i.e.* an oxydiarylcarbocation) was so highly stabilised in this case that it resisted reduction. For apparently similar reasons the ketone **7** was recovered unchanged from an attempt to form a thioketal by treatment with 1,2-disulfanylethane and boron trifluoride. With this rationale in mind, the ketone **7** was conventionally reduced with $NaBH_4$ to the alcohol **9**. This reduction proceeded smoothly, no doubt because the more reactive boranuide ion itself was the attacking species, rather than tris(trifluoroacetoxy)boranuide.[14] Once the diarylmethanol **9** was obtained, it could be reduced by sodium boranuide–TFA.[15] Again a deeply coloured diarylcarbocation was formed when the alcohol **9** contacted the acidic solvent but since it lacked additional α-oxy stabilisation, the cation could be reduced to the diarylmethane **10**. Nevertheless this reduction step was capricious, requiring large volumes of TFA and very slow addition of the alcohol. Unless these conditions were employed the product was often very difficult to purify, probably because of contamination with side-products resulting from alkylation of the required compound **10** by the intermediate carbocation. However, when the solvent was changed to acetic acid–TFA (9:1), the diarylmethane **10** was readily obtained in pure form. Interestingly, only a fleeting colour developed in this solvent when the alcohol **9** was added, which suggests that the intermediate carbocation was present only transiently and at low concentration. Since the alcohol **9** was found to be a necessary intermediate, the overall convenience of the sequence was improved by treatment of 4,8-dimethoxy-1-naphthaldehyde **11** with 4-bromophenyllithium,[16] which directly gave the required alcohol.

It would be advantageous if the cheaper and more convenient reduction procedure described above were applicable to diaryl ketones and/or diarylmethanols with less strongly electron-donating substituents. However neither benzophenone nor benzhydrol was reduced under the modified conditions, although we note the recently described reduction of a steroidal α,β-unsaturated ketone in TFA–HOAc–MeCN (1:1:1).[17] It is clear that the reaction conditions can advantageously be tuned to the properties of particular substrates.

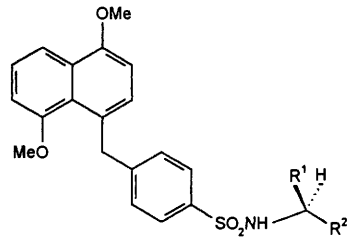
Conversion of the bromoarene **10** into the sulfonyl chloride **13** has been reported[18] to proceed in excellent yield *via* initial halogen–lithium exchange and treatment with sulfur dioxide, followed by chlorination of the intermediate lithium sulfinate **12** with sulfuryl chloride. In our hands neither step was satisfactory and the overall yield of sulfonyl chloride **13** averaged *ca.* 35%. In model experiments which aimed first to improve the halogenation of the sulfinate salt, almost quantitative yields of toluene-4-sulfonyl chloride were obtained by treatment of lithium toluene-4-sulfinate with *N*-chlorosuccinimide in a two-phase system of ethyl acetate and aqueous sodium phosphate buffer, pH 6.0. When *N*-bromosuccinimide was used instead, a similarly clean conversion into toluene-4-sulfonyl bromide was achieved, and the method appears to provide a convenient general means to convert sulfinates into the corresponding sulfonyl halides. Application of the procedure to the sulfinate salt **12** cleanly gave the sulfonyl chloride **13** but the overall yield was still poor because a substantial amount of the starting bromoarene **10** remained and it was apparent that the initial halogen–lithium exchange was incomplete. This was confirmed in model experiments in which the bromide **10** was treated with a 20% excess of butyllithium followed by a quench with 4-tolualdehyde, which provided an expedient means to obtain an easily isolated product for purposes of quantification and characterisation. Under these conditions (4 °C, diethyl ether solvent) the product alcohol **14** and starting material **10** were found to be present in approximately equal proportions. Increased contact time of butyllithium with bromide **10** did not improve the ratio, while a larger excess of butyllithium resulted in formation of other

unidentified products. However, when the metallation was performed with a 20% excess of 1:1 BuLi–*N*,*N*,*N*′,*N*′-tetramethylethylenediamine[19] (TMEDA) the alcohol **14** was obtained in good yield.

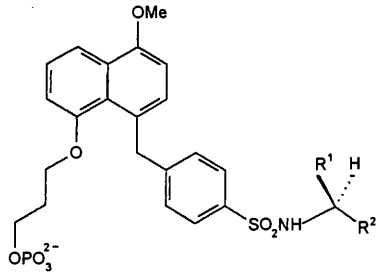
Despite this pleasing result, when the organolithium reagent obtained under these conditions was added to a solution of sulfur dioxide, the resultant sulfinate salt **12** was contaminated with a substance which appeared to be a TMEDA–SO_2 complex. Upon treatment of the crude product mixture with 1 equivalent of *N*-chlorosuccinimide as described above, very little of the sulfonyl chloride **13** was obtained and a large amount of material remained which was insoluble in either the organic or aqueous phase. Evidently the complexed SO_2 was an effective scavenger of the *N*-chlorosuccinimide and consumed the reagent in preference to its oxidation of the sulfinate salt. However, upon addition of a further two equivalents of *N*-chlorosuccinimide to the two-phase oxidation mixture, the sulfonyl chloride **13** could be isolated from the organic phase in *ca.* 54% overall yield (*cf.* 71% yield for the related sulfonyl chloride **26** described below), while all the insoluble material initially present had dissolved. The procedure described here provides a reproducible and satisfactory means to effect the conversion from the bromoarene **10** into the sulfonyl chloride **13**. Some questions nevertheless remain, particularly the resistance of the bromoarene **10** to halogen–lithium exchange but we have not addressed this matter here.

With an adequate route to the sulfonyl chloride **13** established, preparation of the required *N*-sulfonyl amino acids was readily achieved. Methyl glycinate and di-*tert*-butyl glutamate gave the sulfonamide esters **15** and **16** respectively, and the latter compound was deprotected with TFA to yield the derivatised glutamate salt **17**. As could be expected this compound was markedly hydrophobic and this property was highlighted in the ^1H NMR spectrum of its sodium salt, which when recorded in D_2O solution showed very broad signals, which displayed none of the expected fine structure. This was consistent with aggregation, which would be expected to be diminished or abolished by the addition of a water-miscible organic co-solvent. This was confirmed when the spectrum was recorded in D_2O–CD_3OD (1:1) and showed sharp, well-defined signals. Because of this behaviour, it seemed likely that the compound would have an undesired tendency to partition into lipid membranes of tissue samples. Since preliminary photolysis studies (monitored by disappearance of the starting compound) were encouraging, we decided to modify the chemistry so as to obtain better hydrophilic properties prior to detailed study of the photocleavage reaction. The modification shown in the general structure **18** was expected to be suitable, since the phosphate group would aid water-solubility but its position remote from the chromophore would be anticipated not to disturb the photochemistry.

The aldehyde **11** was selectively demethylated with boron tribromide as described[20] and the product phenol **19** was converted into its allyl ether **20** (Scheme 3). The sequence described above for preparation of compound **10** then smoothly gave the alcohol **21** and diarylmethane **22**. Attempted lithium–halogen exchange between compound **22** and butyllithium consistently gave ill-defined products, which appeared to derive from reactivity of the allyloxy group. Removal of the unsaturation in the side chain at this stage of the synthesis therefore seemed desirable and was consistent with the proposed functionality in the target product. Hydroboration of compound **22** followed by peroxide oxidation gave a mixture of the secondary and primary alcohols **23** and **24** (ratio *ca.* 1:5.5) but disiamylborane[21] led solely to the primary alcohol, which was protected under phase transfer conditions[22] as its benzyl ether **25**. Conversion of this compound into the sulfonyl chloride **26** was smoothly achieved using the methods described above. It was notable in initial experiments that treatment of the bromoarene **25** with butyllithium alone gave an intense

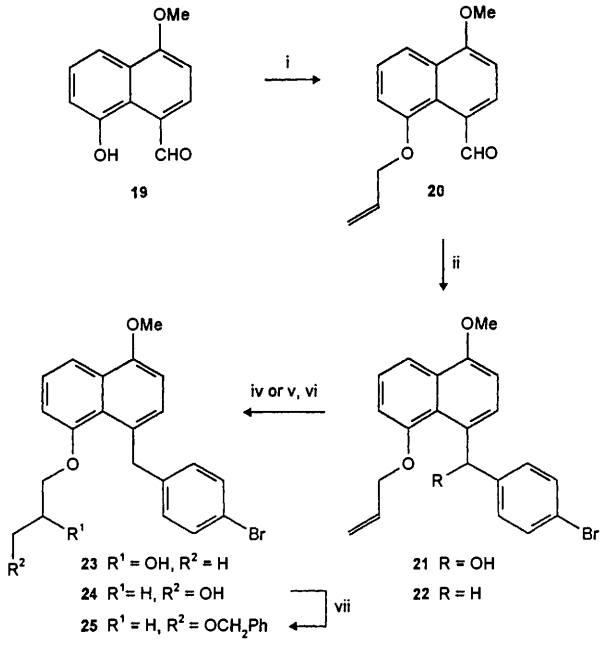


15 $R^1 = H$, $R^2 = CO_2Me$
16 $R^1 = CH_2CH_2CO_2Bu^t$, $R^2 = CO_2Bu^t$
17 $R^1 = CH_2CH_2CO_2^-$, $R^2 = CO_2^-$



18a $R^1 = H$, $R^2 = CO_2^-$
18b $R^1 = CH_2CH_2CO_2^-$, $R^2 = CO_2^-$
18c $R^1 = H$, $R^2 = CH_2CO_2^-$

blood-red colour which appeared to be indefinitely stable. When the 1:1 butyllithium–TMEDA reagent was used, only a faint transient colour developed. As indicated above, the nature of the metallation reaction for these substrates may be worthy of further study.



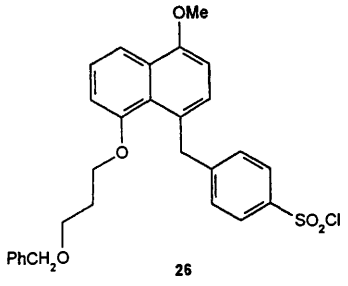
Scheme 3 *Reagents:* i, allyl bromide–K_2CO_3–acetone; ii, 4-BrC_6H_4Li–TMEDA–Et_2O; iii, $NaBH_4$–HOAc–TFA; iv, BH_3·Me_2S–THF; v, disiamylborane–THF; vi, NaOH–H_2O_2; vii, $PhCH_2Br$–NaOH–Bu_4NOH

The sulfonyl chloride **26** reacted smoothly with the methyl esters of glycine, glutamic acid and β-alanine to give the sulfonamides **27a–c**. Attempted catalytic hydrogenolysis of the benzyl protecting group in these compounds was accompanied by partial hydrogenation of the naphthalene nucleus, but sodium iodide–boron trifluoride[23] readily gave the required alcohols **28a–c**. Phosphorylation of the alcohols by sequential treatment with bis(2-cyanoethyl) diisopropylphosphorami-

Table 1 Theoretical and actual product yields for photolysis of sulfonamides

Entry	Compound[a]	Solvent	Co-reagent	[Co-reagent]/mM	Free amino acid formation		
					Theoretical yield (%)	Actual yield (%)	Actual yield / Theoretical yield
1	**18a**	Buffer[b]	None		56.2	3.5	0.06
2			Ascorbate	2	61.1	5.5	0.09
3				10	66.3	10.5	0.16
4				90	45.4	30	0.66
5			Dithiothreitol	1	62.6	6.0	0.09
6				10	61.8	5.3	0.08
7			Acetate	180	57.5	3.8	0.07
8			Phenylacetate	180	38.2	1.4	0.04
9	**18a**	Buffer[b]–MeOH (1:2)	None		74.6	Trace	< 0.02
10			Ascorbate	10	64.3	35.1	0.55
11			Ascorbate	100	39.0	30.6	0.78
12	**15**	Buffer[b]–MeOH (1:2)	None		91.7	40.0	0.44
13			Ascorbate	10	85.8	53.2	0.62
14			Ascorbate	100	89.8	55.1	0.61
15	**18c**	Buffer[b]	None		43.0	10.4	0.24
16			Ascorbate	10	36.2	22.1	0.61

[a] Solutions for irradiation contained the various sulfonamides at *ca.* 0.5 mM concentration. The exact concentrations were determined by UV spectroscopy. [b] 10 mM Na phosphate, pH 7.0.



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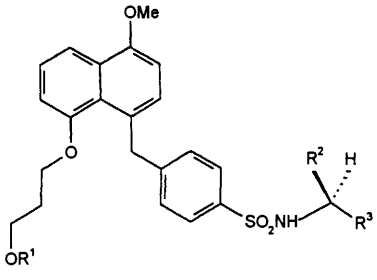

27a $R^1 = CH_2Ph$, $R^2 = H$, $R^3 = CO_2Me$
27b $R^1 = CH_2Ph$, $R^2 = CH_2CH_2CO_2Me$, $R^3 = CO_2Me$
27c $R^1 = CH_2Ph$, $R^2 = H$, $R^3 = CH_2CO_2Me$
28a R^1, $R^2 = H$, $R^3 = CO_2Me$
28b $R^1 = H$, $R^2 = CH_2CH_2CO_2Me$, $R^3 = CO_2Me$
28c R^1, $R^2 = H$, $R^3 = CH_2CO_2Me$
29a $R^1 = P(O)(CH_2CH_2CN)_2$, $R^2 = H$, $R^3 = CO_2Me$
29b $R^1 = P(O)(CH_2CH_2CN)_2$, $R^2 = CH_2CH_2CO_2Me$, $R^3 = CO_2Me$
29c $R^1 = P(O)(CH_2CH_2CN)_2$, $R^2 = H$, $R^3 = CH_2CO_2Me$

dite–1*H*-tetrazole and *m*-chloroperbenzoic acid (MCPBA)[24] gave the phosphotriesters **29a–c**. These were treated with alkali to effect concurrent conversion into the required monophosphates and hydrolysis of the methyl ester groups, thereby yielding the desired compounds **18a–c**. The glutamate and β-alanine derivatives **29b** and **29c** required more prolonged alkaline treatment than for the glycine derivative **29a** to effect complete ester cleavage, since the ester groups remote from the α-sulfonamide were, as expected, more resistant to hydrolysis.

The preparation of compounds **18a–c** completed the synthetic phase of this work. The objective of improved water solubility appeared to have been satisfied since ^1H NMR spectra of each of the compounds in D_2O solution showed no evidence of line broadening arising from aggregation. We next turned our attention to probing the photocleavage of these compounds. Until this point, we had demonstrated only qualitatively for the initially synthesised compound **17** that irradiation (300–360 nm light) caused efficient photodisappearance, and it was necessary to establish in quantitative terms the efficiency of photorelease of the free amino acid products. The latter parameter is centrally important to the utility of caged compounds in biological experiments. Table 1 summarises the results of a number of experiments, discussed below, which were based principally on the glycine derivative **18a**. Other data (not shown) indicated that the conclusions are applicable also to the glutamate derivative **18b**, and by extension are presumed to be valid for all α-amino acids. The experimental protocol involved irradiation of solutions of known concentration for a time sufficient to effect *ca.* 50% photolysis. The extent of reaction was monitored by reversed-phase HPLC and for each of the entries in Table 1, this value was taken to be the theoretical yield of free amino acid. The actual yield was determined by quantitative amino acid analysis, using ninhydrin detection.

For irradiation of compound **18a** in the absence of a reducing agent (entry 1), the yield of glycine was only *ca.* 6% of the theoretical value, while in the presence of increasing amounts of ascorbate (entries 2–4) the yield rose steadily to reach 66% of the theoretical when the reductant was present in 180-fold excess. Dithiothreitol, which like other thiols is commonly used as a reducing agent in photolyses of conventional 2-nitrobenzyl caged compounds,[4] was ineffective as a reductant in photolysis of compound **18a** (entries 4 and 5). The Yonemitsu group[10] had used a variety of reducing agents including sodium boranuide, ammonia–borane, hydrazine and ascorbate (all typically in 4–10 fold molar excess) but since our focus was on potential application in living systems, we did not examine the more toxic of these reductants.

This set of results suggested that an unexpected side reaction was causing destruction of the photoreleased glycine unless an overwhelming excess of ascorbate was present, and to gain some insight on this process we used the technique of flash photolysis coupled with fast FTIR spectroscopy. We have recently described the application of this method to study the photochemistry of another caged compound, the P^3-1-(2-nitrophenyl)ethyl ester of adenosine triphosphate.[25] Difference spectra before and after photolysis, with or without the presence of 10 mM ascorbate, revealed *inter alia* an intense

negative band at 1598 cm^{-1}, which was suggestive of disappearance of a carboxylate group as a consequence of the photoreaction. A sharp positive band at 2342 cm^{-1} was consistent with formation of carbon dioxide.[26] This result can be rationalised on the premise that one or both radical sites in the intermediate **4** (Scheme 1) may perform a one-electron oxidation of the carboxylate group of the photoreleased glycine, generating a carboxyl radical which subsequently undergoes decarboxylation and further transformation to products as yet unidentified. In an attempt to intercept this process by providing an alternative carboxylate target, photolyses of compound **18a** were performed in the presence of 360-fold molar excesses of acetate or phenylacetate (entries 7 and 8 respectively) but the yield of glycine was unaffected, which suggests that the decarboxylation may occur largely within a solvent cage. Precedents exist for related photodecarboxylations, mediated for example by 1-methoxynaphthalene,[27a] acridine,[27b] benzophenone and quinones,[28] or titanium dioxide.[29]

If the above proposal is taken as a working hypothesis it is possible to make predictions, of which the first is that a glycine ester such as **15** should undergo much more efficient formation of the photoproduct since no competing decarboxylation is possible. Because of its insolubility in water, compound **15** was photolysed in a buffer–MeOH mixture (1:2 v/v) and for comparison the photolysis of compound **18a** was repeated in the same solvent. Following photolysis, the products from compound **15** were saponified to enable quantification of the released product as glycine. Control experiments with authentic methyl glycinate confirmed that the ester was quantitatively hydrolysed under our experimental conditions. Hydrolysis also facilitated HPLC quantification of the non-photolysed ester **15** as its related carboxylate.

We were gratified to find that compound **15**, even in the absence of an added reducing agent, produced the expected photoproduct in 44% of the theoretical yield (entry 12), which was raised to 62% in the presence of as little as 10 mM ascorbate (entry 13). The latter value approaches the lower end of the range (77–91%) reported by the Yonemitsu group for a variety of simple amines.[10b] The comparable results for photolysis of compound **18a** (entries 9–11) show that the reaction was vanishingly inefficient in the absence of ascorbate, although a low concentration of ascorbate was much more effective than in purely aqueous solutions (*cf.* entries 3 and 10).

The second but more speculative prediction of the hypothetical decarboxylation was that an increase in the length of the chain linking the carboxylate and photolabile sulfonamide groups might disfavour the decarboxylation process. Entries 15 and 16 show the results for the β-alanine derivative **18c** and for photolysis in the absence of a reducing agent reveal a 4-fold increase over the glycine derivative **18a** in the yield of amino acid. It may be relevant that the Yonemitsu group reported a good yield for photodeprotection of some N^{ε}-tosyllysine derivatives in the presence of 1,5-dimethoxynaphthalene or a water-soluble analogue thereof.[10a] In these compounds the sulfonamide is still further distal to the carboxylate group, although given the obvious differences between this intermolecular photoreaction and the present intramolecular version, the comparison should be treated with caution.

Thus the decarboxylation hypothesis appears to remain credible. It raises the possibility that a carboxylate group suitably located on the naphthylmethylphenylsulfonyl assembly might be able effectively to compete with the released amino acid as an electron donor and hence rescue the present strategy. To identify an appropriate locus for such a group will require new synthetic endeavours and such experiments are currently in hand. Because of the decarboxylation reaction, we have not attempted with this series of compounds to determine the rate of liberation of free amino acid following flash photolysis. Such measurements will become appropriate only if efficient photorelease can be achieved.

Experimental

Microanalyses were carried out by MEDAC Ltd., Brunel University, Uxbridge. Amino acid analyses were performed by the Advanced Biotechnology Centre, Charing Cross Hospital Medical School, London using an LKB-Pharmacia 4151 Alpha Plus analyser. NMR spectra were determined on JEOL FX90Q, Bruker AM400 and Varian Unity 600 spectrometers with tetramethylsilane as internal standard for solutions in deuteriochloroform unless otherwise stated. *J* Values are given in Hz. Infrared spectra were determined for Nujol mulls. FAB mass spectra were run at low resolution in negative ion mode on a VG 70-250SE instrument, and positive ion spectra at high resolution were obtained on a VG ZAB-SE instrument. Merck 9385 silica gel was used for flash chromatography. Thin layer chromatography was performed on Whatman MK6F silica gel plates. Light petroleum describes the fraction boiling between 40–60 °C. Organic extracts were dried over Na_2SO_4 and solvents were evaporated under reduced pressure. Sodium phosphate buffer solutions were prepared from $NaH_2PO_4 \cdot 2H_2O$ at the specified molarities in water and adjusted to the required pH value with 2 M NaOH.

Anion-exchange chromatography was performed on a column of DEAE–cellulose (2.5 × 40 cm). Triethylammonium bicarbonate (TEAB) buffer for elution was prepared by bubbling CO_2 into an ice-cold 1 M solution of triethylamine in water until the pH stabilised at ~7.4. Pooled column fractions were evaporated at ~1 mmHg and freed from buffer salts by repeated evaporation with methanol. For NMR spectroscopy, triethylammonium salts were converted into sodium salts by treatment with Dowex 50 (Na form).

1,5-Dimethoxynaphthalene was prepared by methylation of 1,5-dihydroxynaphthalene with Me_2SO_4–K_2CO_3 in acetone and had mp 181–183 °C (lit.,[30] 183–184 °C). This procedure gave a much cleaner product than that described[30] in aqueous alkaline solution. Bis(2-cyanoethyl) diisopropylphosphoramidite was prepared and purified by published procedures.[31–33]

1-(4-Bromobenzoyl)-4,8-dimethoxynaphthalene 7 and 1,5-bis-(4-bromobenzoyl)-4,8-dimethoxynaphthalene 8

A mixture of 1,5-dimethoxynaphthalene (1 g, 5.3 mmol) and dry nitrobenzene (14 ml) was warmed until the solid dissolved, then cooled in an ice-bath. 4-Bromobenzoyl chloride (1.25 g, 5.7 mmol) was added, followed by portionwise addition of powdered $AlCl_3$ (0.76 g, 5.7 mmol) over 5 min. The mixture was allowed to warm to room temp. and kept for 24 h, then poured onto a mixture of ice and conc. hydrochloric acid. The nitrobenzene was removed by steam distillation and the residue was extracted with ethyl acetate. The organic extract was dried and evaporated, and the residue was triturated with ether to give a solid (1.8 g) which contained the monoketone **7** and diketone **8** (91:9 by ^1H NMR spectroscopy). A portion was flash chromatographed (EtOAc–light petroleum 15:85) to give a less polar and a more polar fraction. The less polar fraction was crystallised from aq. acetone to give the *monoketone* **7** as pale yellow prisms, mp 168–169 °C (Found: C, 61.7; H, 3.9. $C_{19}H_{15}BrO_3$ requires C, 61.5; H, 4.1%); λ_{max}(EtOH)/nm 225 (ε/M^{-1} cm^{-1} 52 000), 257 (20 200), 296 (9800), 309 (8300) and 325 (5900); ν_{max}/cm^{-1} 1665, 1590, 1510, 1330, 1245, 1075, 1067, 885, 810 and 760; δ_H(90 MHz) 7.93 (1 H, dd, *J* 8.3, 0.9, naphthalene-5 H), 7.25–7.53 (6 H, m, Ar-H), 6.74–6.91 (2 H, m, Ar-H), 4.03 (3 H, s, OMe) and 3.46 (3 H, s, OMe).

The more polar fraction was crystallised from aq. acetone to give the *diketone* **8** as plates, mp 255–256 °C (Found: C, 56.1; H, 3.1. $C_{26}H_{18}Br_2O_4$ requires C, 56.3; H, 3.3%); λ_{max}(EtOH)/nm 257 (ε/M^{-1} cm^{-1} 39 000), 302 (11 300) and 313 (11 100); ν_{max}/cm^{-1} 1665, 1585, 1515, 1320, 1250, 1070, 980, 830 and 770;

δ_H(90 MHz) 7.52 (8 H, s, ArH), 7.35 (2 H, d, *J* 7.9, naphthalene-2, 6 H), 6.82 (2 H, d, naphthalene-3, 7 H) and 3.51 (6 H, s, OMe).

When the reaction was performed with exactly stoichiometric quantities of 4-bromobenzoyl chloride and $AlCl_3$ the monoketone **7** was obtained without chromatography in 88% yield.

1-(4-Bromo-α-hydroxybenzyl)-4,8-dimethoxynaphthalene 9

Method A. A solution of ketone **7** (3.80 g) in THF (45 ml) and ethanol (50 ml) was stirred at 5 °C and $NaBH_4$ (4.0 g) was added. The solution was allowed to warm to room temp. and stirred for 2 h, then treated with additional $NaBH_4$ (2.0 g) and stirred for a further 1.5 h, when TLC showed the reduction to be complete. The solution was diluted with ether and the ether layer was washed with water and brine, dried and evaporated. The residue was crystallised from EtOAc–light petroleum to give the *alcohol* **9** as prisms (2.70 g, 71%), mp 124–126 °C (Found: C, 61.2; H, 4.4. $C_{19}H_{17}BrO_3$ requires C, 61.1; H, 4.6%); λ_{max}(EtOH)/nm 226 (ε/M^{-1} cm^{-1} 62 000), 290 (8500), 300 (11 100), 317 (8600) and 331 (6600); ν_{max}/cm^{-1} 3500, 1605, 1515, 1065, 1010 and 750; δ_H(90 MHz) 8.06 (1 H, d, *J* 9, naphthalene-5 H), 6.76–7.52 (8 H, m, ArH), 6.29 (1 H, d collapsed to s on D_2O exchange, *J* 8, C*H*OH), 4.00 (3 H, s, OMe) and 3.59 (3 H, s, OMe).

Method B. A solution of 1,4-dibromobenzene (7.08 g, 30 mmol) in dry ether (100 ml) was cooled under nitrogen in an ice-bath and treated with butyllithium (1.6 M in hexane; 18.75 ml, 30 mmol) then heated under reflux for 0.5 h. The mixture was cooled to 0 °C in an ice-bath and treated with 4,8-dimethoxy-1-naphthaldehyde **11**[20] (4.325 g, 20 mmol) in ether (50 ml). The solution was then stirred for 1 h at room temp. Water (100 ml) was added and the aqueous phase was separated and extracted with more ether. The combined organic phases were washed with aq. $NaHCO_3$, dried and evaporated. Trituration of the residue with ether gave a solid which was filtered and recrystallised from ether to give the alcohol **9** as a white fine solid (6.95 g, 93%), mp 124–126 °C.

1-(4-Bromobenzyl)-4,8-dimethoxynaphthalene 10

Sodium boranuide pellets (3.78 g, 0.1 mol) were added slowly under nitrogen to a stirred mixture of glacial acetic acid (67.5 ml) and trifluoroacetic acid (7.5 ml) cooled to −15 °C. A solution of the alcohol **9** (4.85 g, 13 mmol) in dichloromethane (25 ml) was added dropwise over 0.5 h and the mixture was stirred at room temp. for further 2 h. The solvents were removed under reduced pressure and water (100 ml) was added slowly with ice cooling. The aqueous solution was basified to pH 14 by addition of NaOH pellets and extracted with ether. The combined organic phases were washed with water and brine, dried and evaporated to dryness. The residue was recrystallised (EtOAc–light petroleum) to afford the *bromoarene* **10** (4.31 g, 93%), mp 116–118 °C. An analytical sample crystallised from aq. acetone as fine needles, mp 119–120 °C (Found: C, 64.1; H, 4.7. $C_{19}H_{17}BrO_2$ requires C, 63.9; H, 4.8%); ν_{max}/cm^{-1} 1600, 1515, 1410, 1385, 1275, 1260, 1230, 1075, 1015, 795, 765 and 740; δ_H(90 MHz) 7.90 (1 H, dd, *J* 0.9, 8.4, naphthalene-5 H), 6.64–7.41 (8 H, m, ArH), 4.51 (2 H, s, ArCH_2), 3.97 (3 H, s, OMe) and 3.62 (3 H, s, OMe).

4-[(4,8-Dimethoxy-1-naphthyl)methyl]benzenesulfonyl chloride 13

A solution of the bromoarene **10** (357 mg, 1 mmol) in dry ether (25 ml) was cooled in an ice-bath and treated with TMEDA (181 μl, 1.2 mmol) and 1.6 M butyllithium in hexane (0.75 ml, 1.2 mmol) under nitrogen. The solution was stirred at 0 °C for 1 h, cooled to −78 °C and transferred with a PTFE cannula to a vigorously stirred solution of sulfur dioxide (5 ml) in dry ether (15 ml) at −78 °C. A white solid precipitated instantly and the mixture was kept at −78 °C for 15 min, then allowed to warm to room temp. over 1 h. The solvent was evaporated and the residue was resuspended in dry ether, filtered, washed thoroughly with ether and dried in air to afford a white solid (0.76 g). This material was suspended in aq. sodium phosphate (500 mM, pH 6.0; 50 ml) and the mixture was readjusted to pH 6.0. Ethyl acetate (50 ml) was added and the flask was cooled in an ice-bath. *N*-Chlorosuccinimide (NCS) (408 mg, 3 mmol) was added and the two phase system was stirred vigorously for 0.5 h. The organic phase was separated and the aqueous phase was washed with ethyl acetate. The combined organic phases were washed with water, dried and evaporated to give the sulfonyl chloride **13** as a viscous oil (202 mg, 54%) which crystallised on standing and was recrystallised from diethyl ether–hexane, mp 116–117 °C (lit.,[18] 115 °C).

{4-[(4,8-Dimethoxy-1-naphthyl)methyl]phenyl}-(4-methylphenyl)methanol 14

A solution of the bromoarene **10** (357 mg, 1 mmol) in dry ether (25 ml) was cooled under nitrogen in an ice-bath and treated with TMEDA (181 μl, 1.2 mmol) and butyllithium (1.6 M in hexane; 0.75 ml, 1.2 mmol). The solution was stirred at 0 °C for 1 h and treated with *p*-tolualdehyde (118 μl, 1 mmol), then stirred at 0 °C for 1 h and quenched with water (20 ml). The organic phase was separated and the aqueous phase was extracted with more ether. The combined organic phases were washed with 2 M HCl and evaporated. The residue was dissolved in ethanol (30 ml), stirred for 1 h in the presence of 2 M aq. $Na_2S_2O_5$ (30 ml), concentrated under reduced pressure and extracted into ether. The organic phase was washed with water, dried and evaporated. The residue was flash chromatographed [EtOAc–light petroleum (1:4)] to give the *alcohol* **14** as a white solid (321 mg, 75%), mp 147–148 °C, which crystallised from EtOAc–light petroleum as plates, mp 148 °C (Found: C, 81.5; H, 6.5. $C_{27}H_{26}O_3$ requires C, 81.4; H, 6.6%); ν_{max}/cm^{-1} 3560, 1600, 1515, 1410, 1380, 1285, 1275, 1065, 800, 770 and 745; δ_H(90 MHz) 7.88 (1 H, dd, *J* 0.9, 8.4, naphthalene-5 H), 6.68–7.40 (12 H, m, ArH), 5.73 (1 H, s, C*H*OH), 4.56 (2 H, s, ArCH_2), 3.95 (3 H, s, OMe), 3.63 (3 H, s, OMe) and 2.30 (3 H, s, Me).

Methyl *N*-{4-[(4,8-dimethoxy-1-naphthyl)methyl]benzenesulfonyl}glycinate 15

To an ice-cooled solution of the sulfonyl chloride **13** (188 mg, 0.5 mmol) in acetonitrile (5 ml) stirred under nitrogen were added methyl glycinate hydrochloride (94 mg, 0.75 mmol) and *N*-methylmorpholine (NMM) (202 mg, 2 mmol) and the mixture was allowed to warm to room temp. over 3 h. The solvent was evaporated and the residue was dissolved in ether (20 ml) and washed with 2 M HCl and water, dried and evaporated to leave a yellow foam. Flash chromatography [EtOAc–light petroleum (1:1)] followed by trituration with diethyl ether gave the *sulfonamide* **15** (126 mg, 59%), mp 117–118 °C (from ethanol–diisopropyl ether) (Found: C, 61.4; H, 5.4; N, 3.2. $C_{22}H_{23}NO_6S$ requires C, 61.5; H, 5.4; N, 3.3%); λ_{max}(MeOH)/nm 300 (ε/M^{-1}cm^{-1} 11 300), 318 (8800) and 332 (7300); δ_H(90 MHz) 7.87 (1 H, d, *J* 8.5, naphthalene-5 H), 7.66 (2 H, d, *J* 8, ArH *ortho* to SO_2NH), 7.00–7.43 (4 H, m, ArH), 6.71 (2 H, d, *J* 8, ArH *meta* to SO_2NH), 4.92 (1 H, t, *J* 5.7, NH, exchangeable with D_2O), 4.60 (2 H, s, ArCH_2), 3.98 (3 H, s, OMe), 3.72 (2 H, d, *J* 5.7 collapsed to s on D_2O exchange, NHCH_2), 3.58 (3 H, s, CO_2Me) and 3.52 (3 H, s, OMe).

Di-*tert*-butyl *N*-{4-[(4,8-dimethoxy-1-naphthyl)methyl]-benzenesulfonyl}-L-glutamate 16

This compound was prepared as described above for compound **15** from di-*tert*-butyl L-glutamate hydrochloride. Flash chromatography of the crude product [EtOAc–light petroleum (1:4)] followed by trituration with diethyl ether–light petroleum gave the *sulfonamide* **16** (225 mg, 75%), mp 97–98 °C (from diethyl ether–hexane) (Found: C, 63.9; H, 6.9; N, 2.4.

$C_{32}H_{41}NO_8S$ requires C, 64.1; H, 6.9; N, 2.3%); λ_{max}(EtOH)/nm 300 (ε/M^{-1}cm^{-1} 11 300), 318 (8900) and 332 (7600); ν_{max}/cm^{-1} 3290, 1730, 1715, 1600, 1515, 1375, 1365, 1350, 1265, 1165, 1150 and 1075; δ_H(400 MHz) 7.91 (1 H, d, $J_{5,6}$ 9, naphthalene-5 H), 7.65 (2 H, d, *J* 8, ArH *ortho* to SO_2NH), 7.35 (1 H, t, $J_{6,7}$ 8, naphthalene-6 H), 7.16 (2 H, d, Ar-H *meta* to SO_2NH), 7.11 (1 H, d, *J* 8, ArH), 6.76–6.79 (2 H, m, ArH), 5.12 (1 H, d, *J* 9, NH), 4.59 (2 H, s, ArCH_2), 4.00 (3 H, s, OMe), 3.72–3.81 (1 H, m, CH), 3.61 (3 H, s, OMe), 2.31–2.43 (2 H, m, CH_2CO), 1.96–2.11 (2 H, m, CH_2CH), 1.44 (9 H, s, CMe_3) and 1.17 (9 H, s, CMe_3).

N-{4-[(4,8-Dimethoxy-1-naphthyl)methyl]benzenesulfonyl}-L-glutamic acid 17

A solution of the sulfonamide **16** (47 mg, 78 μmol) in trifluoroacetic acid (4 ml) was kept at room temp. for 1 h, then evaporated and kept under high vacuum for a further 1 h. The residue was suspended in water (10 ml) and adjusted to pH 7.1 with 2 M NaOH to give a solution which was subjected to anion-exchange chromatography using a linear gradient formed from 350 and 700 mM TEAB (each 1000 ml). Fractions containing the product, which eluted at ~ 500 mM TEAB, were processed as described above to afford the *title compound* **17** as its triethylammonium salt (46 μmol, 59%) (Found: M^-, 486. $C_{24}H_{23}NO_8S$ + H requires *M*, 486); λ_{max}[EtOH–25 mM Na phosphate, pH 7.0 (1:9)]/nm 301 (ε/M^{-1} cm^{-1} 11 300), 318.5 (8900) and 332.5 (6600); δ_H[400 MHz, D_2O–CD_3OD (1:1 v/v)] 7.84 (1 H, d, *J* 7.6, naphthalene-5 H), 7.68 (2 H, d, *J* 8.4, ArH *ortho* to SO_2NH), 7.40 (1 H, t, naphthalene-6 H), 7.29 (1 H, d, naphthalene-7 H), 7.19 (2 H, d, ArH *meta* to SO_2NH), 6.99 (1 H, d, *J* 7.8, ArH), 6.91 (1 H, d, ArH), 4.61 (2 H, s, ArCH_2), 4.03 (3 H, s, OMe), 3.57 (3 H, s, OMe), 3.45–3.50 (1 H, m, CHCH$_2$), 2.04–2.16 (2 H, m, CH_2CO) and 1.74–1.97 (2 H, m, CHCH_2).

8-Allyloxy-4-methoxy-1-naphthaldehyde 20

A mixture of the phenol **19**[20] (14.88 g, 73.6 mmol), allyl bromide (9.8 g, 81 mmol) and anhydrous K_2CO_3 (11.6 g, 84 mmol) in acetone (300 ml) was heated under reflux for 6 h and cooled to room temp. The solid was filtered and washed thoroughly with acetone, the combined filtrates were evaporated and the residue after evaporation was dissolved in ether. The solution was washed with 2 M NaOH and water, dried and evaporated and the residue was crystallised from EtOAc–light petroleum to give the *aldehyde* **20** (16.95 g, 95%), mp 115–116 °C (Found: C, 74.4; H, 5.85. $C_{15}H_{14}O_3$ requires C, 74.4; H, 5.8%); ν_{max}/cm^{-1} 1665, 1515, 1375, 1270, 1220, 1060, 800 and 755; δ_H(90 MHz) 11.06 (1 H, s, CHO), 8.04 (1 H, d, *J* 8, 2-H), 7.95 (1 H, d, *J* 8, 5-H), 7.40 (1 H, t, 6-H), 7.00 (1 H, d, *J* 8, 7-H), 6.86 (1 H, d, 3-H), 5.93–6.36 (1 H, m, CH=CH$_2$), 5.26–5.53 (2 H, m, CH=CH_2), 4.72 (2 H, d, *J* 5.3, OCH_2) and 4.03 (1 H, s, OMe).

8-Allyloxy-1-(4-bromo-α-hydroxybenzyl)-4-methoxynaphthalene 21

A solution of 1,4-dibromobenzene (10.62 g, 45 mmol) in dry ether (100 ml) was cooled under nitrogen in an ice-bath and treated with butyllithium (1.6 M in hexane; 28.1 ml, 45 mmol), then heated under reflux for 0.5 h. The solution was cooled in an ice-bath and treated with a solution of the aldehyde **20** (7.27 g, 30 mmol) in ether (50 ml). The solution was allowed to warm to room temp. and stirred for 2.5 h. Water (50 ml) was added and the mixture was poured into 2 M aq. NaOH (200 ml). The organic phase was separated and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with water, dried and evaporated and the residue was triturated with ether. The resulting solid was recrystallised from cyclohexane to give the *alcohol* **21** as colourless crystals (9.43 g, 79%), mp 121–122 °C (Found: C, 63.4; H, 4.8. $C_{21}H_{19}BrO_3$ requires C, 63.2; H, 4.8%); ν_{max}/cm^{-1} 3500, 1600, 1515, 1410, 1260, 1045, 810 and 765; δ_H(90 MHz) 8.01 (1 H, d, *J* 8.4, naphthalene-5 H), 6.70–7.45 (8 H, m, ArH), 6.40 (1 H, d collapsed to s on D_2O exchange, *J* 7, CHOH), 5.55–5.91 (1 H, m, CH=CH$_2$), 5.15–5.33 (2 H, m, CH=CH_2), 4.40–4.62 (2 H, m, OCH_2) and 3.98 (1 H, s, OMe).

8-Allyloxy-1-(4-bromobenzyl)-4-methoxynaphthalene 22

Sodium boranuide pellets (5.67 g, 150 mmol) were added slowly under nitrogen to a mixture of glacial acetic acid (90 ml) and trifluoroacetic acid (10 ml) cooled to −15 °C, and a solution of the alcohol **21** (7.99 g, 20 mmol) in dichloromethane (40 ml) was added dropwise over 40 min. The mixture was stirred at room temp. for a further 4 h and the solvents were removed under reduced pressure. Water (200 ml) was added carefully with ice-cooling and the aqueous solution was basified to pH 14 by addition of sodium hydroxide pellets and extracted with dichloromethane. The combined organic phases were washed with water and brine, dried and evaporated and the residue was recrystallised from EtOAc to give the *diarylmethane* **22** as a colourless solid (6.60 g, 86%), mp 126–127 °C (Found: C, 66.0; H, 4.9. $C_{21}H_{19}BrO_2$ requires C, 65.9; H, 4.9%); ν_{max}/cm^{-1} 1600, 1515, 1410, 1275, 1105, 805 and 770; δ_H(90 MHz) 7.91 (1 H, d, *J* 9, naphthalene-5 H), 6.66–7.46 (8 H, m, ArH), 5.54–6.00 (1 H, m, CH=CH$_2$), 5.04–5.29 (2 H, m, CH=CH_2), 4.57 (2 H, s, ArCH_2), 4.41 (2 H, d, *J* 8, OCH_2) and 3.97 (1 H, s, OMe).

Hydroboration of 8-allyloxy-1-(4-bromobenzyl)-4-methoxynaphthalene 22

Method A. A solution of the diarylmethane **22** (383 mg, 1 mmol) in dry THF (3 ml) was cooled under nitrogen in an ice-bath and borane–dimethyl sulfide complex (1 M in THF; 0.3 ml, 0.3 mmol) was added slowly. After 5 min the ice-bath was removed and the mixture was stirred at room temp. for 2.5 h. The solution was then cooled in an ice-bath, sequentially treated dropwise with ethanol (0.3 ml), water (0.4 ml), 1 M NaOH (1 ml) and 30% aq. H_2O_2 (1 ml) and heated under reflux for 1.5 h. The cooled solution was poured into water (10 ml) and extracted with ether. The combined organic phases were washed with water, dried and evaporated to give a foam (345 mg) which was flash chromatographed [EtOAc–light petroleum (3:7)]. The first product eluted was 1-(4-*bromobenzyl*)-8-(2-*hydroxypropoxy*)-4-*methoxynaphthalene* **23** as a colourless oil (33 mg, 8%); δ_H(90 MHz) 7.96 (1 H, dd, *J* 1, 9, naphthalene-5 H), 6.71–7.43 (8 H, m, ArH), 4.48 and 4.73 (2 H, ABq, *J* 17, ArCH_2), 3.98 (3 H, s, OMe), 3.74–3.91 (3 H, m, CH_2CHOH) and 1.15 (3 H, d, *J* 5.7, CHCH_3). This minor product was not characterised further. The second fraction was recrystallised from cyclohexane to give **24** (145 mg, 36%), mp 119–120 °C (Found: C, 63.1; H, 5.3. $C_{21}H_{21}BrO_3$ requires C, 62.85; H, 5.3%); ν_{max}/cm^{-1} 3220, 1600, 1515, 1415, 1380, 1275, 1070, 795 and 775; δ_H(90 MHz) 7.91 (1 H, dd, *J* 1 and 9, naphthalene-5 H), 6.66–7.46 (8 H, m, ArH), 4.58 (2 H, s, ArCH_2), 4.00 (2 H, t, *J* 7.7, ArOCH_2), 3.97 (3 H, s, OMe), 3.60 (2 H, t, *J* 7.7, CH_2OH) and 1.76 (2 H, quintet, OCH_2CH_2).

Method B. A solution of 2-methylbut-2-ene (2 M in THF; 16.8 ml, 33.7 mmol) was cooled under nitrogen in an ice-bath and treated with borane–dimethyl sulfide (10 M in THF; 1.5 ml, 15 mmol). The mixture was stirred at room temp. for 2 h, then cooled in an ice-bath and a solution of the diarylmethane **22** (4.60 g, 12 mmol) in dry THF (30 ml) was added. After 5 min the ice-bath was removed and the mixture was stirred at room temp. for further 2.5 h. The solution was cooled in an ice-bath and sequentially treated dropwise with ethanol (8 ml), water (2 ml), 1 M aq. NaOH (4 ml) and 30% aq. H_2O_2 (2 ml), then heated under reflux for 2 h. After cooling to room temp. it was poured into water (100 ml) and extracted with ether. The combined organic phases were washed with water, dried and evaporated to give a white solid, which appeared as a single compound by TLC [EtOAc–light petroleum (3:7)] and crystallised from

cyclohexane to yield the primary alcohol **24** (3.94 g, 82%), identical with the material prepared above.

8-(3-Benzyloxypropoxy)-1-(4-bromobenzyl)-4-methoxynaphthalene 25

A solution of the primary alcohol **24** (2.0 g, 5 mmol) in benzene (40 ml) was stirred at 10 °C with 50% (w/v) aq. NaOH (40 ml). Aq. tetrabutylammonium hydroxide (40% v/v; 2 ml) and benzyl bromide (0.89 ml, 7.5 mmol) were added and the mixture was stirred at room temp. overnight. Water (30 ml) and light petroleum (20 ml) were added and the mixture was acidified by dropwise addition of conc. HCl. The organic phase was separated and the aqueous phase was extracted with ether. The combined organic phases were washed with water, dried and evaporated to give a brown oil, which was dissolved in ethanol (50 ml) and triethylamine (5 ml) to destroy excess benzyl bromide. The solution was stirred overnight, concentrated under reduced pressure and the residue was dissolved in water, acidified with 2 M aq. HCl and extracted with ether. The combined organic phases were dried and evaporated and the residual oil was triturated with diethyl ether–light petroleum, cooled to −78 °C and allowed to warm slowly to room temp. The precipitated solid was recrystallised from ethanol to give the *benzyl ether* **25** as colourless needles (1.84 g, 75%), mp 69–70 °C (Found: C, 68.4; H, 5.5. $C_{28}H_{27}BrO_3$ requires C, 68.4; H, 5.5%); ν_{max}/cm^{-1} 1600, 1515, 1415, 1370, 1275, 1080, 1065, 1015, 800, 765 and 705; δ_H(90 MHz) 7.92 (1 H, dd, *J* 0.9 and 8.4, naphthalene-5 H), 6.69–7.42 (8 H, m, ArH), 7.27 (5 H, s, C_6H_5), 4.56 (2 H, s, ArCH_2), 4.41 (2 H, s, PhCH_2O), 4.01 (2 H, t, *J* 7.7, CH_2OAr), 3.97 (3 H, s, OMe), 3.39 (2 H, t, *J* 7.7, OCH_2CH$_2$) and 1.63–1.97 (2 H, quintet, OCH$_2$CH_2).

4-{[8-(3-Benzyloxypropoxy)-4-methoxy-1-naphthyl]methyl}-benzenesulfonyl chloride 26

As described above for compound **10**, a solution of the bromoarene **25** (1.47 g, 3 mmol) in dry ether (30 ml) was sequentially treated with BuLi–TMEDA and SO_2, and the crude sulfinate salt was oxidised with NCS. The final reaction product was flash chromatographed [EtOAc–light petroleum (1:9)] to give a viscous oil (1.08 g, 71%) which crystallised on standing and was recrystallised from diethyl ether–light petroleum to give the *sulfonyl chloride* **26** as pale yellow crystals, mp 95–96 °C (Found: C, 66.2; H, 5.4. $C_{28}H_{27}ClO_5S$ requires C, 65.8; H, 5.3%); ν_{max}/cm^{-1} 1600, 1590, 1518, 1415, 1370, 1280, 1262, 1228, 1185, 1165, 1090, 1060, 835 and 745; δ_H(90 MHz) 7.95 (1 H, dd, *J* 8 and 1, naphthalene-5 H), 7.77 (2 H, d, *J* 8, ArH *ortho* to SO_2Cl), 6.68–7.41 (6 H, m, ArH), 7.24 (5 H, s, C_6H_5), 4.65 (2 H, s, ArCH_2), 4.39 (2 H, s, PhCH_2O), 3.96 (2 H, t, *J* 6, CH_2OAr), 3.93 (3 H, s, OMe), 3.34 (2 H, t, *J* 6, ArOCH_2CH$_2$) and 1.71 (2 H, quintet, OCH$_2$CH_2).

Methyl *N*-(4-{[8-(3-benzyloxypropoxy)-4-methoxy-1-naphthyl]methyl}benzenesulfonyl)glycinate 27a

A solution of the sulfonyl chloride **26** (1.08 g, 2.1 mmol) in dry acetonitrile (50 ml) was cooled under nitrogen in an ice-bath and treated with NMM (0.76 g, 7.5 mmol) and methyl glycinate hydrochloride (0.63 g, 5 mmol). The solution was stirred at room temp. for 3 h and the solvent was evaporated. The residue was dissolved in ether, washed with 2 M HCl and water, dried and evaporated. Flash chromatography [EtOAc–light petroleum (3:2)] and trituration with diethyl ether–light petroleum afforded the *sulfonamide* **27a** as a white solid (1.18 g, 75%), mp 67 °C (from diethyl ether–light petroleum) (Found: C, 65.9; H, 5.9; N, 2.5. $C_{31}H_{33}NO_7S$ requires C, 66.1; H, 5.9; N, 2.5%); δ_H(90 MHz) 7.92 (1 H, d, *J* 8.5, naphthalene-5 H), 7.64 (2 H, d, *J* 8, ArH *ortho* to SO_2NH), 6.67–7.44 (6 H, m, ArH), 7.25 (5 H, s, C_6H_5), 5.26 (1 H, t, *J* 5.8, NH, exchangeable with D_2O), 4.63 (2 H, s, ArCH_2), 4.41 (2 H, s, PhCH_2O), 3.96 (2 H, t, *J* 6.2, CH_2OAr), 3.94 (3 H, s, OMe), 3.68 (2 H, d collapsed to s on D_2O exchange, NHCH_2), 3.51 (3 H, s, CO_2Me), 3.40 (2 H, t, *J* 6.2, ArOCH_2CH$_2$) and 1.77 (2 H, quintet, OCH$_2$CH_2).

Dimethyl *N*-(4-{[8-(3-benzyloxypropoxy)-4-methoxy-1-naphthyl]methyl}benzenesulfonyl)-L-glutamate 27b

Prepared from dimethyl L-glutamate hydrochloride and sulfonyl chloride **26**, as described for compound **27a**, to give a viscous oil (53%), δ_H(90 MHz) 7.92 (1 H, d, *J* 8.5, naphthalene-5 H), 7.61 (2 H, d, *J* 8, ArH *ortho* to SO_2NH), 6.67–7.40 (6 H, m, ArH), 7.25 (5 H, s, C_6H_5), 5.45 (1 H, d, *J* 9.2, NH, exchangeable with D_2O), 4.61 (2 H, s, ArCH_2), 4.42 (2 H, s, PhCH_2O), 3.76–4.12 (3 H, m, CH_2OAr and CH), 3.93 (3 H, s, OMe), 3.59 (3 H, s, CO_2Me), 3.43 (2 H, t, *J* 6.2, ArOCH_2CH$_2$), 3.43 (3 H, s, CO_2Me), 2.40 (2 H, t, *J* 7.0, CH_2CO_2) and 1.60–2.20 (4 H, m, CHCH_2 and OCH$_2$CH_2).

Methyl *N*-(4-{[8-(3-benzyloxypropoxy)-4-methoxy-1-naphthyl]methyl}benzenesulfonyl)-β-alaninate 27c

Prepared from methyl β-alaninate hydrochloride and sulfonyl chloride **26**, as described for compound **27a**, to give a viscous oil (59%) (Found: M^+, 577.2140. $C_{32}H_{35}NO_7S$ requires *M*, 577.2134); δ_H(90 MHz) 7.92 (1 H, d, *J* 8.5, naphthalene-5 H), 7.65 (2 H, d, *J* 8, ArH *ortho* to SO_2NH), 6.71–7.43 (6 H, m, ArH), 7.27 (5 H, s, C_6H_5), 5.06 (1 H, t, *J* 5.8, NH, exchangeable with D_2O), 4.66 (2 H, s, ArCH_2), 4.43 (2 H, s, PhCH_2O), 3.96 (2 H, t, *J* 6.2, CH_2OAr), 3.94 (3 H, s, OMe), 3.51 (3 H, s, CO_2Me), 3.42 (2 H, t, *J* 6.2, ArOCH_2CH$_2$), 3.13 (2 H, dt, *J* 6.6, NHCH_2CH$_2$), 2.46 (2 H, t, *J* 6.2, CH_2CO_2) and 1.76 (2 H, quintet, OCH$_2$CH_2).

Methyl *N*-(4-{[8-(3-hydroxypropoxy)-4-methoxy-1-naphthyl]-methyl}benzenesulfonyl)glycinate 28a

Boron trifluoride–diethyl ether (2.73 g, 19.2 mmol) was added dropwise to a stirred solution of the sulfonamide **27a** (0.72 g, 1.3 mmol) and anhydrous sodium iodide (0.29 g, 1.9 mmol) in dry acetonitrile (25 ml) at 0 °C. The mixture was stirred at 0 °C for 1 h, then at room temp. for a further 3 h. Ice-cold water (100 ml) was added together with a few drops of 15% (w/v) $Na_2S_2O_3$ solution to decolourise the iodine liberated, and the aqueous solution was extracted with dichloromethane. The combined organic phases were washed with water and brine, dried and evaporated and the residue was flash chromatographed [EtOAc–light petroleum (3:2)] to give a white foam which after trituration with diethyl ether afforded the *title compound* **28a** as a white solid (0.53 g, 87%), mp 140–141 °C (EtOAc–light petroleum) (Found: C, 60.9; H, 5.7; N, 2.95. $C_{24}H_{27}NO_7S$ requires C, 60.9; H, 5.75; N, 3.0%); ν_{max}/cm^{-1} 3490, 3140, 1755, 1600, 1415, 1320, 1265, 1230, 1153 and 1060; δ_H(90 MHz) 7.93 (1 H, d, *J* 8.5, naphthalene-5 H), 7.67 (2 H, d, *J* 8, ArH *ortho* to SO_2NH), 6.68–7.49 (6 H, m, ArH), 5.16 (1 H, t, *J* 5.7, NH, exchangeable with D_2O), 4.69 (2 H, s, ArCH_2), 3.99 (2 H, t, *J* 6.2, CH_2OAr superimposed on 3 H, s, OMe), 3.76 (2 H, d, *J* 5.7 collapsed to s on D_2O exchange, NHCH_2), 3.58 (3 H, s, CO_2Me), 3.49 (2 H, t, *J* 6.2, CH_2OH) and 1.68 (2 H, quintet, OCH$_2$CH_2).

Dimethyl *N*-(4-{[8-(3-hydroxypropoxy)-4-methoxy-1-naphthyl]methyl}benzenesulfonyl)-L-glutamate 28b

Compound **27b** was debenzylated as described above to give the *title compound* **28b** as a viscous oil (0.42 g, 70%) (Found: M^+, 559.1870. $C_{28}H_{33}NO_9S$ requires *M*, 559.1876); δ_H(90 MHz) 7.91 (1 H, d, *J* 7.9, naphthalene-5 H), 7.76 (2 H, d, *J* 8.3, ArH *ortho* to SO_2NH), 6.63–7.46 (6 H, m, ArH), 5.81 (1 H, d, *J* 9.2, NH, exchangeable with D_2O), 4.64 (2 H, s, ArCH_2), 3.77–4.09 (3 H, m, CH_2OAr and CH), 3.94 (3 H, s, OMe), 3.58 (3 H, s, CO_2Me), 3.51 (2 H, t, *J* 6.2, CH_2OH), 3.34 (3 H, s, CO_2Me), 2.40 (2 H, t, *J* 7.0, CH_2CO_2) and 1.49–2.23 (4 H, m, CHCH_2 and OCH$_2$CH_2).

Methyl *N*-(4-{[8-(3-hydroxypropoxy)-4-methoxy-1-naphthyl]-methyl}benzenesulfonyl-β-alaninate 28c

Compound **27c** was debenzylated as described above to give the *title compound* **28c** as a white solid (0.36 g, 72%), mp 126–127 °C (EtOAc–light petroleum) (Found: C, 61.7; H, 6.0; N, 2.9. $C_{25}H_{29}NO_7S$ requires C, 61.6; H, 6.0; N, 2.9%); ν_{max}/cm^{-1} 3470, 3145, 1745, 1600, 1415, 1380, 1315, 1265, 1155 and 1060; δ_H(90 MHz) 7.93 (1 H, d, *J* 9.3, naphthalene-5 H), 7.67 (2 H, d, *J* 8.3, ArH *ortho* to SO_2NH), 6.72–7.42 (6 H, m, ArH), 5.22 (1 H, t, *J* 7.7, NH, exchangeable with D_2O), 4.68 (2 H, s, $ArCH_2$), 3.98 (3 H, s, OMe), 3.94 (3 H, t, *J* 5, CH_2OAr), 3.62 (3 H, s, CO_2Me), 3.34–3.57 (2 H, m converted to t after D_2O exchange, CH_2OH), 3.14 (2 H, dt converted to t after D_2O exchange, $NHCH_2$), 2.50 (2 H, t, *J* 6.1, CH_2CO_2Me) and 1.65 (2 H, quintuplet, OCH_2CH_2).

3-(8-{*p*-[*N*-(Carboxymethyl)sulfamoyl]benzyl}-5-methoxy-1-naphthyloxy)propyl dihydrogen phosphate 18a

1*H*-Tetrazole (158 mg, 2.25 mmol) was added under nitrogen to a stirred solution of the *alcohol* **28a** (456 mg, 0.96 mmol) and bis(2-cyanoethyl) diisopropylphosphoramidite (407 mg, 1.5 mmol) in dry THF (10 ml). After 2.5 h at room temp. the mixture was cooled in an ice-bath and treated dropwise over 5 min with a solution of *m*-chloroperbenzoic acid (55% peracid; 627 mg, 2 mmol) in CH_2Cl_2 (5 ml). The solution was stirred at 4 °C for 1 h then diluted with diethyl ether and washed successively with 10% aq. $Na_2S_2O_5$, 1 M aq. HCl, saturated aq. $NaHCO_3$ and brine, dried and evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc) to give the phosphotriester **29a** as viscous oil (621 mg, 98%), which was dissolved in methanol (45 ml) with 2 M aq. NaOH (5 ml) and kept at 50 °C for 0.5 h. The solution was then concentrated under reduced pressure (*ca.* 10 ml), diluted with water, adjusted to pH 7 with 1 M aq. HCl and washed with diethyl ether. The aqueous solution was diluted with water to a conductivity of 800 μmho and purified by anion-exchange chromatography using a linear gradient formed from 10 and 750 mM TEAB (each 1000 ml). Fractions containing the product, which eluted at ~500 mM TEAB, were processed as described above to afford the *title compound* **18a** as its triethylammonium salt (700 μmol, 71%) (Found: M^-, 538. $C_{23}H_{23}NO_{10}PS$ + 2H requires *M*, 538). The sodium salt had δ_H(400 MHz, D_2O, acetone ref.) 7.78 (1 H, d, *J* 8.5, naphthalene-4 H), 7.49 (2 H, d, J_{ortho} 8.4, ArH *ortho* to SO_2NH), 7.35 (1 H, t, *J* 8.1, naphthalene-3 H), 6.99 (2 H, d, ArH *meta* to SO_2NH), 6.91 (1 H, d, naphthalene-2 H), 6.75 (1 H, d, *J* 7.8, ArH), 6.52 (1 H, d, ArH), 4.42 (2 H, s, $ArCH_2$), 3.90 (2 H, t, *J* 6.6, $ArOCH_2$) 3.83 (2 H, dt, *J* 6.3, $J_{H,P}$ 7, CH_2OPO_3), 3.80 (3 H, s, OMe), 3.41 (2 H, s, NCH_2) and 1.65 (2 H, quintet, OCH_2CH_2).

(*S*)-3-(8-{*p*-[*N*-(1,3-Dicarboxypropan-2-yl)sulfamoyl]benzyl}-5-methoxy-1-naphthyloxy)propyl dihydrogen phosphate 18b

The alcohol **28b** was converted as described above into phosphotriester **29b**, which was flash chromatographed [EtOAc–light petroleum (9:1)] to give **29b** as a viscous oil (56%). This material (245 mg) was dissolved in methanol (45 ml) and 2 M aq. NaOH (5 ml) and kept at 50 °C for 3.5 h, then concentrated under reduced pressure (*ca.* 10 ml), diluted with water, adjusted to pH 7 with 1 M aq. HCl and washed with diethyl ether. The aqueous solution was diluted with water to a conductivity of 800 μmho and purified by anion-exchange as above. Fractions containing the product, which eluted at ~500 mM TEAB, were processed as described above to afford the *title compound* **18b** as its triethylammonium salt (182 μmol, 55%) (Found: M^-, 610. $C_{26}H_{26}NO_{12}PS$ + 3H requires *M*, 610). The sodium salt had δ_H(400 MHz, D_2O, acetone ref.) 7.83 (1 H, d, *J* 8.5, naphthalene-4 H), 7.58 (2 H, d, *J* 8.2, ArH *ortho* to SO_2NH), 7.41 (1 H, t, *J* 8.1, naphthalene-3 H), 7.08 (2 H, d, ArH *meta* to SO_2NH), 7.04 (1 H, d, naphthalene-2 H), 6.93 (1 H, d, *J* 7.8, ArH), 6.83 (1 H, d, ArH), 4.55 (2 H, s, $ArCH_2$), 3.96 (3 H, s, OMe), 3.90–3.93 (4 H, m, CH_2OPO_3 and $ArOCH_2$), 3.52 (1 H, dd, *J* 5 and 7.9, $CHCH_2$), 2.11 (2 H, t, *J* 8, CH_2CO_2), 1.74–1.93 (2 H, m, $CHCH_2$) and 1.70 (2 H, quintet, OCH_2CH_2).

3-(8-{*p*-[*N*-(2-Carboxyethyl)sulfamoyl]benzyl}-5-methoxy-1-naphthyloxy)propyl dihydrogen phosphate 18c

The alcohol **28c** was converted as described above into phosphotriester **29c**, which was flash chromatographed [EtOAc–light petroleum (9:1)] to give **29c** as a viscous oil (91%). This material (306 mg) was treated with methanolic NaOH and the solution further processed as described above for compound **29b**. The aqueous solution containing the crude product was purified by anion-exchange chromatography as above. Fractions containing the product, which eluted at ~500 mM TEAB, were processed as described above to afford the *title compound* **18c** as its triethylammonium salt (190 μmol, 61%) (Found: M^-, 552; $C_{24}H_{25}NO_{10}PS$ + 2H requires *M*, 552). The sodium salt had δ_H(600 MHz, D_2O, acetone ref.) 7.86 (1 H, d, *J* 8.4, naphthalene-4 H), 7.55 (2 H, d, *J* 7.2, ArH *ortho* to SO_2NH), 7.44 (1 H, t, naphthalene-3 H), 7.11 (2 H, d, ArH *meta* to SO_2NH), 7.08 (1 H, d, naphthalene-2 H), 6.98 (1 H, d, *J* 7.2, ArH) 6.85 (1 H, d, ArH), 4.61 (2 H, s, $ArCH_2$), 3.97 (3 H, s, OMe), 3.95 (2 H, t, *J* 8.4, $ArOCH_2$), 3.85 (2 H, dt, $J_{H,P}$ 8, CH_2OPO_3), 2.98 (2 H, t, $NHCH_2$), 2.27 (2 H, t, CH_2CO_2) and 1.69 (2 H, quintet, OCH_2CH_2).

Photolysis of compounds 15, 18a and 18c

Aqueous solution. Solutions of **18a** or **18c** (*ca.* 0.5 mM, exact concentrations determined by UV absorption, using ε_{301} 11 300 M^{-1} cm^{-1}) plus co-reagents as appropriate (Table 1) were prepared in 10 mM sodium phosphate, pH 7.0. Aliquots (0.20 ml) were irradiated in a 1 mm path-length cell, using light from a mercury arc lamp which passed through a Hoya U340 filter before illuminating the cell. The extent of conversion of starting compounds was determined by reversed-phase HPLC [Merck Lichrosphere RP8 column (Cat. No. 50832); mobile phase 25 mM sodium phosphate, pH 5.5–MeCN (80:20 or 77.5:22.5 v/v for compounds **18a** and **18c** respectively); flow rate 1.5 ml min^{-1}; UV detection at 313 nm]. Quantification was based on peak heights compared to those of unphotolysed controls. Yields of free amino acids were determined by amino acid analysis.

Aqueous methanol solution. Solutions of **15** or **18a** plus sodium ascorbate as appropriate (Table 1) were prepared in MeOH–10 mM sodium phosphate, pH 7.0 (2:1 v/v) and quantified and photolysed as described above. Following photolysis, aliquots (0.40 ml) of the solutions prepared from compound **15** were mixed with 0.5 M aq. NaOH (0.04 ml) and kept at room temp. for 4 h, then neutralised with 0.45 M aq. HCl (0.04 ml). The extent of conversion of the starting compounds was determined by reversed-phase HPLC as above [mobile phase 25 mM sodium phosphate, pH 5.5–MeCN (68:32 v/v)] and the yield of product amino acid was determined by amino acid analysis.

In some experiments under each set of conditions, norleucine (0.25 mM) was included in solutions as an internal standard for amino acid analysis. Recoveries of norleucine were 100 ± 5%.

Acknowledgements

We are grateful to Dr S. Howell and Dr K. J. Welham for the mass spectral determinations at low and high resolution respectively, and to Mr J. S. Craik, Dr M. Gradwell and Dr T. A. Frenkiel for running high-field NMR spectra. We thank the MRC Biomedical NMR Centre for access to facilities. We are indebted to Prof W. Mäntele and Dr A. Barth for obtaining the flash photolysis-FTIR data.

This work was supported by a grant from the Medical Research Council under the Neurosciences Approach to Human Health Initiative.

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Paper 5/07838E
Received 1*st December* 1995
Accepted 6*th March* 1996