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Synthesis and cycloaddition reactions of strained alkynes derived from 2,2′-dihydroxy-1,1′-biaryls†

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A series of strained alkynes, based on the 2,2′-dihydroxy-1,1′-biaryl structure, were prepared in a short sequence from readily-available starting materials. These compounds can be readily converted into further derivatives including examples containing fluorescent groups with potential for use as labelling reagents. The alkynes are able to react in cycloadditions with a range of azides without the requirement for a copper catalyst, in clean reactions with no observable side reactions.

Introduction

The use of highly reactive strained alkynes, typically within eight-membered rings,[1] in cycloaddition reactions with azides is now a well-established reaction with numerous applications in materials chemistry and in bioconjugation applications.[2] Such reagents are ideal for these applications because the cycloaddition reactions take place spontaneously and without the need for a catalyst to be added – in contrast to the reactions of unstrained terminal alkynes with azides in which case a copper-based catalyst is generally required.[3]

Widely adopted cyclooctyne reagents such as **1–3** and their derivatives (Fig. 1),[4–6] are highly reactive, and can be used at the low concentrations which are often required in bioconjugation applications, particularly for *in vivo* reactions.[7] In applications where the concentration of reagents is more typical of synthetic reactions *e.g.* 0.01–0.5 M, and on larger scales, less reactive larger-ring molecules, which can be prepared through a short synthetic sequence, have also proven to be synthetically valuable reagents.[8] Earlier and less reactive cyclooctynes remain synthetically important, for example (2-cyclooctyn-1-yloxy)acetic acid (a derivative of 'OCT') was the subject of a successful multigram scale up optimisation study reported in 2018.[5d] Some highly strained derivatives are also prone to addition of thiols.[5e]

In a recent paper, we reported the synthesis and applications of a class of strained alkyne based on the 10-membered structure **4**, derived from 2,2′-dihydroxy-1,1′-biaryl compounds.[9] The unfunctionalised compound, 8,13-dioxatricyclo [12.4.0.02,7]octadeca-1(14),2,4,6,15,17-hexaen-10-yne (dioxabiaryldecyne) **4** and its close derivatives are readily prepared in one step through the reaction of 2,2′-biphenol with but-2-yne-1,4-diyl bis(4-methylbenzene)sulfonate in the presence of potassium carbonate.[9] Before our studies, the reactions of alkynes such as **4** with azides had not been reported, and just three papers could be identified which reported the synthesis of the same heterocyclic structure.[10] In addition, we demonstrated that reagents such as **4** and its derivatives react with azides, without the need for a Cu catalyst, at rates similar to unfunctionalised cyclooctyne, although lower than the most reactive and recently reported strained alkynes. Significantly, although longer reaction times are required than would be the case for reagents such as **1–3**, our alkynes reacted with azides in clean reactions with no visible decomposition when followed by ^{1}H-NMR. We also reported the synthesis of acid **5** and the activated ester **6** derivatives and demonstrated applicability to bio-

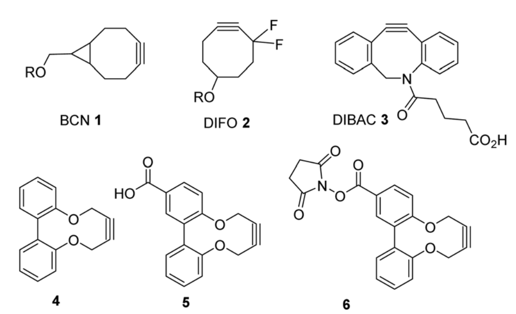

Fig. 1 Strained alkynes **1–3**, dioxabiaryldecyne **4** and its derivatives **5** and **6**.

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† Electronic supplementary information (ESI) available: General experimental details, synthesis of intermediates **7**,[13] **11**,[12] **12**,[12] **13**,[19] **34**,[20] and compounds **29–31** and **41–45**, ^{1}H and ^{13}C NMR spectra, graphs of conversion/time, fluorescence spectra, functionalisation of amino-loaded beads and X-ray crystallographic data. CCDC 1852221, 1852222 and 1852224. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ob01768a. The research data supporting this publication can be accessed at http://wrap.warwick.ac.uk/.

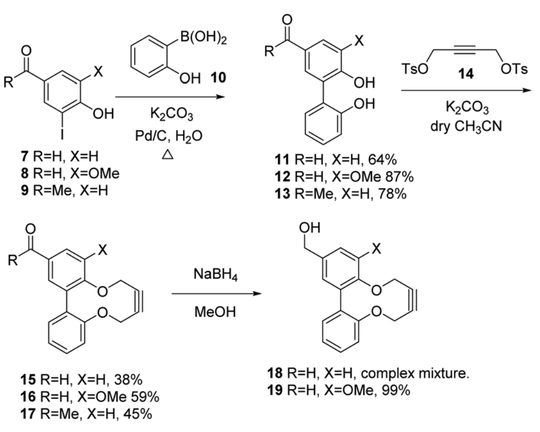
conjugation through its attachment to a number of peptides and one protein in *in vitro* studies.[9] Following our report, another group reported the preparation of some of the same derivatives, as well as N-containing heterocyclic variants, together with a comprehensive molecular modelling study to explain the enhanced reactivity of the reagents.[11] This group also demonstrated that the dioxabiaryldecynes do not rapidly undergo reactions with thiols.[11]

In this paper we report the synthesis of a series of functionalised analogues of the strained alkyne structure **4**, in as little as two steps, from readily available and inexpensive starting materials, their subsequent functionalisation and representative applications to a number of cycloaddition reactions with several azides.

Results and discussion

In order to develop an extended synthesis of dioxabiaryldecyne reagents, we employed the reported coupling reactions of iodobenzaldehyde reagents **7** and **8** (iodovanillin) and 4-hydroxy-3′-iodoacetophenone **9** with 2-(hydroxyphenyl)boronic acid **10**,[12] to give diols **11–13** respectively. This was followed by the cyclisation reactions with ditosylate **14** using our previously-reported procedure (Scheme 1).[9] Strained alkynes **15**, **16** and **17** were isolated respectively (Scheme 1). 3-Iodo-4-hydroxybenzaldehyde was prepared from 4-hydroxybenzaldehyde through careful iodination using ICl/acetic acid.[13] Iodovanillin can be prepared by the same method but is readily commercially available.

Both the Pd-catalysed coupling and the cyclisation to form aldehydes **15** and **16** worked more efficiently for the product containing a methoxy group adjacent to the strained alkyne, giving a product in unoptimised but acceptable yield in each case. In the case of the transformation of aldehyde **12** to **16**, we followed the reaction over time using chiral HPLC, which resolved the two non-interconverting enantiomers of product and allowed the conversion to be monitored over time (see ESI† for HPLC details and graph of conversion over time). The X-ray crystallographic structures of aldehyde **16** (Fig. 2) and ketone **17** (Fig. 3) revealed the strained nature of the alkyne within the constrained ring.



Scheme 1 Synthesis of aldehyde-functionalised CBD strained alkynes **15–17** and alcohol **19**.

Alkyne **16** could also be reduced to the alcohol **19** using sodium borohydride, which gave a clean product, however attempts to reduce substrate **15**, lacking the methoxy group, to **18** gave a complex mixture of products, for reasons that are not clear.[14]

The strained alkynes prepared in this project are stable solids at rt which can be stored for months without significant decomposition. However a thermal gravimetric analysis (TGA) was carried out in order to examine their stability at higher temperatures. Aldehyde **16** exhibited a drop of *ca.* 10% mass around 180 °C which may be associated with the loss of C═O from the aldehyde, followed by a gradual mass loss of just over 20% as the temperature was raised to 600 °C. The TGA analysis of the previously reported methyl ester of acid **5** was stable to *ca.* 300 °C then gradually lost *ca.* 40% of its mass as the temperature was increased to 600 °C (see ESI†).

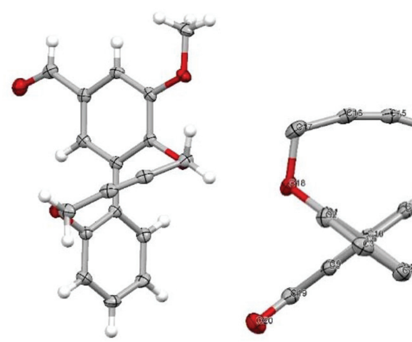


Fig. 2 Single crystal X-ray crystallographic structure of **16** (two views; ellipsoids are plotted at the 50% probability level). The bond angles at the sp atoms are 165.2° and 165.3° and the biphenyl torsion angle is 72.2°.

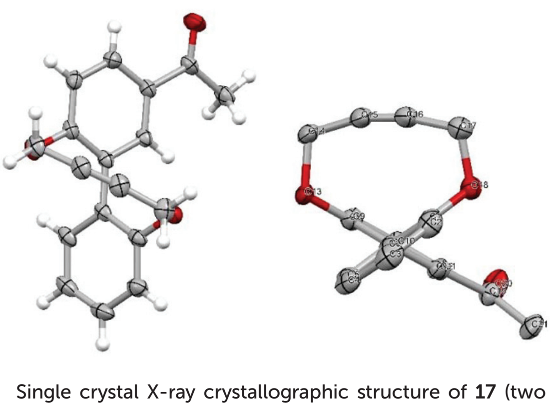
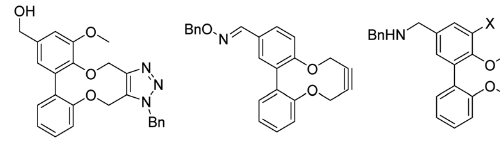


Fig. 3 Single crystal X-ray crystallographic structure of **17** (two views: ellipsoids are plotted at the 50% probability level). The bond angles at the sp atoms are 165.1° and 168.6° and the biphenyl torsion angle is 66.4°.

Given the improved synthesis of the methoxy-substituted aldehyde **16** over **15**, we focussed our studies on the former reagent. Its reaction with a range of functionalised azides was studied (Scheme 2) and in each case the reactions were followed over time, using ^{1}H NMR to monitor the cyclisations of a 1 : 1 mixture of reagents in solution; the spectra are in the ESI.† The reaction of **16** with benzylazide **20** was also carried out in MeCN, the product **21** being isolated in 84% yield. In all cases, the cycloadditions proceeded smoothly, with no obvious accompanying decomposition of reagents. Conversions (by NMR) and yields (isolated products) are given in Scheme 2. In all cases the products were formed as inseparable regioisomeric mixtures in *ca.* 1 : 1–3 : 2 ratios. Benzylazide gave a clean product **21** of addition, in analogy with previous reactions.[9,11] An azide attached to a red dye, disperse red, **22**[15a] gave a red product **23** from the cycloaddition, which was carried out at 0.128 M, 9 days at rt (95% conversion, 76% isolated yield). An azide containing a PEG-2000 chain, **24**, also added cleanly to the strained alkyne **16**, and the product in this case (**25**) was characterised by GPC as well as by NMR, revealing the expected increase to the molar mass of the polymeric product (ESI†). This was gratifying as the reagent concentration (0.025 M) in this example was lower than for other cycloadditions. The cycloaddition of coumarin azide **26** gave a highly fluorescent product **27** (see ESI†) as has been reported previously for this class of reagent.[15b,c] For improved solubility, deuterated acetonitrile was used as the solvent, and the reaction at 0.11 M proceeded to *ca.* 80% conversion to **27**. Although long reaction times are required relative to the more reactive strained alkynes such as **1–3**, the benefits of the catalyst-free conditions and clean cycloadditions make these reagents potentially valuable for the preparation of materials for biological applications.

The addition of benzyl azide to alcohol **19** to give adduct **28** as a 3 : 2 regioisomeric mixture of products (Fig. 4) proceeded at a similar rate (0.17 M, 5 d at rt, 97% yield, ESI†) indicating that the functional group has minimal influence on the rate of the cycloaddition, probably because of the separation from the alkyne.



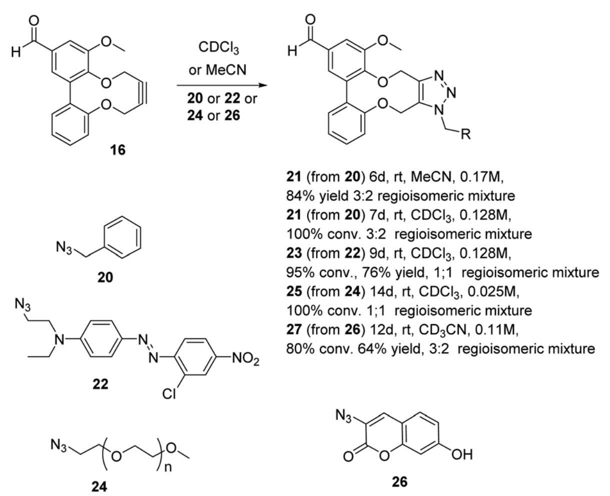
28 97% yield (3:2 regioisomeric mixture) **29** 66% yield **30** X=OMe, 81% **31** X=H, 45%

Fig. 4 Derivatives of **15–17**.

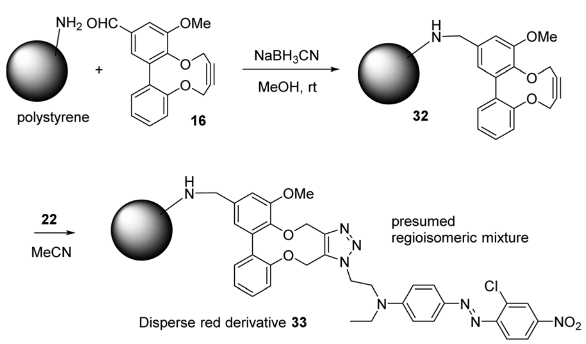
The aldehyde group on **15** and **16** permits their functionalisation with other reagents. The reaction of **15** with benzylhydroxylamine in MeOH overnight at 45 °C gave oxime ether **29** in 66% isolated yield. The formation of oxime ethers represents a valuable method for functionalisation due to their high stability and ease of preparation.[16] Also, notably, reductive amination with benzylamine led to the synthesis of amine-containing derivatives **30** and **31**. The reaction of methoxy-substituted **30** with benzylazide was found to proceed at a similar rate to aldehyde-containing reagents **16** (ESI†). It was gratifying that these functionalisations could be completed without damaging the strained alkyne group.

The treatment of amine-functionalised polystyrene beads with **16** and sodium cyanoborohydride was followed by reaction of the functionalised beads **32** with disperse red azide **22**. After washing, the strong red colour of the dye remained on the beads **33** (Scheme 3). As a control reaction, stirring the solution of red dye-azide **22** with unfunctionalised beads gave only lightly coloured beads after washing, indicating that the cycloaddition had taken place on the dioxabiaryldecyne reagent on the beads (ESI†).

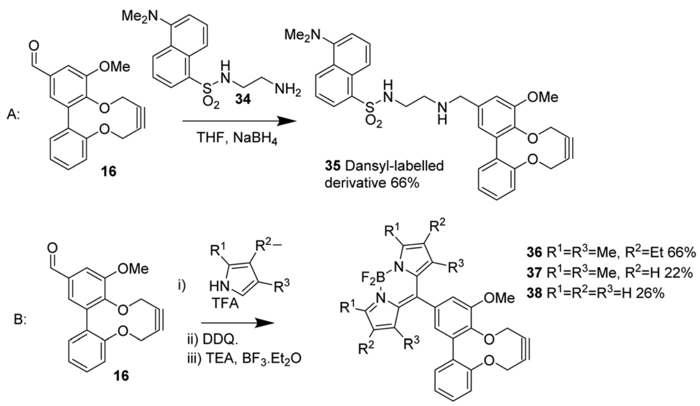
Other reagents were prepared through reactions of the aldehyde, notably fluorescent groups. The reductive amination of **16** with the amine-functionalised dansyl reagent **34** resulted in formation of **35** (Scheme 4A), which showed strong fluorescent behaviour upon irradiation. A number of BoDIPY derivatives **36–38** were also prepared through the direct reaction of pyrroles with the aldehyde and BF_3 in good yield (Scheme 4B).[17] Again, the ability to functionalise aldehyde **16** with a variety of reagents, without damaging the strained alkyne, is noteworthy.



Scheme 2 Use of aldehyde alkyne **16** in addition reactions with a range of azides.



Scheme 3 Functionalisation of beads with disperse red dye.



Scheme 4 Synthesis of fluorescent derivatives of **16**.

The X-ray crystallographic structure of **38** (Fig. 5) revealed the strained nature of the alkyne but also that the BoDIPY component was orientated almost perpendicular to the connected arene ring, presumable with restricted rotation about the connecting C–C bond. This accounts for the observed differences in chemical shifts of the groups attached to the heterocyclic rings of the BoDIPY unit in each of **36–38**, which will be in sharply different diastereotopic environments.

The fluorescence spectra for compounds **35–38** are given in the ESI.† However the strong and contrasting fluorescence behaviour of the BoDIPY dyes **36–38** is sharply illustrated by their response to UV irradiation. Compound **36** and **37** both show strong fluorescence upon irradiation whereas **38** gives a weaker response (ESI†).

The addition of benzylazide to BoDIPY derivative **36** was tested and worked efficiently to give two regiosiomers **39** and **40** in a 1 : 1 ratio (Fig. 6). In this case, we were able to separate the isomers by flash chromatography and independently characterise them. We have not unambiguously established which regiosiomer is which, of the two possibilities, however on the basis of the positions of the methylene groups in the ^{13}C-NMR spectra compared to previous examples, we have tentatively assigned them as shown in Fig. 6 (see ESI†).

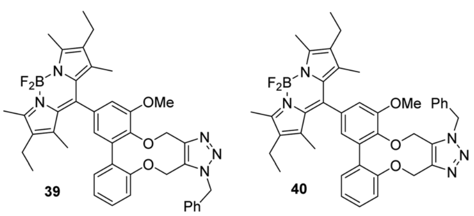


Fig. 6 Separated cycloaddition products **39** and **40**.

Further derivatives were also prepare from the corresponding alcohol **19** using a variety of coupling methods (Fig. 7). These included a biotin-containing reagent **41** which was formed through formation of an ester bond to biotin in one step.

It was also possible to attach a group through a carbamate *i.e.* **42**, using *N*,*N*′-disuccinimidyl carbonate (DSC) as a coupling agent to attach alcohol **19** to form the dansyl amine derivative **34**.[7d,18] Finally, from the alcohol, the direct reaction with an isocyanate could also be employed to create a derivative

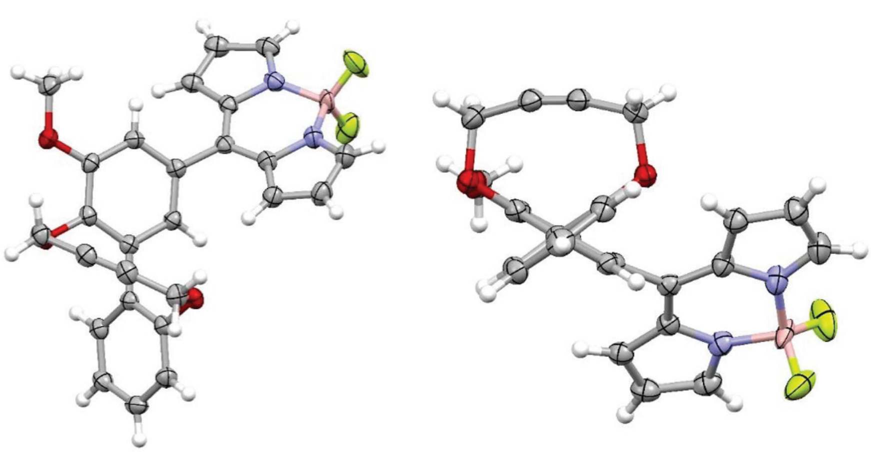


Fig. 5 X-ray crystallographic structure of **38** (ellipsoids are plotted at the 50% probability level). The bond angles at the sp atoms are 165.7° and 168.1° and the biphenyl torsion angle is 68.6°.

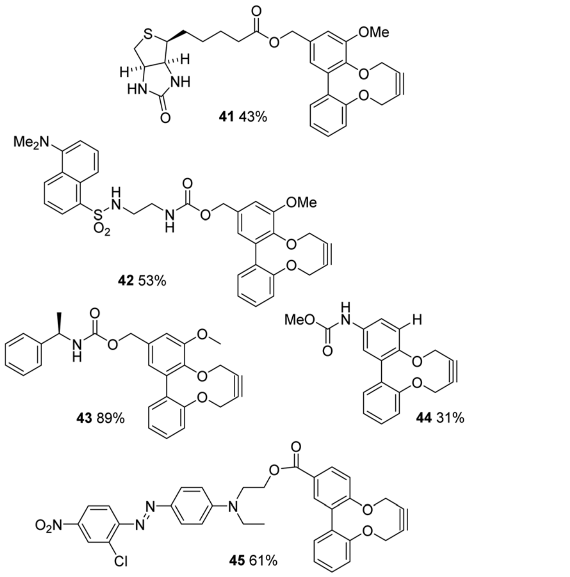


Fig. 7 Functionalised derivatives of alcohol **19** and acid **5** strained alkynes which were prepared in this project.

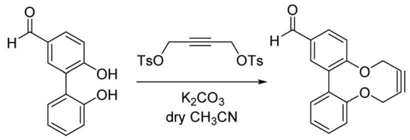
with a carbamate linkage *i.e.* **43**. Formation of derivatives from the acid **5** was also investigated; the *in situ* formation of isocyanate from acid **5** using diphenylphosphoryl azide and trapping with MeOH gave carbamate derivative **44** through a method that could be used for future functionalisation. Acid **5** was also linked using EDC·HCl to create the disperse-red functionalised **45**. These results (Fig. 7) illustrate the range of methods which can be employed to functionalise the strained alkynes.

In conclusion, we have prepared a selection of derivatives, including fluorescently-labelled variants, of a new class of strained alkyne, which benefit from ease of synthesis from readily available and inexpensive starting materials through a short sequence of reactions. We have demonstrated that this class of alkyne undergoes uncatalysed cycloaddition reactions with azides with minimal decomposition or side product formation. Studies of the applications of these reagents are ongoing and further results will be published in due course.

Experimental section

General experimental details, synthesis of intermediates **7**,[13] **11**,[12] **12**,[12] **13**,[19] **34**[20] and compounds **29–31** and **41–45** are in the ESI.†

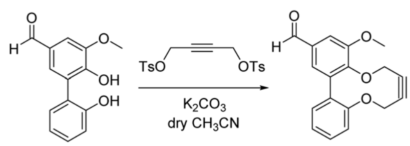
Alkyne 15



A series of strained alkynes, based on the 2,2′-dihydroxy-1,1′-biaryl structure, were prepared in a short sequence from readily-available starting materials. This compound is novel.

2′,6-Dihydroxybiphenyl-3-carbaldehyde **11** (3.20 g, 14.9 mmol), potassium carbonate (10.22 g, 73.95 mmol) and but-2-yne-1,2-diyl bis(4-methylbenzenesulfonate) **14** (5.31 g, 13.5 mmol) were added to a clean dry schlenk. The schlenk was then put under nitrogen and purged, thereafter dry acetonitrile (747 mL) was added to the mixture and the reaction left to stir at rt for 10 days. The organics were removed under vacuum, water (500 mL) and DCM (500 mL) were added and the product extracted with DCM (3 × 300 mL). The organic extracts were washed with brine and dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by column chromatography (8 : 2 hexane : ethyl acetate) to afford the product **15** as a white solid (1.50 g, 5.68 mmol, 38%). Mp 143–145 °C; (found (ESI-Q-TOF) $[M + Na]^+$ 287.0675. $C_{17}H_{12}O_3Na$ requires 287.0679); ν_{max} 2910, 2863, 1686, 1568, 1495, 1473, 1415, 1345, 1305, 1288, 1188 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.98 (1H, s, CHO), 7.94 (1H, dd, *J* 8.4, 2.9, ArH), 7.75 (1H, d, *J* 2.0, ArH), 7.44–7.40 (1H, m, ArH), 7.32 (1H, d, *J* 8.3, ArH), 7.22–7.19 (3H, m, ArH), 4.63–4.61 (1H, m, CH_2), 4.54–4.50 (m, 1H, CH_2), 4.41–4.32 (m, 2H, CH_2); δ_C (125 MHz, $CDCl_3$) 191.2, 159.8, 154.4, 136.8, 134.9, 134.6, 132.6, 131.7, 129.7, 129.6, 124.3, 123.6, 122.6, 87.3, 86.0, 63.8, 63.5; *m*/*z* (ESI) 287.1 ($[M + Na]^+$).

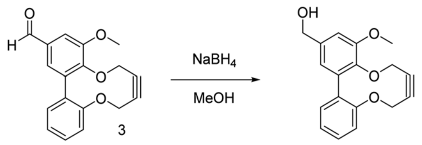
Alkyne 16



This compound is novel.

2′,6-Dihydroxy-5-methoxybiphenyl-3-carbaldehyde **12** (1.70 g, 6.96 mmol), potassium carbonate (4.76 g, 34.4 mmol) and but-2-yne-1,2-diyl bis(4-methylbenzenesulfonate) **14** (2.47 g, 6.27 mmol) were added to a schlenk. The schlenk was then put under nitrogen and purged, thereafter dry acetonitrile (346 mL) was added to the mixture and the reaction was left to stir at rt for 10–14 days. The organics were removed under vacuum, water (400 mL) and DCM (400 mL) were added and the product extracted with DCM (3 × 200 mL). The organics were collected and washed with brine and dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by column chromatography (8 : 2 hexane : ethyl acetate) to afford **16** as a white solid (1.2 g, 4.08 mmol, 59%). Mp 171–173 °C; (found (ESI-Q-TOF) $[M + Na]^+$ 317.0787. $C_{18}H_{14}O_4Na$ requires 317.0784); ν_{max} 2951, 2923, 2852, 1687, 1601, 1580, 1491, 1459, 1426, 1384, 1334, 1290, 1240, 1180, 1163, 1127 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.92 (1H, s, C*H*O), 7.49 (1H, s, Ar*H*), 7.44–7.40 (1H, m, Ar*H*), 7.33 (1H, s, ArH), 7.22–7.19 (3H, m, ArH), 4.69–4.66 (1H, m, CH_2), 4.56–4.60 (2H, m, CH_2), 4.37–4.34 (1H, m, CH_2) 3.98 (3H, s, OCH_3); δ_C (125 MHz, $CDCl_3$) 191.5, 154.4, 154.2, 148.1, 137.6, 134.7, 132.7, 131.7, 129.7, 129.0, 124.4, 122.6, 108.6, 86.9, 86.7, 63.6, 60.5, 55.9; *m*/*z* (ESI) 317.1 ($[M + Na]^+$). This reaction was also monitored by HPLC over 14 days, using 15 : 85 IPA : Hexane, 1 ml min^{-1}, IB column. Full details are in the ESI.† The X-ray crystallographic structure of this compound was obtained and is described in the ESI.†

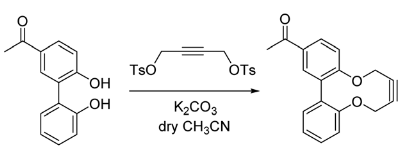
Alkyne alcohol 19



This compound is novel.

$NaBH_4$ (15 mg, 0.41 mmol, 1.0 eq.) was added carefully at 0 °C to a stirring solution of **16** (0.12 g, 0.41 mmol, 1.0 eq.) in methanol (10 mL) under a nitrogen atmosphere and the reaction was left for 1 hour to react at rt. The methanol was removed under vacuum and the residue was redissolved in ethyl acetate (15 mL). The organic extracts were washed with sat. NH_4Cl (15 mL) and then brine (15 mL). The organics collected, dried over Na_2SO_4, filtered and concentrated under vacuum to afford a white solid. This was purified by column chromatography (1 : 1 hexane : ethyl acetate) to afford the product **19** as a white solid (0.12 g, 0.40 mmol, 99%). Mp 165–168 °C; (found (ESI-Q-TOF) $[M + Na]^+$ 319.0940. $C_{18}H_{16}O_4Na$ requires 319.0941); ν_{max} 3522, 2927, 2866, 2835, 1587, 1494, 1446, 1421, 1338, 1264, 1246, 1192, 1165, 1133, 1122 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.39–7.34 (1H, m, Ar*H*), 7.19–7.17 (2H, m, Ar*H*), 7.14 (1H, d, *J* 7.9, Ar*H*), 7.01 (1H, d, *J* 1.7, ArH), 6.74 (1H, d, *J* 1.8, ArH), 4.65 (2H, s, CH_2OH), 4.63–4.57 (1H, m, CH_2), 4.53–4.47 (1H, m, CH_2), 4.41–4.36 (1H, m, CH_2), 4.34–4.28 (1H, m, CH_2), 3.91 (3H, s, OCH_3); δ_C (100 MHz, $CDCl_3$) 154.2, 153.3, 141.7, 137.0, 136.8, 135.8, 131.9, 129.1, 124.2, 122.4, 122.2, 109.9, 87.5, 85.9, 65.0, 63.5, 60.2, 55.7; *m*/*z* (ESI) 319.1 ($[M + Na]^+$).

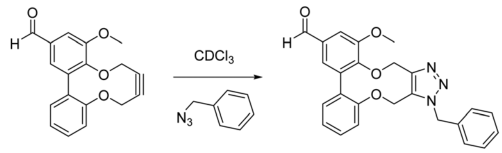
Ketoalkyne 17



This compound is novel.

In a round bottom flask under nitrogen atmosphere **13** (550 mg, 2.41 mmol, 1.2 equiv.) and but-2-yne-1,4-diyl-bis (4-methylbenzenesulfonate) (792 mg, 2.01 mmol) were dissolved in anhydrous acetonitrile (111 mL). K_2CO_3 (1.39 g, 10.0 mmol) was added and the mixture was stirred at RT for 14 days. The volatiles were removed in vacuum and H_2O (50 mL) was added. The product was extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and solvent removed *via* rotary evaporation. The product was purified by column chromatography on silica (hexane/EtOAc = 4 : 1) to give **17** (252 mg, 0.906 mmol, 45%) as a crystalline white solid. Crystals suitable for X-ray spectroscopy were grown by vapour diffusion of hexane into a $CHCl_3$ solution of the compound. Mp 137–139 °C. (Found (ESI-Q-TOF) $[M + Na]^+$ 301.0834. $C_{18}H_{14}O_3Na$ requires 301.0835); ν_{max} 2158, 1679, 1499, 1357, 1307, 1251, 1188, 1106, 963 cm^{-1}; δ_H (500 MHz, $CDCl_3$); 8.00 (1H, d, *J* 8.4, ArH), 7.82 (1H s, ArH), 7.42–7.39 (1H, m, ArH), 7.25–7.18 (4H, m, ArH), 4.60–4.50 (2H, m, CH_2), 4.39–4.32 (2H, m, CH_2), 2.57 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 197.3 (C=O), 158.7 (C), 154.2 (C), 136.1 (C), 135.0 (C), 133.5 (C), 132.9 (CH), 131.8 (CH), 129.1 (CH), 129.0 (CH), 124.8 (CH), 123.2 (CH), 123.0 (CH), 87.5 (C), 86.5 (C), 64.0 (CH_2). 63.7 (CH_2), 26.8 (CH_3); *m*/*z* (ESI) 278.08 ($[M]^+$), 301.08 ($[M + Na]^+$).

Cycloadduct 21

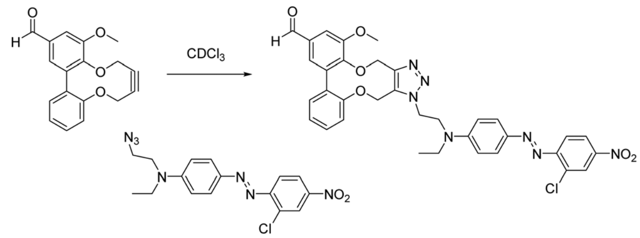


This compound is novel.

Alkyne **16** (30 mg, 0.102 mmol) and benzyl azide **20** (13.8 mg, 13 μL, 0.102 mmol) were stirred in MeCN (0.6 mL) for 6 days at rt (*ca.* 0.17 M), monitoring each day by TLC. At the end of this time the solvent was removed under vacuum and the product purified by flash chromatography on silica gel (hexane : EtOAc, 7 : 3) to yield the product **21** as a white solid (40 mg, 0.94 mmol, 84%). TLC (hexane : EtOAc, 7 : 3), silica, R_f 0.15; M.p. 181–184 °C; (found (ESI+): $[M + Na]^+$ 450.1426. $C_{25}H_{21}N_3NaO_4$ requires 450.1424); ν_{max} 1684, 1575, 1493, 1155, 722 cm^{-1}; δ_H (500 MHz, $CHCl_3$, two regioisomers 3 : 2); 9.94 (0.6H, s, CHO, major regiosomer). 9.91 (0.4H, s, CHO, minor regiosomer), 7.52 (1H, s, ArH), 7.47–7.43 (2H, m, ArH), 7.35–7.30 (3H, m, ArH), 7.20–7.05 (2.6H, m, ArH, 3 × major and 2 × minor regiosiomer), 7.01 (0.6H, t, *J* 7.0, ArH, major regiosomer), 6.96 (0.4H, t, *J* 7.5, ArH, minor regiosomer), 6.90 (0.4H, t, *J* 7.5, ArH, minor regiosomer), 6.09 (0.4H, d, *J* 8.0, CH, minor regiosomer), 5.87 (0.4H, d, *J* 11.0, CH, minor regiosomer), 5.80–5.72 (1.2H, m, CH, 2 × major regiosomer), 5.57 (0.6H, d, *J* 13.0, CH, minor regiosomer), 5.52–5.45 (1.4H, m, CH, 1 × major and 2 × minor regioisomer), 5.20 (0.6H, d, *J* 15.0, CH, major regiosomer), 5.04 (0.4H, d, *J* 14.0, CH, minor regiosomer), 4.96 (0.4H, d, *J* 11.0, CH, minor regiosomer), 4.83 (0.6H, d, *J* 13.0, CH, major regiosomer), 4.02 (3H, s, OCH_3), 3.95 (3H, s, OCH_3); δ_C (125 MHz, $CDCl_3$) 191.0 (CH), 191.0 (CH), 153.8 (C), 153.6 (C), 152.7 (C), 152.6 (C), 151.7 (C), 145.0 (C), 144.2 (C), 134.9 (C), 134.1 (C), 133.6 (C), 133.1 (C), 133.0 (C), 132.6 (C), 132.4 (C), 131.4 (CH), 130.7 (CH), 129.5, (CH), 129.3 (CH), 129.0 (CH), 128.5 (C), 128.0 (C), 127.7 (CH), 127.1 (CH), 126.7 (CH), 122.3 (CH), 121.9 (CH), 113.2 (CH), 111.2 (CH), 110.6 (CH), 109.9 (CH), 67.5 (CH_2), 62.6 (CH_2), 61.0 (CH_2), 57.7 (CH_2), 56.2 (CH_3), 56.1 (CH_3), 53.0 (CH_2), 52.0 (CH_2). *m*/*z* (ES-API+) 450.0 ($[M + Na]^+$). The reaction was also followed over time by ^1H NMR and full details are in the ESI.†

Alkyne **16** (15 mg, 51.0 μmol) and benzyl azide **20** (6.4 mg, 51.0 μmol) were added together in deuterated chloroform (0.4 mL) (0.128 M in both reagents) and the reaction was followed at rt by ^1H NMR.

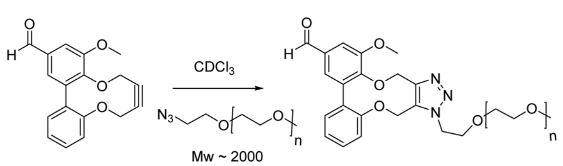
Disperse red cycloadduct 23



This compound is novel.

Aldehyde **16** (15 mg, 51.0 μmol) and azide **22** (19 mg, 51.0 μmol) were combined in deuterated chloroform (0.4 mL) and the reaction (*ca.* 0.128 M in both reagents) was left at rt. The progression of the reaction was monitored daily. The progression of the reaction was monitored daily by ^{1}H NMR (ESI†). Upon completion, the reaction was worked up and the product purified by column chromatography (DCM→85 : 15 DCM : EtOAc) to give **23** as a red solid (26 mg, 0.039 mmol, 76%). TLC DCM, silica, R_f 0.05; M.p. 155–158 °C; (found (ESI+): $[M + Na]^+$ 690.1843. $C_{34}H_{30}ClN_7NaO_6$ requires 690.1838); ν_{max} 1688, 1597, 1513, 1333, 1121, 745 cm^{-1}; δ_H (300 MHz, $CHCl_3$) (two regioisomers 1 : 1); 9.95 (0.5H, s, CHO). 9.90 (0.5H, s, CHO), 8.50 (1H, s, ArH), 8.20–8.15 (1H, m, ArH), 8.05–8.00 (1H, m, ArH), 7.95–7.90 (1H, m, ArH), 7.80–7.75 (1H, m, ArH), 7.45 (1H, d, *J* 13.0, ArH), 7.30–7.24 (3H, m, ArH), 7.15–7.05 (1H, m, ArH), 6.90–6.85 (1H, m, ArH), 6.80 (1H, d, *J* 12.0, ArH), 6.75 (1H, d, *J* 12.0 ArH), 4.85 (1H, d, *J* 14.0, CH), 5.50–4.50 (5H, m, OCH and NCH), 4.10–3.80 (5H, m, NCH + OMe), 3.35–3.00 (1H, m, NCH), 2.60–2.40 (1H, m, NCH), 1.15 (3H, t, *J* 6.5, CH_3), 0.88 (3H, t, *J* 6.5, CH_3); δ_C (125 MHz, $CDCl_3$) 190.9, 190.8, 154.1, 153.8, 153.0, 152.8, 152.6, 152.5, 151.7, 151.3, 150.7, 150.5, 149.5, 147.3, 144.8, 144.7, 144.5, 134.3, 133.5, 133.0, 132.8, 132.8, 132.3, 131.5, 130.8, 129.1, 129.1, 129.0, 128.0, 127.0, 126.6, 126.0, 124.7, 122.6, 118.1, 116.0, 118.1, 113.1, 112.1, 111.4, 110.7, 109.9, 62.1, 60.8, 60.1, 58.6, 56.4, 50.4, 50.3, 46.0, 45.4, 11.8; *m*/*z* (ES-API+) 690.2 ($[M + Na]^+$).

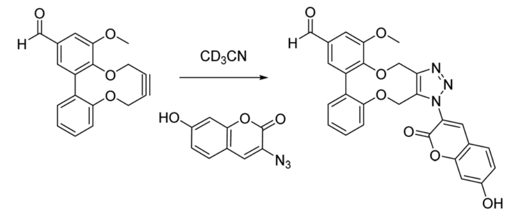
PEG-2000 azide cycloadduct 23



This compound is novel.

PEG2000-azide **24** (25 mg, 12.5 μmol) and alkyne **16** (3.0 mg, 12.5 μmol) were added together in deuterated chloroform (0.5 mL) and the reaction left at r.t. (*ca.* 0.025 M in both reagents). The progression of the reaction was monitored daily. The final product was also analysed by GPC, *ca.* 14 days for 100% conversion. The stacked spectra and the graph of conversion/time, as well as GPC data, are in the ESI.† Characteristic peaks of product were observed as follows: δ_H (300 MHz, $CDCl_3$) (*ca.* 1 : 1 ratio) 9.82 + 9.80 (1H, s × 2, *CHO*), 7.80–6.80 (6H, m, ArHs), 5.80–4.50 (6H, m, 2 × OCH_2, NCH_2 of addition product), 3.98 (3H, s, OCH_3), 3.90 (3H, s, PEG OCH_3), 3.60–3.30 (*ca.* 190H, m, PEG OCH_2 groups). Due to its heterogeneous nature, only the ^{1}H NMR and GPC data was recorded for this complex, and the product was not purified further.

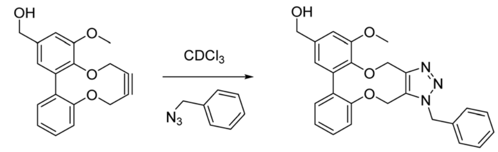
Fluorescent coumarin dye cycloadduct 27



This compound is novel.

Compound **16** (13 mg, 44.2 μmol) and coumarin azide **26** (9.0 mg, 44.2 μmol) were added together in deuterated acetonitrile (0.4 mL) and the reaction left at r.t. (*ca.* 0.11 M in both reagents). The progression of the reaction was monitored daily. Stacked NMR spectra and the conversion/time graph are in the ESI.† At the end of this time (80% conversion after 12 d) the solvent was removed and the product **27** was purified by column chromatography using a gradient of EtOAc in hexane (14 mg, 28 μmol, 64%,). TLC hexane : EtOAc 3 : 7, silica, R_f 0.60; M.p. 222–228 °C; (found (ESI+): $[M + Na]^+$ 520.1119. $C_{27}H_{19}N_3NaO_5$ requires 520.1115); ν_{max} 1725, 1688, 1605, 1574, 1223, 1133, 966, 684 cm^{-1}; δ_H (500 MHz, $CHCl_3$) (two regioisomers *ca.* 3 : 2); 9.89 (1H, s, CHO), 8.30–8.25 (0.4H, brs, NH or OH; by HSQC, minor regioisomer), 8.12 (0.4H, s, CH, minor regioisomer), 8.10–8.05 (0.6H, brs, NH or OH; by HSQC, major regioisomer), 7.95 (0.6H, s, CH, major regioisomer), 7.50–7.45 (1H, m, ArH), 7.42 (0.6H, s, ArH, major regioisomer), 7.35–7.30 (1H, m, ArH), 7.25–7.15 (2H, m, ArH), 6.95–6.85 (2H, m, ArH), 6.82–6.80 (1.8H, m, ArH, 1 × major, 3 × minor regioisomer), 6.65 (0.6H, d, *J* 10.0, ArH, major regioisomer), 5.88 (0.4H, d, *J* 13.0, OCH, minor regioisomer), 5.75 (0.6H, d, *J* 13.0, OCH, major regioisomer), 5.52 (0.4H, d, *J* 12.0, OCH, minor regioisomer), 5.35–5.25 (1H, m, OCH), 5.25 (0.6H, d, *J* 13.0, OCH, major regioisomer), 5.05–4.95 (1H, m, 0.4 OCH, minor regioisomer + 0.6 OCH, major regioisomer), 3.98 (1.2H, s, OCH_3, minor regioisomer); 3.88 (1.8H, s, OCH_3, major regioisomer), 1.65 (1H, brs, OH); δ_C (125 MHz, $CDCl_3$), 191.3 (CH), 191.2 (CH), 162.6 (C), 162.3 (C), 157.7 (C), 157.5 (C), 155.9 (C), 153.8 (C), 152.7 (C), 152.5 (C), 151.4 (C), 147.5 (C), 142.5 (CH), 141.1 (CH), 136.0 (C). 134.9 (C), 132.7 (C), 132.5 (C), 131.6 (CH), 130.9 (CH), 130.8 (CH), 129.4 (C), 128.9 (C), 128.5 (CH), 128.1 (CH), 127.2 (C), 126.7 (C), 122.5 (CH), 122.1 (CH), 118.9 (C), 118.5 (C), 115.2 (CH), 114.9 (CH), 113.0 (CH), 111.1 (C), 111.0 (C), 110.9 (CH). 110.7 (CH), 110.1 (CH), 103.6 (CH), 103.5 (CH), 67.1 (CH_2), 63.2 (CH_2), 60.7 (CH_2), 58.4 (CH_2), 56.2 (CH_3), 56.1 (CH_3); *m*/*z* (ES-API+) 520.0 ($[M + Na]^+$).

Alcohol 19/benzyl azide Cycloadduct 28

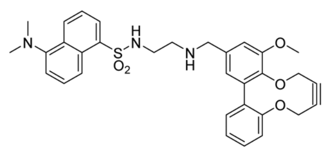


This compound is novel.

Alcohol **19** (30 mg, 0.096 mmol) and benzyl azide **20** (13 mg, 12 μL, 0.096 mmol) were stirred in MeCN (0.6 mL) for 5 days, monitoring each day by TLC (0.16 M in each reagent). At the end of this time the solvent was removed under vacuum and the product purified by flash chromatography on silica gel (hexane : EtOAc, 7 : 3) to yield the product **28** as a white solid (40 mg, 0.093 mmol, 97%). TLC hexane : EtOAc, 7 : 3, silica, R_f 0.1; M.p. 126–129 °C; (found (ESI+): $[M + Na]^+$ 452.1579. $C_{25}H_{23}N_3NaO_4$ requires 452.1581); ν_{max} 1589, 1492, 1444, 1423, 1335, 1273, 1161, 1138, 1108, 1004, 845, 798, 721 cm^{-1}; δ_H (500 MHz, $CHCl_3$) (two regioisomers 3 : 2); 7.45–7.40 (1H, m, ArH), 7.40–7.70 (10H, m, ArH), 5.95 (0.4H, d, *J* 8.0, CH, minor regioisomer), 5.70–5.55 (2H, m, CH), 5.45–5.25 (2H, m, CH), 5.05 (0.6H, d, *J* 14.0, CH, major regioisomer), 4.90 (0.4H, d, *J* 16.0, CH, minor regioisomer). 4.70 (0.4H, d, *J* 12.0, CH, minor regioisomer). 4.62 (0.6H, d, *J* 13.0, CH, major regioisomer), 4.58 (1.2H, brs, OCH_2Ar, 2 × major regioisomer), 4.54 (0.8H, brs, OCH_2Ar, 2 × minor regioisomer), 3.82 (1.4H, s, OCH_3, minor regioisomer), 3.80 (1.6H, s, OCH_3, major regioisomer), 2.20 (1H, brs, OH). δ_C (125 MHz, $CDCl_3$) 152.7 (C), 152.4 (C), 151.0 (C), 150.9 (C), 145.5 (C), 144.9 (C), 143.8 (C), 143.7 (C), 136.5 (C), 135.7 (C), 134.0 (C), 133.1 (C), 131.7 (C), 130.9 (C), 130.5 (C), 129.8 (CH), 128.5 (CH), 128.1 (C), 127.9 (C), 127.8 (CH), 127.7, (CH), 127.4 (CH), 127.3 (CH), 126.8 (CH), 126.2 (CH), 124.8 (CH), 123.5 (CH), 121.1 (CH), 112.0 (CH), 110.1 (CH), 110.0 (CH), 109.4 (CH), 66.2 (CH_2), 64.0 (CH_2), 63.9 (CH_2), 61.4 (CH_2), 59.8 (CH_2), 56.5 (CH_2), 55.0 (CH_3), 54.8 (CH_3), 51.9 (CH_2), 50.9 (CH_2).

m/*z* (ES-API+) 452.0 ($[M + Na]^+$). The reaction was followed over time in a separate run using alcohol **19** (15 mg, 0.050 mmol) and benzyl azide (6.5 mg, 0.050 mmol) in $CDCl_3$ (0.4 mL) ([**19**] *ca.* 0.13 M). The conversion/time graph for a separate reaction is in the ESI.†

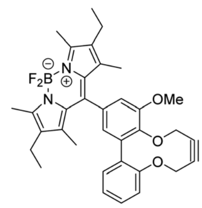
01Dansyl amine alkyne 35



This compound is novel.

N-(2-Aminoethyl)-5-(dimethylamino)naphthalene-1-sulfonamide **34** (100 mg, 0.34 mmol) was added to aldehyde strained alkyne **16** (100.3 mg, 0.34 mmol) in THF (1 mL) and heated to reflux for two hours. The reaction was cooled to ambient temperature, $NaBH_4$ (25.7 mg, 0.68 mmol) was added and stirred for 18 hours. The reaction was diluted with EtOAc (5 mL), washed with sat. aq. $NaHCO_3$ (3 × 5 mL), and dried over $MgSO_4$. Purification by column chromatography (silica; EtOAc/Hex; 20 : 80 → 50 : 50) afforded **35** as a waxy green solid (128 mg, 0.22 mmol, 66%). Mp 67–73 °C. (Found (ESI) $[M + H]^+$, 572.2212. $C_{32}H_{34}N_3O_5S$ requires 572.2214). ν_{max} 2923, 2784, 1587, 1489, 1234, 1102, 1003 and 757 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.52 (1H, d, *J* 8.5, ArH), 8.31–8.23 (2H, m, ArH), 7.54–7.48 (1H, m, ArH), 7.45–7.37 (2H, m, ArH), 7.22–7.15 (3H, m, ArH), 7.08 (1H, d, *J* 7.5, ArH), 6.79 (1H, d, *J* 2.0, ArH), 6.53 (1H, d, *J* 1.9, ArH), 4.62–4.49 (2H, m, OCH_2), 4.43–4.27 (2H, m, OCH_2), 3.90 (3H, s, OCH_3), 3.45 (2H, d, *J* 5.3, NCH_2), 2.95 (2H, t, *J* 5.6, NCH_2), 2.85 (6H, s, $N(CH_3)_2$). δ_C (126 MHz, $CDCl_3$) 154.5, 153.3, 152.1, 141.5, 136.9, 136.1, 135.9, 134.7, 132.1, 130.5, 130.0, 129.9, 129.7, 129.3, 128.6, 124.4, 123.3, 123.3, 122.7, 118.8, 115.3, 110.9, 87.7, 86.2, 63.7, 60.4, 55.9, 53.0, 47.3, 45.5, 42.6. *m*/*z* (ESI) 570 ($[M + H]^+$, 100%) and 606 ($[M + Na]^+$, 10%); UV-Vis (MeCN) λ_{max} (ε/M^{-1} cm^{-1}): 338 (10 500), 234 ((36 200) nm; fluorescence (MeCN; λ_{ex} = 367 nm); λ_{em} 510 nm.

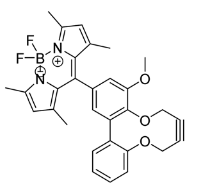
2,4-Dimethyl-3-ethyl BoDIPY strained alkyne 36



This compound is novel.

To a solution of alkyne **16** (100 mg, 0.340 mmol, 1.0 eq.) in DCM (22 mL) was added 3-ethyl-2,4-dimethylpyrrole (87.3 mg, 0.1 mL, 0.71 mmol, 2.1 eq.), at which point the solution became red, TFA (3.9 mg, 2 μL, 34 μmol, 0.1 eq.) was added, resulting in the formation of a green solution which was stirred for 3 h, during which time it returned to a red colour. The solution was then washed with a saturated solution of $NaHCO_3$ (20 mL), turning the organic layer yellow, and brine (20 mL). The organic layer was then dried over $MgSO_4$, which was subsequently removed by filtration, and the solvent was evaporated. The residue was then dissolved in toluene (12.3 mL) and a suspension of DDQ (84 mg, 0.37 mmol, 1.1 eq.) in toluene (6 mL) was added, resulting in the solution turning purple. The mixture was then stirred for 1 h before TEA (141 mg, 0.20 mL, 1.4 mmol, 4.1 eq.) was added along with $BF_3 \cdot Et_2O$ (290 mg, 0.25 ml, 2.04 mmol, 6.0 eq.) and the mixture was refluxed at 75 °C for 45 min. The mixture was then cooled before being filtered through a silica plug eluted with DCM. The resultant solution was then concentrated under vacuum to afford the crude product. The product was purified by column chromatography using an eluent of 2 : 8 EtOAc : pet. ether to afford the pure product **36** as a red/green metallic solid (128 mg, 0.225 mmol, 66%). (Found (ESI) $[M + Na]^+$ 591.2609 $C_{34}H_{35}BF_2N_2NaO_3$ requires 591.2601; ν_{max} 2962, 2928, 2868, 1536, 1454, 1315, 1182, 972 and 960 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.38 (1H, t, *J* 7.5, ArH), 7.17–7.22 (1H, m, ArH), 7.14 (1H, d, *J* 7.9, ArH), 6.87 (1H, d, *J* 1.5, ArH), 6.78 (1H, d, *J* 1.7, ArH), 4.62–4.71 (1H, m, CH*H*), 4.46 (2H, d, *J* 13.9, 2 × C*H*H), 4.31–4.39 (1H, m, CH*H*), 3.89 (3H, s, OCH_3), 2.54 (3H, s, CH_3), 2.51 (3H, s, CH_3), 2.35 (2H, q, *J* 7.5, CH_2CH_3), 2.29 (2H, q, *J* 7.6, CH_2CH_3), 1.64 (3H, s, CH_3), 1.45 (3H, s, CH_3), 1.03 (3H, t, *J* 7.6, CH_2CH_3), 0.97 (3H, t, *J* 7.5, CH_2CH_3); δ_C (125 MHz, $CDCl_3$) 154.4, 154.1, 153.8, 153.7, 142.7, 139.5, 138.7, 138.2, 138.0, 135.3, 132.7, 131.7, 131.6, 130.8, 130.7, 129.4, 124.3, 124.1, 122.6, 111.2, 87.2, 86.1, 63.3, 60.5, 56.1, 17.2, 17.1, 14.7, 14.6, 12.5, 11.8 and 11.4; δ_F (376 MHz, $CDCl_3$) −146.53–−145.15 (brm); *m*/*z* (ESI) 591 ($[M + Na]^+$). Fluorescence (MeCN; λ_{ex} = 524 nm); λ_{em} = 534 nm; UV-Vis (MeCN) λ_{max} (ε/M^{-1} cm^{-1}): 520 (14 700) nm.

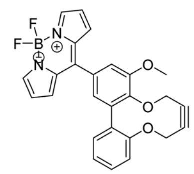
2,4-Dimethyl BoDIPY Strained alkyne 37



This compound is novel.

To a solution of aldehyde **16** (100 mg, 0.340 mmol, 1.0 eq.) in DCM (22 mL), 2,4-dimethylpyrrole (67 mg, 0.71 mmol, 2.1 eq.), TFA (3.8 mg, 34 μmol, 0.1 eq.) was added and the solution was stirred for 3 h. The solution was then washed with a saturated solution of $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was then dried over $MgSO_4$, which was subsequently removed by filtration, and the solvent evaporated. The residue was then dissolved in toluene (12.3 mL) and a suspension of DDQ (84 mg, 0.37 mmol, 1.1 eq.) in toluene (6 mL) was added. The mixture was then stirred for 1 h before TEA (141 mg, 1.4 mmol, 4.1 eq.) was added along with $BF_3{\cdot}Et_2O$ (290 mg, 2.04 mmol, 6.0 eq.) and the mixture was refluxed at 80 °C for 45 min. The mixture was then cooled to rt, before being filtered through a silica plug eluted with DCM. The resulting solution was then concentrated under vacuum to afford the crude product. The crude product was purified by flash column chromatography to afford the pure product **37** as an orange/green metallic solid (38 mg, 0.074 mmol, 22%). R_f = 0.44 (Hexane–EtOAc 3 : 1); (found (ESI)) $[M + Na]^+$ 535.1983. $C_{30}H_{27}BF_2N_2NaO_3$ requires 535.1980; ν_{max} 2955, 2922, 2853, 1536, 1504, 1456, 1264 and 964 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.35–7.41 (1H, m, Ar*H*), 7.23–7.25 (1H, m, Ar*H*), 7.17–7.22 (1H, m, ArH), 7.11–7.16 (1H, m, ArH), 6.86 (1H, s, ArH), 6.77 (1H, s, ArH), 6.03 (1H, s, MeCC*H*CMe), 5.97 (1H, s, MeCC*H*CMe), 4.66 (1H, d, *J* 15.4, C*H*H), 4.40–4.48 (2H, m, 2 × CH*H*), 4.33 (1H, d, *J* 15.4, C*H*H), 3.88 (3H, s, OCH_3), 2.56 (3H, s, CH_3), 2.53 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 155.5, 155.4, 154.4, 154.2, 143.5, 142.9, 141.0, 138.2, 135.2, 131.5, 131.3, 130.7, 129.4, 124.3, 123.8, 122.6, 121.2, 121.1, 110.8, 87.2, 86.1, 63.2, 60.5, 56.1, 14.5 and 14.1; *m*/*z* (ESI) 535 ($[M + Na]^+$); fluorescence (MeCN; λ_{ex} = 504 nm); λ_{em} = 510 nm; UV-Vis (MeCN) λ_{max} (ε/M^{-1} cm^{-1}): 498 (18 407) nm.

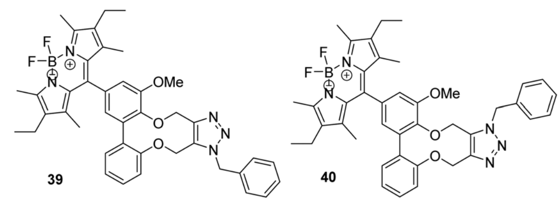
BoDIPY strained alkyne 38



This compound is novel.

To a solution of aldehyde **16** (100 mg, 0.340 mmol, 1.0 eq.) in DCM (22 mL) pyrrole (47 mg, 0.71 mmol, 2.1 eq.), TFA (3.8 mg, 34 μmol, 0.1 eq.) was added and the solution was stirred for 3 h. The solution was then washed with a saturated solution of $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was then dried over $MgSO_4$, which was subsequently removed by filtration, and the solvent evaporated. The residue was then dissolved in toluene (12.3 mL) and a suspension of DDQ (84 mg, 0.37 mmol, 1.1 eq.) in toluene (6 mL) was added. The mixture was then stirred for 1 h before TEA (141 mg, 1.4 mmol, 4.1 eq.) was added along with $BF_3{\cdot}Et_2O$ (290 mg, 2.04 mmol, 6.0 eq.) and the mixture was refluxed at 80 °C for 45 min. The mixture was then cooled to rt, before being filtered through a silica plug eluted with DCM. The resulting solution was then concentrated under vacuum to afford the crude product. The crude product was purified by flash column chromatography to afford the pure product **38** as an orange/green metallic solid (42 mg, 0.089 mmol, 26%). R_f = 0.55 (DCM); (found (ESI)) $[M + Na]^+$ 479.1351 $C_{26}H_{19}BF_2N_2NaO_3$ requires 479.1354; ν_{max} 1545, 1410, 1385, 1261, 1114, 1078 and 956 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.94 (2H, brs, 2 × NC*H*CHCH), 7.40–7.45 (1H, m, ArH), 7.27–7.31 (2H, m, ArH), 7.23–7.26 (1H, m, ArH), 7.20–7.22 (1H, m, ArH) 7.18–7.20 (2H, m, ArH + NCHCHC*H*), 7.08–7.10 (1H, m, NCHCHC*H*), 6.59 (2H, brs, 2 × NCHC*H*CH), 4.71 (1H, d, *J* 15.4, C*H*H), 4.62 (1H, d, *J* 15.4, CH*H*), 4.50 (1H, d, *J* 15.4, CH*H*), 4.41 (1H, d, *J* 15.4, C*H*H), 3.97 (3H, s, OCH_3); δ_C (125 MHz, $CDCl_3$) 154.5, 153.2, 146.8, 145.1, 143.9, 137.3, 134.9, 131.7, 129.8, 126.7, 127.0, 124.4, 122.6, 118.6, 113.6, 87.2, 86.7, 63.7, 60.6, 56.1; *m*/*z* (ESI) 479 ($[M + Na]^+$; fluorescence (MeCN; λ_{ex} = 508 nm); λ_{em} = 519 nm; UV-Vis (MeCN) λ_{max} (ε/M^{-1} cm^{-1}): 497 (58 563) nm.

(Me, Et, Me) BoDIPY clicked product 39 and 40



These compounds are novel. We have not confirmed which regioisomer is which, however tentative assignments have been made; full details are in the ESI.†

To a solution of (Me, Et, Me) BoDIPY alkyne (28.4 mg, 0.05 mmol, 1 eq.) in $CDCl_3$ (0.5 mL), benzylazide (0.56 mg, 5.2 μL, 0.05 mmol, 1 eq.) was added. The reaction was followed by ^{1}H NMR. The solvent was then removed under vacuum to give the crude product. This was then purified by flash column chromatography (eluent EtOAc–Hexane gradiant 1 : 4–1 : 1), to give the pure products **39** and **40** in a 1 : 1 ratio as two isolable regioisomers A (first to elute) and B (second to elute). **Regioisomer A**: (13 mg, 0.0185 mmol, 37%). R_f = 0.4 (EtOAc–Hexane 1 : 1); (found (ESI)) $[M + Na]^+$ 724.3238. $C_{41}H_{42}BF_2N_5NaO_3$ requires 724.3248; ν_{max} 2960, 2923, 2853, 1539, 1472, 1314, 1181, 973 and 751 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.29–7.33 (3H, m, ArH), 7.21–7.25 (1H, m, ArH), 7.16 (1H, d, *J* 8.4, ArH), 7.09–7.14 (2H, m, ArH), 7.04 (1H, d, *J* 7.0, ArH), 6.95, (1H, t, *J* 7.4, ArH), 6.87 (1H, s, ArH), 6.82 (1H, s, ArH), 5.75 (1H, d, *J* 15.6, NC*H*H), 5.49 (1H, d, *J* 14.3, OC*H*H), 5.51 (1H, d, *J* 12.8, OC*H*H), 5.43 (1H, d, *J* 15.6, NCH*H*), 5.19 (1H, d, *J* 14.3, OCH*H*), 4.77 (1H, d, *J* 12.8, OCH*H*), 3.87 (3H, s, OCH_3), 2.54 (3H, s, CH_3), 2.52 (3H, s, CH_3), 2.25–2.38 (4H, m, 2 × CH_2CH_3),1.52 (3H, s, CH_3), 1.45 (3H, s, CH_3) 1.03 (3H, t, *J* 7.4, CH_2CH_3), 0.98 (3H, t, *J* 7.4, CH_3); δ_C (125 MHz, $CDCl_3$) 154.0, 152.5, 146.9, 145.2, 145.2, 139.4, 135.1, 134.3, 132.9, 132.5, 131.7, 130.6, 129.1, 129.0, 128.7, 128.4, 127.0, 122.4, 121.7, 113.4, 111.5, 63.0, 61.4, 56.2, 52.0, 23.6, 17.1, 12.5, 11.9 and 11.6; *m/z* (ESI) 724 ($[M + Na]^+$); fluorescence (MeCN; λ_{ex} = 528 nm); λ_{em} = 535 nm; UV-Vis (MeCN) λ_{max} (ε/M^{-1} cm^{-1}): 521 (14 466) nm. **Regioisomer B**: (13 mg, 0.0185 mmol, 37%). R_f = 0.3 (EtOAc–Hexane 1 : 1); (Found (ESI)) $[M + Na]^+$ 724.3245 $C_{41}H_{42}BF_2N_5NaO_3$ requires 724.3241; ν_{max} 2960, 2923, 2853, 1539, 1472, 1314, 1181, 973 and 751 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.42–7.46 (3H, m, ArH), 7.27–7.33 (3H, m, ArH), 7.16 (1H, d, *J* 8.4, ArH), 7.01–7.06 (1H, m, ArH), 6.90–6.93 (2H, m, ArH), 6.86, (1H, d, *J* 2.0, ArH), 6.73 (1H, d, *J* 2.0, ArH), 6.82 (1H, s, ArH), 5.80 (1H, d, *J* 11.6, OC*H*H), 5.73 (1H, d, *J* 14.3, NC*H*H), 5.53 (1H, d, *J* 14.3, NC*H*H), 5.38 (1H, d, *J* 14.5, OC*H*H), 5.02 (1H, d, *J* 14.5, OCH*H*), 4.95 (1H, d, *J* 11.6, OCH*H*), 3.91 (3H, s, OCH_3), 2.49–2.55 (6H, m, 2 × CH_3), 2.24–2.37 (4H, m, 2 × CH_2CH_3), 1.53 (3H, s, CH_3), 1.39 (3H, s, CH_2CH_3), 0.94–1.06 (6H, m, 2 × CH_3); δ_c (125 MHz, $CDCl_3$) 153.9, 153.8, 147.3, 144.6, 139.7, 134.3, 133.4, 133.1, 131.4, 130.8, 129.5, 129.3, 129.0, 128.9, 128.8, 127.6, 127.0, 122.3, 122.1, 113.5, 112.1, 67.6, 58.1, 56.3, 52.9, 17.1, 12.5, 12.0, 11.6; *m/z* (ESI) 724 ($[M + Na]^+$); fluorescence (MeCN; λ_{ex} = 528 nm); λ_{em} = 535 nm; UV-Vis (MeCN) λ_{max} (ε/M^{-1} cm^{-1}): 521 (14 466) nm.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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