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Photoinduced Cycloadditions in the Diversity-Oriented Synthesis Toolbox: Increasing Complexity with Straightforward Post-Photochemical Modifications

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Rapid growth of complexity and unprecedented molecular architectures is realised via the excited state intramolecular proton transfer (ESIPT) in *o*-acylamidobenzaldehydes and ketones followed by [4+2] or [4+4] cycloadditions with subsequent post-photochemical modifications. The approach is congruent with diversity-oriented synthesis, whereby photoprecursors are synthesised in a modular fashion allowing for up to four diversity inputs. The complexity of the primary photoproducts is further enhanced using straightforward and high-yielding post-photochemical modification steps such as reactions with nitrile oxides and nitrones, and Povarov and oxa-Diels–Alder reactions.

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Introduction

Despite large investments in pharmaceutical R&D[1] and a massive synthetic effort at the bench, as reflected by the number of new compounds synthesised annually,[2] new drugs – and especially new drugs with the novel mechanisms of action – are still rare, and the number of untreatable health conditions persists. It can be safely assumed that 'well in excess of 10000 medicinal chemistry compounds are synthesised for each approved drug.'[3] Such a moderate degree of success is often associated with the lack of structural diversity of compounds in the existing libraries which, in turn, results from the inadequate variety in the synthetic methods employed. Relatively few classes of reactions are used to access the majority of the compounds prepared for biological testing,[4] and the range of the used reactions is noticeably biased towards the 'easy' chemistry of sp^2–sp^2 carbon coupling.

Photochemical reactions are conspicuously absent from the toolbox of modern combinatorial and medicinal chemists, although one hopes that the visible light photoredox synthetic 'revolution' will bring the much needed change of this status quo.[5,6] Research efforts in our group are aimed at demonstrating the potential of photochemical methods in the context of diversity-oriented synthesis, leading to complex and topologically novel structures, potentially attractive from the medicinal chemistry standpoint. A sample selection of the scaffolds synthesised through photochemical methods in our group are presented in Fig. 1.[7]

The compounds depicted in Fig. 1 represent eight distinct molecular scaffolds, with a high content of sp^3-hybridised carbons (as indicated by fsp3 value),[8] relatively low molecular weight (MW), optimal lipophilicity (logP) and a small number of rotatable bonds. All these diverse compounds are accessible through a general and efficient strategy based on intramolecular [4+2] and [4+4] cycloadditions of azaxylylenes. These intermediates can be conveniently generated by the excited state intramolecular proton transfer (ESIPT) from photoprecursors that are, in turn, readily accessible through standard amide bond-forming reactions (Scheme 1).

Upon irradiation, *o*-formyl or *o*-acyl anilides undergo fast and efficient ESIPT to their tautomeric form, azaxylylene, with likely intersystem crossing into the triplet manifold.[9] The involvement of a triplet state is supported by (1) heavy atom acceleration of the reaction upon introduction of bromine atom in the azaxylylene precursor and (2) quenching of the cycloaddition reaction by such typical triplet state quenchers as oxygen or *trans*-piperylene. As Scheme 1 illustrates, the reaction is completed via another intersystem crossing and the intramolecular collapse of the singlet radical pair to form the products of formal [4+2] or [4+4] cycloadditions. Intramolecular fluorescence quenching with tethered unsaturated pendants revealed that the cycloaddition reaction is unlikely to occur in the singlet excited state. It was also ruled out for the ground state singlet.[9]

This photochemical reaction is fully congruent with the philosophy of diversity-oriented synthesis. The synthesis of the photoprecursor is straightforward and amenable to modular assembly, allowing for up to four diversity inputs. The photochemical step results in a dramatic growth of complexity, yielding two or more distinct molecular scaffolds, which can be further introduced into a post-photochemical reaction step. We have previously shown that the primary photoproducts lend themselves to various post-photochemical modifications, for

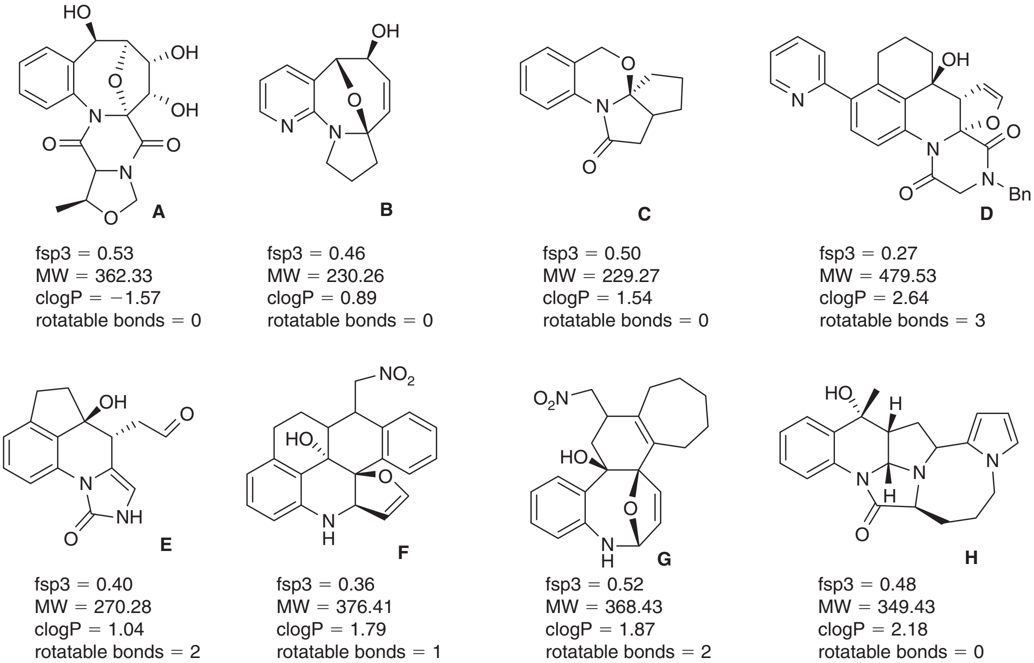
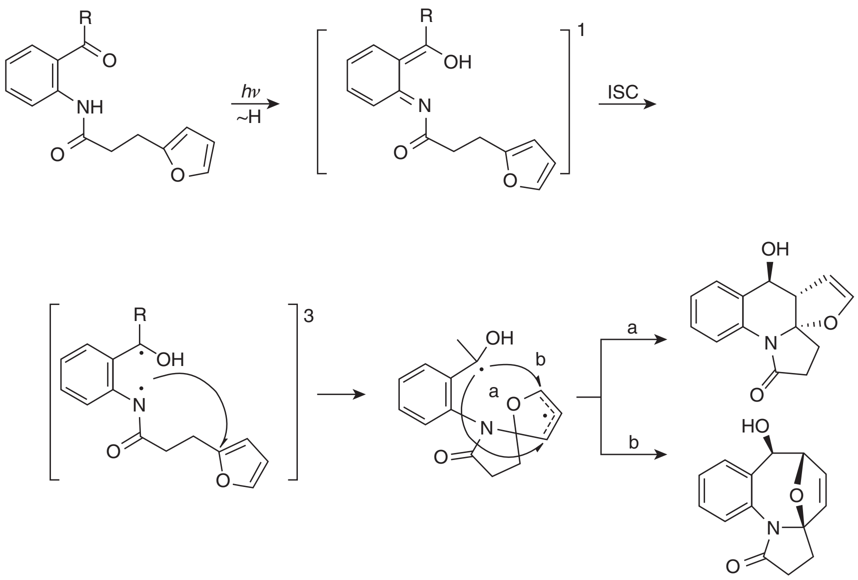


Fig. 1. A subset of diverse molecular scaffolds previously synthesised via intramolecular cycloadditions of photogenerated azaxylylenes.

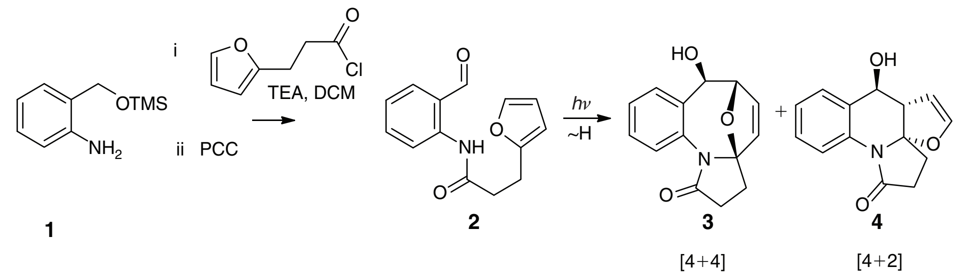


Scheme 1. Photochemical generation of azaxylylenes via ESIPT and their intramolecular cycloadditions. ISC = Intersystem crossing.

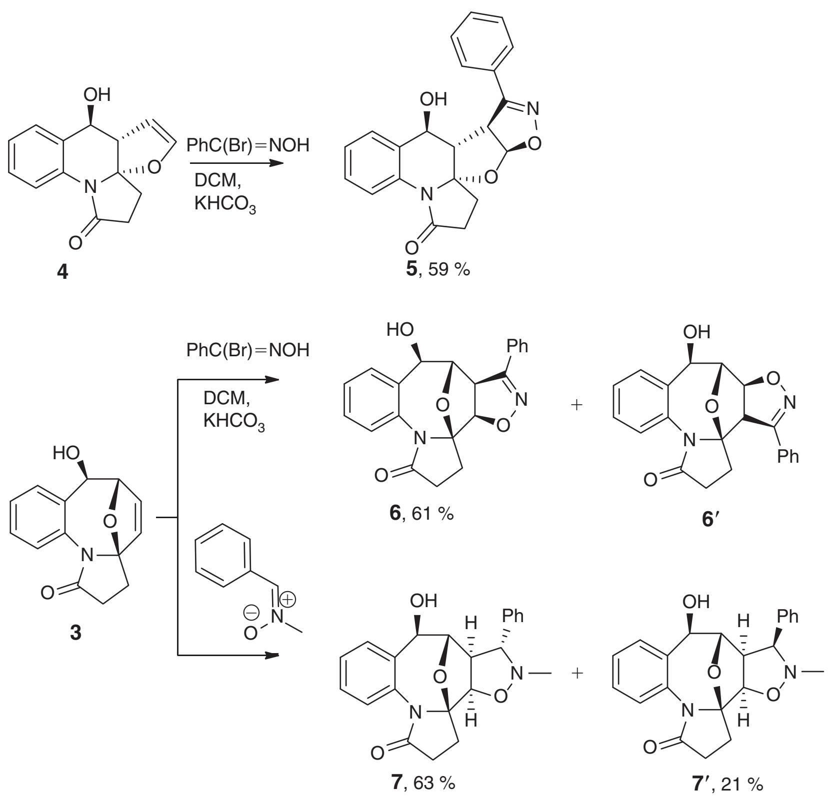
example, the Suzuki reaction.[7d] Further modifications offered by the double bonds in the [4+2] and [4+4] frameworks could allow for an increase in scaffold diversity and complexity via the addition of dipoles or heterodienes. Thus, the aim of the current study was to evaluate the scope of post-photochemical modifications and the opportunities for rapid access to extended polyheterocyclic sheets of unprecedented topology. We also utilised computer-aided property prediction for the synthesised compounds, and assessed their skeletal diversity and other properties. Specifically, we now report the post-photochemical reactions of the primary [4+4] and [4+2] photoproducts with phenylnitrile oxide, N-(phenylmethylene)methanamine N-oxide, 1-oxabutadienes, generated from the 1,3-dicarbonyl compounds and N-phenyl-aryl-2-ylmethanimines (Povarov reaction).

Results and Discussion

The model system for these studies was prepared via photo-induced cyclisation of 2-(3-(fur-2-yl)propanamido)benzaldehyde as shown in Scheme 2. The acylation of TMS-protected *o*-aminobenzyl alcohol **1**, followed by pyridinium chlorochromate (PCC) oxidation yielded photoprecursor **2**, which upon irradiation in a Rayonet photoreactor equipped with RPR-3500 UV lamps (a broad band 300–400nm UV source, with λ_{max} ~350 nm) underwent [4+2] and [4+4] cycloadditions to yield two distinct polyheterocyclic scaffolds in good yields.



Scheme 2. Synthesis of model compounds. TEA = triethylamine, DCM = dichloromethane, PCC = pyridinium cholorochromate.



Scheme 3. Reactions with dipoles (**6′** was observed by NMR but not isolated).

The reaction occurs diastereospecifically, yielding only *syn*-[4+4] and *anti*-[4+2], where *syn*- and *anti*- refers to the respective arrangement of the benzylic hydroxy group in the quinolinol or benzoazacane ring, and the oxygen in furan.

Reactions with Dipoles

Both [4+4] and [4+2] cycloadducts react with nitrile oxides,[10] generated from the corresponding oximes (Scheme 3). In both cases, the 1,3-dipolar cycloaddition of benzonitrile oxide occurs from the *exo*-face. Similarly to the previously described reaction with bromonitrile oxide, [4+4] cycloadduct produces two regioisomers **6** and **6′** in the ratio of 3 : 1, whereas [4+2] reacts regioselectively to give the charge-controlled **5** as the only product. The observed differences can be explained by the stereoelectronic properties of the alkenes: the [4+2] photoproduct possesses a dihydrofuran moiety, and the 1,3-dipolar cycloaddition is expected to proceed through a charge-controlled transition state, whereas the double bond in the [4+4] substrate is not as polarised, hence, both regioisomers are observed. The structure of the adducts was confirmed by analysis of their NMR spectra and comparison with the previously isolated adducts of bromonitrile oxide.[7g]

The [4+2] photoproduct does not tolerate the conditions for the addition of the nitrones,[11] degrading in the process, whereas the [4+4] photoproduct reacts cleanly to give two stereoisomers **7** and **7′** in the 3 : 1 ratio (Scheme 3). Both isomers result from the attack of the nitrone from the least hindered *exo*-face and differ in the relative position of the phenyl ring with the phenyl group pointing away from the pyrrolidinone moiety. We were able to obtain an X-ray structure for the major isomer **7**, and based stereochemical assignment of the minor isomer on the results of NOE experiments. The aliphatic regions of the ^{1}H NMR spectra of both stereoisomers **7** and **7′** possess two separate spin systems: H_a–H_b and H_c–H_d–H_e. The spin–spin coupling constant H_b–H_e is not observed experimentally. In both cases, H_e signal is a triplet at 2.73 (**7**) or 2.82 (**7′**) ppm. To unambiguously prove the structure of the products, we conducted NOE differences experiments for both isomers (Fig. 2). In **7**, upon irradiating the triplet H_e at 2.73 ppm, we see NOE of 3 % with H_a, which is indicative of the regiochemistry shown, as well as NOE of 13 % on H_b and H_c,[12] but no signal from H_d, which implies that protons H_d and H_e reside on the opposite faces of the isoxazoline ring. Similarly, in **7′**, upon irradiating the triplet H_e at 2.82 ppm, we see NOE of 8 % with protons H_a and H_b,[13] and again indicated that the phenyl group is located on the 'northern' side of the molecule, *syn* to the benzylic OH group and *anti* to the pyrrolidone moiety. Additionally, we see NOE on both H_c and H_d (13 % and 11 %, respectively), suggesting that all three protons are *syn* to each other.

Reaction with Dichlorocarbene

One observation that we made during this study was that the general reactivity of the remaining double bond in primary [4+4] photoproduct **3** was very low. Product **3** was then modified through the sequence of acid-induced bicyclo[4.2.1] → bicyclo[3.3.1] rearrangement and oxidation as shown in Scheme 4.[7g] Dichlorocarbene was generated in situ from chloroform and sodium hydroxide, but the reaction yielded α-chloroester **8**, which is presumably formed as a result of Jocic–Reeve reaction of the carbene with the ketone functionality[14].

We hypothesised that the carbene attacked from *exo*-side of the bicyclic benzoazacane ring, and the initially formed epoxide is ring-opened by the nucleophile (Cl^-) from the sterically accessible *exo*-side.

Hetero-Diels–Alder Reactions

Expectedly, the [4+4] adduct was not reactive in either the Povarov or the oxa-Diels–Alder reaction. However, the [4+2] product possessing a much more reactive vinyl ether moiety proved to react smoothly, yielding a single regio- and stereoisomer as a result of the Povarov reaction, and the reactions with both Meldrum's acid and barbituric acid-based *s-cis* oxabutadienes as shown in Scheme 5.

Povarov reaction[15,16] was conducted in 2,2,2-trifluoroethanol, as a solvent, at 40°C. Again, the 2-azadiene expectedly attacks from the less hindered *exo*-face, with the pyridine ring winding up in the thermodynamically favoured equatorial position. The structure of the product was supported by the NMR data. Among the aliphatic protons, H_c has the highest chemical shift, observed at 5.25 ppm as a doublet, *J* 7.7 Hz. H_b is characterised by ddd at 2.54 ppm with the spin–spin coupling constants of 10.4 Hz (with H_a), 7.8 Hz (with H_c), and 2.9 Hz (with H_d). The value of the biggest constant corresponds to axial–axial interaction, which puts the pyridine ring in equatorial position (Fig. 3).

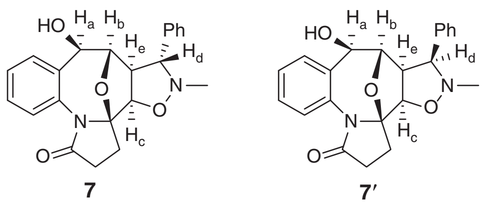


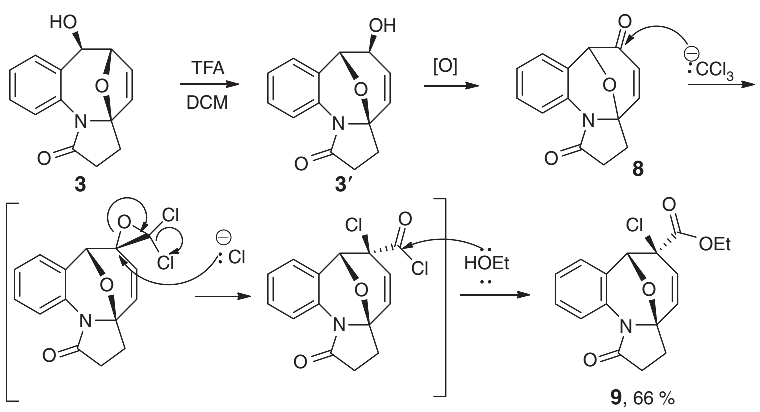
Fig. 2. Nuclear Overhauser Enhancement experiments.

Next, we attempted oxa-Diels–Alder reactions using oxabutadienes,[17] generated in situ from 1,3-dicarbonyl compounds (Meldrum's acid and dimethylbarbituric acid). The reaction with dimethylbarbituric acid proceeds smoothly, giving one stable product of *exo*-addition of the diene. The Meldrum's acid adduct was unstable, undergoing ketal hydrolysis followed by decarboxylation. The structure of the product was unambiguously proven by X-ray analysis. The structures of both products are supported by ^{1}H NMR analysis.

These post-photochemical modifications are not limited to furan-based photoproducts and can be carried out with thiophene- and pyrrole-based systems as well. Thiophene-based [4+2] photoproduct **13**, obtained in a manner similar to furanyl adduct **11**, was introduced into the reaction with dimethylbarbituric acid (Scheme 6). The reaction yielded a single product of a charge-controlled cycloaddition of the in situ-generated oxabutadiene to the dihydrothiophene moiety of **13**.

Similarly to furan-based compounds **11** and **12″**, the structure of **13** was determined by NMR analysis, which was further supported by the prediction of proton spin–spin coupling constants (SSCCs). For this, we used a density functional theory (DFT) *relativistic force field* method that we have recently developed and which is based on fast and accurate scaling of Fermi contacts.[18] As Fig. 4 shows, for all three post-photochemical cycloadducts experimental SSCCs matched the computed constants very well, leaving no doubt that our stereochemical assignment is accurate.

Pyrrolines, such as **16**, accessed via intramolecular cycloadditions of azaxylylenes, photogenerated from amino acid-based pyrroles, such as **15**, are also well suited for post-photochemical modifications, although in this case an unexpected *double addition* occurred. For example, when phenylalanine-based *enantiopure* photoprecursor **15** was irradiated in DMSO and, without further purification, subjected to hetero-Diels–Alder reaction with methylenebarbituric acid generated in situ, the reaction yielded a product incorporating two pyrimidinetrione moieties (Scheme 7). We believe that the first equivalent of the diene adds to the enamine moiety, forming



Scheme 4. Addition of dichlorocarbene to α,β-unsaturated ketone **8**. TFA = trifluoroacetic acid.

transient intermediate **17** similar to **11** and **14**. However, due to additional stability of the iminium ion, intermediate **17** exists in equilibrium with its zwitterionic form **17**+/−, which captures the second equivalent of methylenebarbituric acid, effectively resulting in a [2+2+2] product (**18**). We have found one example only of a somewhat related cycloaddition in the literature.[19]

The structure of the product **18** was supported by additional NMR experiments (^{13}C APT, HMBC and HMQC),[20] as well as by comparison of the experimental and calculated NMR spectra, Fig. 5. The HMBC spectrum of the initial photoproduct skeleton revealed an expected pattern of C–H cross-peaks, indicating that the pyrrolo-quinolinone skeleton remains unchanged. Characteristic features observed are the protons C_d–H and C_d–H′, which are represented by two doublets at 2.14 and 2.48 ppm with ^2J 15.3 Hz. In the HMBC spectrum, these doublets exhibit cross-peaks with quaternary carbons C_c and C_e at 51.5 and 56.1 ppm. The peak at 56.1 ppm is attributed to carbon C_e judging by the cross-peaks with C_f–H and C_a–H in the HMBC spectrum. The peak at 51.5 ppm, which has a cross-peak with C_b–H, is attributed to carbon C_c. The calculated spin–spin coupling constants for the proposed structure are in an excellent agreement with the experiment (rmsd = 0.36 Hz and mue = 0.81 Hz).

It is clear that a combination of the [4+4] and [4+2] scaffolds generated via the photochemical step and further modified in simple post-photochemical steps, involving mostly 1,3-dipolar, or [4+2], or [2+2+2] cycloadditions, produced complex polyheterocyclic sheets with 'visibly' diverse frameworks. Out of the ten compounds synthesised, nine distinct molecular scaffolds were prepared in a total of 19 steps. Although compared with typical combinatorial chemistry libraries, the number of compounds in this library is very small; we believe that the 'steps per scaffold efficiency'[21] (2.11 steps per scaffold) is very appealing, as is the rapid growth of complexity from the readily available photoprecursors to the post-photochemical final products.

To quantify the diversity of the combined mini library of the compounds **5**–**18** synthesised in this work and supplemented with previously synthesised compounds **A**–**H**, we employed computed Tanimoto similarity coefficients.[22] As Table 1 illustrates, the off-diagonal elements are in the 0.2–0.5 range for the majority of compounds that amounts to significant scaffold diversity.

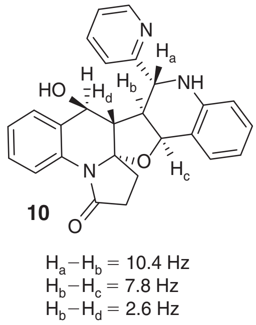
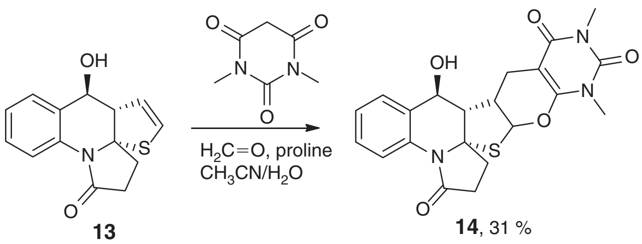
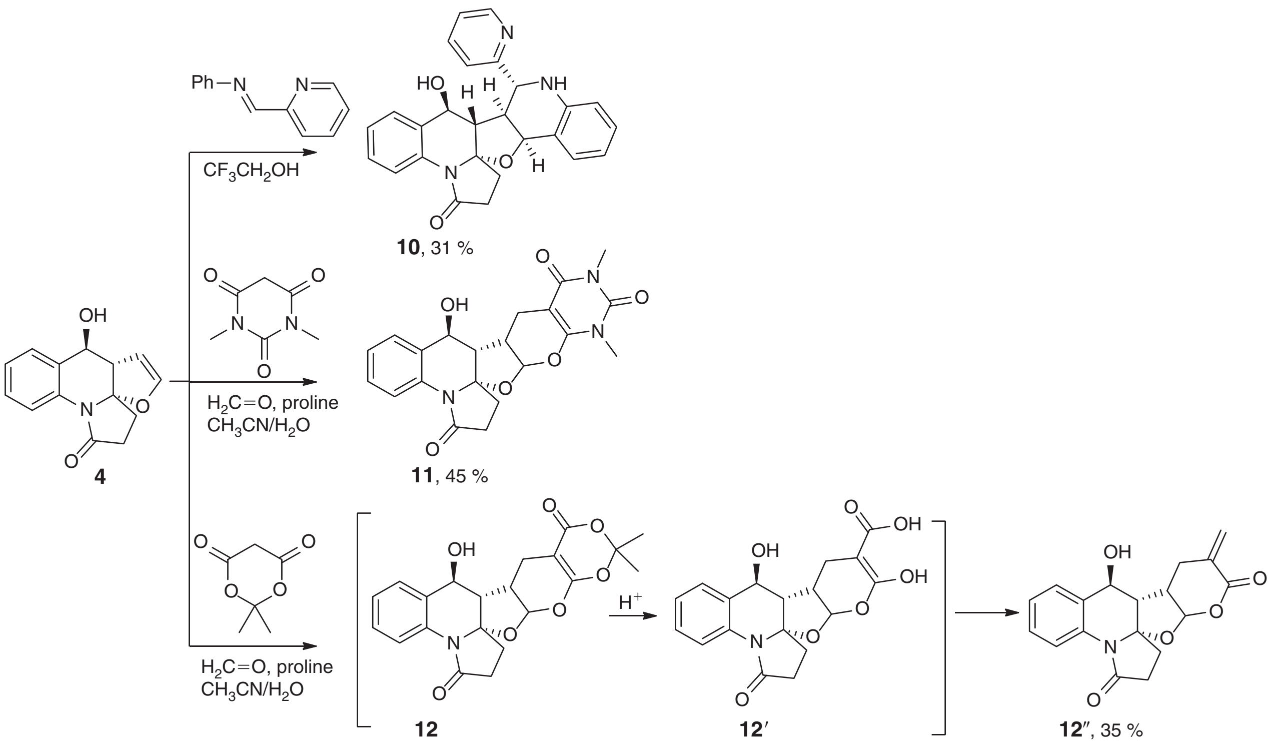


Fig. 3. Spin–spin coupling constants in structures **10**.



Scheme 6. Thiophene-based [4+2] adduct in the reaction with dimethylbarbituric acid.



Scheme 5. Postphotochemical [4+2] cycloadditions of heterodienes to primary photoproducts.

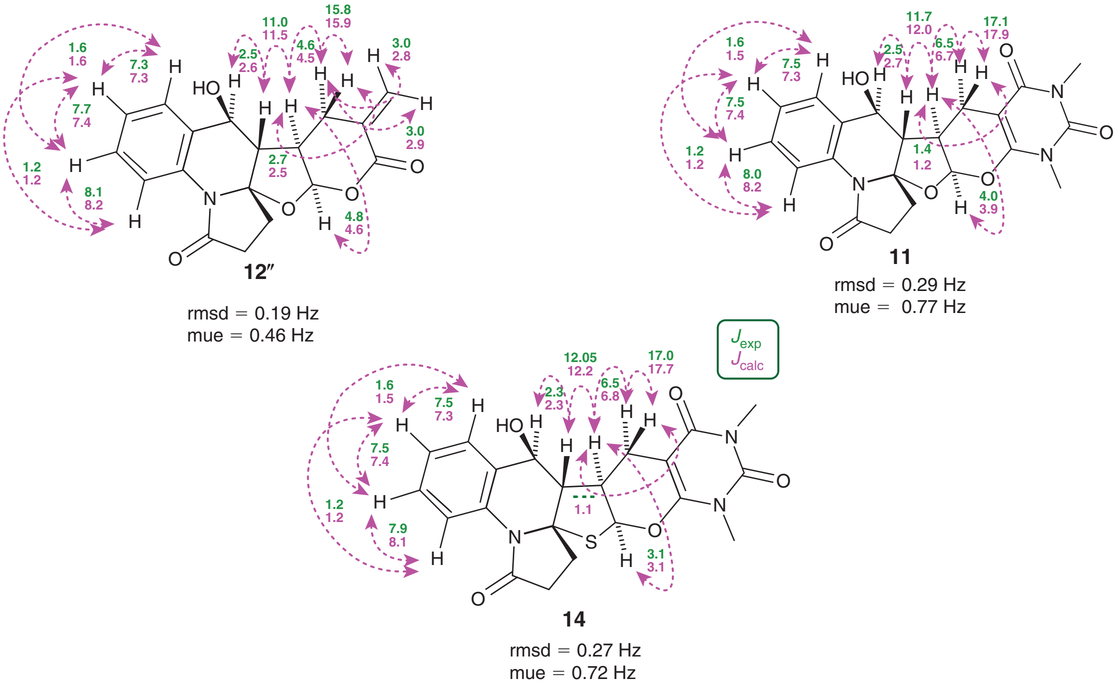
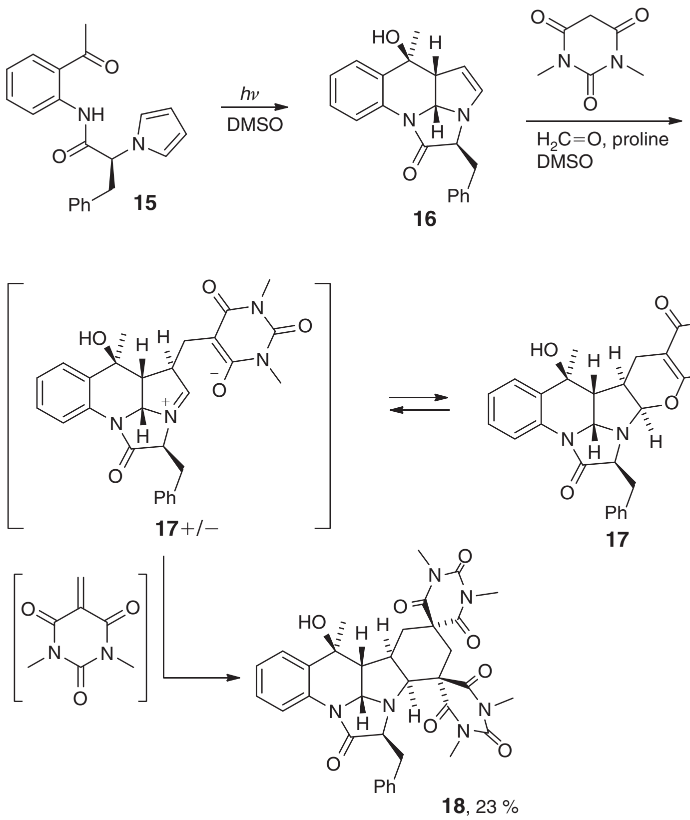


Fig. 4. Comparison of experimental and predicted SSCC for compounds **11**, **12″**, and **14**. rmsd = root-mean-square deviation, mue = maximum unsigned error.



Scheme 7. Reaction with pyrroles.

Table 2 shows comparison of the additional properties exhibited by our compounds with the general properties of compounds appearing in *Journal of Medicinal Chemistry* publications in 2005–2009.[3]

Instructively, our mini library has compounds with higher fsp3, lower logP values, and a very small number of rotatable bonds, thereby making the synthesised molecules attractive candidates for fragment-based drug discovery approach that is

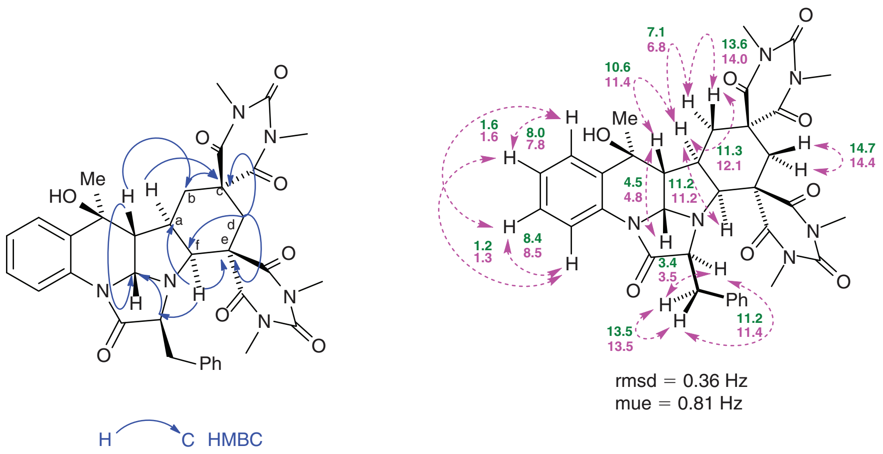


Fig. 5. Selected HMBC relationships between carbon and hydrogen atoms and comparison of calculated and experimental SSCCs for compound **18**.

Table 1. Tanimoto coefficients for the library of synthesised compounds

	A	B	C	D	E	F	G	H	5	6	7	9	10	11	12″	14	18
A	1	0.37	0.44	0.47	0.27	0.33	0.43	0.38	0.44	0.56	0.6	0.42	0.48	0.43	0.52	0.33	0.42
B	0.37	1	0.41	0.32	0.24	0.34	0.46	0.27	0.34	0.36	0.38	0.63	0.4	0.31	0.37	0.26	0.26
C	0.11	0.41	1	0.31	0.22	0.27	0.33	0.32	0.44	0.42	0.46	0.52	0.55	0.39	0.52	0.28	0.37
D	0.47	0.32	0.31	1	0.33	0.43	0.3	0.46	0.4	0.36	0.4	0.35	0.5	0.4	0.45	0.36	0.4
E	0.27	0.24	0.22	0.33	1	0.37	0.22	0.34	0.29	0.25	0.25	0.21	0.33	0.31	0.3	0.28	0.33
F	0.33	0.34	0.27	0.43	0.37	1	0.4	0.34	0.35	0.34	0.36	0.29	0.37	0.34	0.38	0.32	0.35
G	0.43	0.46	0.33	0.3	0.22	0.4	1	0.25	0.32	0.42	0.46	0.45	0.34	0.32	0.39	0.25	0.26
H	0.38	0.27	0.32	0.46	0.34	0.34	0.25	1	0.39	0.33	0.34	0.3	0.52	0.37	0.44	0.36	0.67
5	0.44	0.34	0.44	0.4	0.29	0.35	0.32	0.39	1	0.7	0.5	0.42	0.58	0.52	0.65	0.37	0.42
6	0.56	0.36	0.42	0.36	0.25	0.34	0.42	0.33	0.7	1	0.7	0.42	0.47	0.42	0.5	0.32	0.33
7	0.6	0.38	0.46	0.4	0.25	0.36	0.46	0.34	0.5	0.7	1	0.44	0.54	0.45	0.53	0.35	0.35
9	0.42	0.63	0.52	0.35	0.21	0.29	0.45	0.3	0.42	0.42	0.44	1	0.48	0.37	0.49	0.28	0.31
10	0.48	0.4	0.55	0.5	0.33	0.37	0.34	0.52	0.58	0.47	0.54	0.48	1	0.53	0.65	0.38	0.46
11	0.43	0.31	0.39	0.4	0.31	0.34	0.32	0.37	0.52	0.42	0.45	0.37	0.53	1	0.57	0.62	0.38
12″	0.52	0.37	0.52	0.45	0.3	0.38	0.39	0.44	0.65	0.5	0.53	0.49	0.65	0.57	1	0.38	0.49
14	0.33	0.26	0.28	0.36	0.28	0.32	0.25	0.36	0.37	0.32	0.35	0.28	0.38	0.62	0.38	1	0.38
18	0.42	0.26	0.37	0.4	0.33	0.35	0.26	0.67	0.42	0.33	0.35	0.31	0.46	0.38	0.49	0.38	1

Table 2. Comparison of the computed properties of the synthesised library and compounds appearing in the *Journal of Medicinal Chemistry* publications in 2005–2009[3]

MW, molecular weight; fsp3, see reference [8]; clogP, calculated logP; HB, hydrogen bonds; TPSA, total polar surface area

	MW	fsp3	clogP	HB donors	HB acceptors	Rotatable bonds	TPSA
Average values for present synthesised mini library	374.51	0.43	1.71	1.22	5.83	0.94	78.66
Average values for compounds reported in *J. Med. Chem.*	403.29	0.34	3.1	1.77	4.24	6.33	87.05

gaining momentum.[23] Synthesised polyheterocyclic sheets **11**, **12′**, and **14** have a 'belt' of polyacetal moieties – a structural feature somewhat similar to oxatriquinane motif found in biologically active gracilins J, K, H,[24] paracaseolide A,[25] and novel non-peptide HIV-1 protease inhibitors from the Ghosh laboratory.[26]

Conclusion

In conclusion, we have demonstrated that significant structural diversity can be generated with a high *steps per scaffold efficiency* via a combination of intramolecular cycloadditions of photogenerated azaxylylenes and experimentally simple and straightforward post-photochemical modifications of the primary photoproducts.

Experimental

Common solvents were purchased from Pharmco and used as received, except for THF, which was refluxed and distilled from sodium benzophenone ketyl before use. Common reagents were purchased from Aldrich and used without additional purification, unless indicated otherwise. NMR spectra were recorded at 25°C on a Bruker Avance III 500 MHz in $CDCl_3$ (unless noted otherwise). X-Ray structures were obtained with a Bruker APEX II instrument (for details see Supplementary Material). High-resolution mass spectroscopy (HRMS) was conducted on a MDS SCIEX/Applied Biosystems API QSTARTM Pulsar i Hybrid LC/MS/MS System mass spectrometer from the University of Colorado at Boulder. Flash column chromatography was performed using Teledyne Ultra Pure Silica Gel (230–400 mesh) on a Teledyne Isco Combiflash R_f using hexanes/ethyl acetate (EtOAc) as an eluent.

Synthesis of Photoprecursor and Photoproducts

The compounds **3**, **4**, and **13** were synthesised as previously described by our group. N-hydroxy-benzenecarboximidoyl bromide,[10] (1*E*)-N-phenyl-1-pyridin-2-ylmethanimine,[15] and N-oxide-N-(phenylmethylene)-methanamine[11] were prepared according to the existing procedures.

Post-Photochemical Modifications

Addition of Nitile Oxide

General Procedure I. Typically, 1 equiv. photoproduct was dissolved in EtOAc, followed by addition of 3 equiv. N-hydroxy-benzenecarboximidoyl bromide and 6 equiv. $KHCO_3$. Additional 3 equiv. N-hydroxy-benzenecarboximidoyl bromide and 6 equiv. $KHCO_3$ were added after stirring for 12 h. The reaction was monitored by NMR until the starting photoproduct was consumed. The resulting mixture was diluted with water, extracted with EtOAc (3 × 20 mL), washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The mixture was then purified by flash chromatography.

12-Hydroxy-15-phenyl-17,19-dioxa-5,16-diazapentacyclo [11.5.1.0^{1,5}.0^{6,11}.0^{14,18}]nonadeca-6,8,10,15-tetraen-4-one (6). General procedure **I** was followed using 0.25 g **1** (1.0 mmol), 1.2 g N-hydroxy-benzenecarboximidoyl bromide (6.2 mmol), and 1.2 g $KHCO_3$ (12.3 mmol) to generate the *title compound* (0.15 g, 61 %). δ_H ($CDCl_3$, 500 MHz) 7.65 (2H, m), 7.57 (1H, dd, *J* 8.4, 1.3), 7.48 (5H, m), 7.35 (1H, m), 4.86 (1H, d, *J* 8.8), 4.78 (2H, m), 3.87 (1H, dd, *J* 8.8, 1.0), 2.88 (2H, m), 2.77 (1H, dt, *J* 14.1, 9.9), 2.66 (1H, ddd, *J* 16.7, 9.5, 0.9), 2.46 (1H, ddd, *J* 14.1, 8.8, 1.0). δ_C ($CDCl_3$, 126 MHz) 173.8, 156.3, 133.4, 133.1, 132.6, 130.7, 129.9, 129.2, 128.5, 127.6, 127.5, 126.7, 104.9, 88.1, 82.2, 77.6, 56.3, 29.4, 27.2. *m/z* (HRMS ESI (electrospray ionisation)) 369.1405; [M + Li]$^+$ requires 369.1427.

12-Hydroxy-15-phenyl-17,19-dioxa-5,16-diazapentacyclo [11.6.0.0^{1,5}.0^{6,11}.0^{14,18}]nonadeca-6(11),7,9,15-tetraen-4-one (5). General procedure **I** was followed using 0.25 g **2** (1.0 mmol), 1.2 g N-hydroxy-benzenecarboximidoyl bromide (6.1 mmol), and 1.2 g $KHCO_3$ (12.4 mmol) to generate the *title compound* (0.14 g, 59 %). δ_H ($CDCl_3$, 500 MHz) 7.98 (1H, d, *J* 8.0), 7.73 (2H, m), 7.54 (3H, m), 7.49 (1H, td, *J* 7.9, 1.5), 7.46 (1H, dd, *J* 7.5, 1.3), 7.27 (1H, td, *J* 7.5, 1.2), 5.81 (1H, d, *J* 6.2), 4.97 (1H, d, *J* 3.0), 3.84 (1H, dd, *J* 6.2, 3.3), 3.29 (1H, t, *J* 3.1), 2.84 (1H, m), 2.40 (3H, m). δ_C ($CDCl_3$, 126 MHz) 173.3, 158.7, 134.5, 130.8, 130.0, 129.8, 129.2, 128.7, 127.7, 127.1, 125.5, 122.9, 107.0, 101.4, 70.7, 57.1, 55.1, 34.1, 30.1. *m/z* (HRMS ESI) 369.1407; [M + Li]$^+$ requires 369.1427.

Nitrone Cycloadditions

In a typical procedure, 1 equiv. photoproduct was dissolved in 1 mL anhydrous toluene and 4 equiv. N-oxide-N-(phenylmethylene)-methanamine. The reaction was sealed in a high-pressure reaction vessel and heated to completion as confirmed by ^{1}H NMR analysis. The toluene was removed under vacuum and the residue purified by flash chromatography.

***anti*-12-Hydroxy-16-methyl-15-phenyl-17,19-dioxa-5,16-diazapentacyclo[11.5.1.0^{1,5}.0^{6,11}.0^{14,18}]nonadeca-6,8,10-trien-4-one (7)**. Using 100 mg **1** (0.41 mmol) and 0.22 g N-oxide-N-(phenylmethylene)-methanamine (1.6 mmol), the *title compound* was isolated (98 mg, 63 %). δ_H ($CDCl_3$, 500 MHz) 7.50 (1H, d, *J* 8.0), 7.39 (4H, m), 7.32 (2H, m), 7.24 (2H, m), 4.59 (1H, d, *J* 4.4), 4.38 (2H, m), 3.32 (1H, d, *J* 8.6), 2.87 (1H, m), 2.74 (1H, t, *J* 7.5), 2.58 (2H, m), 2.43 (1H, m), 2.20 (3H, s). δ_C ($CDCl_3$, 126 MHz) 173.9, 134.0, 133.6, 132.5, 129.5, 129.1, 128.7, 128.2, 127.8, 127.8, 127.1, 102.6, 84.2, 81.4, 79.5, 77.4, 61.2, 29.6, 27.1. *m/z* (HRMS ESI) 385.1724; [M + Li]$^+$ requires 385.1740.

***syn*-12-Hydroxy-16-methyl-15-phenyl-17,19-dioxa-5,16-diazapentacyclo[11.5.1.0^{1,5}.0^{6,11}.0^{14,18}]nonadeca-6,8,10-trien-4-one (7′)**. Using 100 mg **1** (0.41 mmol) and 0.22 g N-oxide-N-(phenylmethylene)-methanamine (1.6 mmol) to generate *title compound* (33.0 mg, 21 %). δ_H ($CDCl_3$, 500 MHz) 7.55 (1H, dd, *J* 8.0, 0.9), 7.39 (6H, m), 7.25 (2H, m), 4.33 (1H, d, *J* 7.0), 4.19 (2H, m), 3.61 (1H, d, *J* 7.7), 2.92 (1H, m), 2.81 (1H, t, *J* 7.4), 2.68 (1H, m), 2.58 (3H, s), 2.54 (1H, m). δ_C ($CDCl_3$, 126 MHz) 173.9, 135.8, 133.9, 133.8, 132.5, 129.4, 128.9, 128.3, 128.2, 128.0, 126.8, 103.6, 83.9, 78.7, 77.7, 75.4, 55.9, 43.6, 29.9, 26.7. *m/z* (HRMS ESI) 385.1724; [M + Li]$^+$ requires 385.1740.

Ethyl 13-Chloro-4-oxo-16-oxa-5-azatetracyclo[10.3.1.0^{1,5}.0^{6,11}]hexadeca-6,8,10,14-tetraene-13-carboxylate (9). The following procedure was used: 0.14 g **5** (0.58 mmol) was dissolved in 50 mL chloroform. To this solution, 30 mg tetrabutylammonium hydrogen sulfate (0.084 mmol) and 10 mL NaOH solution (50 % w/w) were added. The mixture was vigorously stirred at ambient temperature for 20 h, then poured into 200 mL water and extracted with $CHCl_3$. The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The mixture was purified by flash chromatography to yield the *title compound* (0.12 g, 66 %). δ_H ($CDCl_3$, 500 MHz) 8.42 (1H, dd, *J* 8.3, 1.0), 7.38 (1H, ddd, *J* 8.7, 7.5, 1.6), 7.19 (1H, dd, *J* 8.0, 1.4), 7.09 (1H, td, *J* 7.7, 1.3), 6.38 (1H, dd, *J* 9.9, 1.2), 5.83 (1H, d, *J* 9.9), 5.47 (1H, s), 4.27 (2H, m), 2.74 (2H, m), 2.42 (2H, m), 1.30 (3H, t, *J* 7.2). δ_C ($CDCl_3$, 126 MHz) 170.8, 167.3, 133.1, 129.7, 126.9, 126.8, 126.4, 123.8, 120.4, 119.9, 85.9, 77.3, 64.2, 62.9, 30.3, 29.9, 13.8. *m/z* (HRMS ESI) 340.0920; [M + Li]$^+$ requires 340.0928.

14-Hydroxy-11-(pyridin-2-yl)-2-oxa-10,21-diazahexacyclo [11.11.0.0^{1,21}.0^{3,12}.0^{4,9}.0^{15,20}]tetracosa-4(9),5,7,15,17,19-hexaen-22-one (10). The following procedure was used: 0.22 g (1*E*)-N-phenyl-1-pyridin-2-ylmethanimine (1.2 mmol) and 0.15 g **4** (0.61 mmol) were dissolved in 1.5 mL 2,2,2-trifluoroethanol and warmed to 40°C until the reaction was complete as observed by ^{1}H NMR analysis. The resulting mixture was concentrated under vacuum and purified by flash chromatography, yielding the *title compound* (80 mg, 31 %). δ_H ($CDCl_3$, 500 MHz) 8.74 (1H, ddd, *J* 4.9, 1.8, 0.9), 7.88 (1H, td, *J* 7.7, 1.8), 7.85 (1H, d, *J* 8.1), 7.57 (1H, d, *J* 7.9), 7.39 (3H, m), 7.17 (3H, td, *J* 7.6, 1.0), 7.11 (2H, td, *J* 7.5, 1.1), 6.85 (1H, td, *J* 7.5, 1.2), 6.77 (2H, dd, *J* 7.4, 1.1), 5.25 (1H, d, *J* 7.7), 4.82 (1H, d, *J* 1.4), 4.65 (1H, s), 3.38 (1H, dd, *J* 10.4, 2.5), 3.10 (1H, d, *J* 2.5), 2.69 (1H, ddd, *J* 16.3, 10.9, 8.2), 2.54 (1H, ddd, *J* 10.4, 7.9, 2.5), 2.18 (1H, dd, *J* 16.6, 8.6), 2.06 (1H, ddd, *J* 12.4, 10.9, 8.8), 1.68 (1H, dd, *J* 12.6, 8.0). δ_C ($CDCl_3$, 126 MHz) 173.7, 159.2, 149.5, 143.4, 137.1, 134.0, 130.6, 130.0, 129.9, 128.9, 128.6, 125.5, 123.8, 123.1, 121.6, 120.8, 119.3, 115.6, 100.2, 77.2, 74.7, 70.2, 56.6, 50.5, 45.9, 36.0, 29.9. *m/z* (HRMS ESI) 432.1889; [M + Li]$^+$ requires 432.1900.

Oxa-Diels–Alder Reactions

General Procedure II. Typically, 1 equiv. photoproduct and 1 equiv. 1,3-dicarbonyl compound were dissolved in 0.7 mL dry acetonitrile. To this solution, 0.08 equiv. L-proline and 1.3 equiv. 37 % aqueous formaldehyde solution were added. The reaction was stirred at ambient temperature until complete consumption of the photoproduct, as determined by ^{1}H NMR analysis. The reaction was diluted with water and extracted with EtOAc. The organic layer was separated, dried over Na_2SO_4, and concentrated under vacuum. The mixture was then purified by flash chromatography.

12-Hydroxy-16-methylidene-18,20-dioxa-5-azapentacyclo[11.7.0.0^{1,5}.0^{6,11}.0^{14,19}]icosa-6,8,10-triene-4,17-dione (12′). General procedure **II** was followed using 0.10 g **2** (0.41 mmol), 0.06 g of Meldrum's acid (0.41 mmol), 3.8 mg L-proline (0.033 mmol), and 0.04 mL formaldehyde solution (37 % w/w) in water (0.53 mmol) to generate the *title compound* (52 mg, 35 %). δ_H (CDCl$_3$, 500 MHz) 7.82 (1H, d, *J* 8.0), 7.42 (1H, td, *J* 7.7, 1.5), 7.33 (1H, d, *J* 7.3), 7.21 (1H, td, *J* 7.7, 1.2), 6.59 (1H, s), 5.77 (1H, s), 5.66 (1H, d, *J* 4.8), 4.64 (1H, d, *J* 2.4), 2.89 (1H, dd, *J* 11.0, 2.5), 2.75 (3H, m), 2.47 (1H, dd, *J* 12.6, 8.4), 2.35 (1H, tdd, *J* 12.7, 9.8, 1.7), 2.23 (1H, dt, *J* 16.4, 8.1), 2.16 (1H, dtd, *J* 11.3, 4.7, 2.6). δ_C (CDCl$_3$, 126 MHz) 173.7, 173.7, 163.5, 133.4, 130.9, 130.0, 130.0, 129.8, 129.3, 125.9, 123.8, 102.9, 102.0, 68.8, 51.7, 40.4, 35.8, 29.6, 27.3. *m/z* (HRMS ESI) 334.1253; [M + Li]$^+$ requires 334.1267.

14-Hydroxy-6,8-dimethyl-2,4-dioxa-6,8,21-triazahexacyclo[11.11.0.0^{1,21}.0^{3,12}.0^{5,10}.0^{15,20}]tetracosa-5(10),15,17,19-tetraene-7,9,22-trione (11). General procedure **II** was followed using 100 mg **2** (0.41 mmol), 0.064 g 1,3-dimethylbarbituric acid (0.41 mmol), 3.8 mg L-proline (0.033 mmol), and 0.04 mL formaldehyde solution (37 % w/w) in water (0.53 mmol) to generate the *title compound* (76 mg, 45 %). δ_H (CDCl$_3$, 500 MHz) 7.89 (1H, d, *J* 8.0), 7.48 (1H, td, *J* 7.8, 1.6), 7.36 (1H, dd, *J* 7.5, 1.5), 7.26 (1H, td, *J* 7.4, 1.2), 5.57 (1H, d, *J* 4.0), 4.79 (1H, d, *J* 2.6), 3.42 (3H, s), 3.39 (3H, s), 2.90 (1H, m), 2.85 (1H, dd, *J* 11.6, 2.6), 2.77 (1H, d, *J* 17.1), 2.56 (1H, dd, *J* 17.1, 6.5), 2.42 (4H, m), 2.16 (1H, dddd, *J* 11.6, 6.5, 4.0, 1.4). δ_C (CDCl$_3$, 126 MHz) 173.4, 163.0, 154.0, 151.0, 133.2, 130.3, 129.8, 129.1, 126.1, 124.0, 102.1, 100.0, 82.5, 69.2, 51.6, 39.6, 36.5, 29.6, 28.7, 28.1, 18.1. *m/z* (HRMS ESI) 418.1571; [M + Li]$^+$ requires 418.1591.

14-Hydroxy-6,8-dimethyl-4-oxa-2-thia-6,8,21-triazahexacyclo[11.11.0.0^{1,21}.0^{3,12}.0^{5,10}.0^{15,20}]tetracosa-5(10),15,17,19-tetraene-7,9,22-trione (14). General procedure **II** was followed using DMSO as a solvent. Using 70.0 mg **13** (0.27 mmol), 0.13 g 1,3-dimethylbarbituric acid (0.81 mmol), 7.5 mg L-proline (0.065 mmol), and 0.08 mL formaldehyde (37 %) in water (1.1 mmol), the *title compound* was obtained (36 mg, 31 %). δ_H (CDCl$_3$, 500 MHz) 7.78 (1H, d, *J* 7.9), 7.49 (1H, td, *J* 7.7, 1.2), 7.35 (1H, dd, *J* 7.5, 1.5), 7.27 (1H, dd, *J* 7.5, 1.0), 5.55 (1H, d, *J* 3.1), 4.84 (1H, d, *J* 3.1), 3.40 (3H, s), 3.38 (3H, s), 2.86 (1H, dd, *J* 12.1, 2.3), 2.78 (1H, dd, *J* 17.0, 0.8), 2.65 (2H, m), 2.60 (1H, dd, *J* 17.0, 6.5), 2.50 (2H, m), 2.39 (1H, dddd, *J* 12.05, 6.5, 3.2, 0.8), 2.30 (1H, s). δ_C (CDCl$_3$, 126 MHz) 171.8, 163.1, 154.5, 150.9, 133.5, 130.9, 130.4, 128.9, 126.4, 124.4, 88.8, 85.0, 82.9, 70.4, 56.2, 45.4, 42.4, 30.7, 28.7, 28.1, 20.3. *m/z* (HRMS ESI) 434.1353; [M + Li]$^+$ requires 434.1362.

14-Benzyl-5-hydroxy-5,21,23,28,30-pentamethyl-17,19-dioxa-12,15,21,23,28,30-hexaazaoctacyclo[16.8.4.1^{4,12}.0^{1,18}.0^{3,16}.0^{6,11}0^{20,25}.0^{15,31}]hentriaconta-6,8,10,20(25)-tetraene-13,22,24,27,29-pentone (18). The following procedure was used: 0.10 g (*S*)-N-(2-acetylphenyl)-3-phenyl-2-(1H-pyrrol-1-yl)propanamide (**15**) (0.3 mmol) was dissolved in 1.5 mL DMSO. This was degassed and irradiated in a Pyrex reaction vessel under LED-365 until the reaction was complete, as determined by ^{1}H NMR analysis. The solution was then added directly to 0.05 g 1,3-dimethylbarbituric acid (0.3 mmol). To this solution, 3.0 mg L-proline (0.024 mmol), and 0.03 mL formaldehyde solution (37 % w/w) in water (0.39 mmol) were added. The reaction was heated to 70°C until complete consumption of the photoproduct, as determined by ^{1}H NMR analysis. The reaction was diluted with water and extracted with EtOAc. The organic layer was separated, dried over Na_2SO_4, and concentrated under vacuum. The mixture was then purified by flash chromatography, yielding the *title compound* (46 mg, 23 %). δ_H (CDCl$_3$, 500 MHz) 8.63 (1H, dd, *J* 8.3, 1.2), 7.58 (1H, dd, *J* 7.8, 1.5), 7.37 (1H, ddd, *J* 8.5, 7.3, 1.6), 7.19 (6H, m), 5.04 (1H, d, *J* 4.5), 4.34 (1H, d, *J* 11.1), 3.76 (1H, dd, *J* 11.2, 3.4), 3.40 (3H, s), 3.27 (3H, s), 3.22 (3H, s), 3.17 (1H, dd, *J* 10.6, 4.5), 2.99 (3H, s), 2.96 (1H, dd, *J* 13.6, 3.4), 2.78 (1H, dd, *J* 13.5, 11.3), 2.75 (1H, dd, *J* 13.5, 11.3), 2.53 (1H, qd, *J* 11.2, 7.2), 2.52, (1H, d, *J* 14.8), 2.45 (1H, dd, *J* 13.6, 7.1), 2.32 (1H, d, *J* 14.8), 2.04 (1H, s), 1.65 (3H, s). δ_C (CDCl$_3$, 126 MHz) 173.6, 172.1, 171.3, 170.7, 170.6, 150.7, 150.3, 138.2, 132.4, 130.4, 129.7, 128.8, 127.8, 126.6, 126.1, 124.7, 117.9, 78.3, 71.9, 71.5, 66.7, 56.0, 53.3, 51.4, 39.1, 37.1, 36.5, 36.0, 34.6, 29.4, 29.4, 29.3, 29.1. *m/z* (HRMS ESI) 675.2742; [M + Li]$^+$ requires 675.2755.

Supplementary Material

NMR spectra and X-ray structures (33 pages) are available on the Journal's website.

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