Generation of molecular diversity using a complexity-generating MCR-platform towards triazinane diones†

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Triazinane diones, readily generated by a recently reported multicomponent reaction, can be easily alkylated with various alkyl halides, allowing a wide variety of complexity-generating secondary reactions. Because of the high variability of the initial multicomponent reactions and the multiple possibilities for participation of substituents in the secondary reactions, a highly diverse set of complex products was obtained in short and efficient reaction sequences.

Introduction

Recent advances in genomics, proteomics, metabolomics, and structural biology highlight a clear need for small molecules that can modulate biological processes.[1] Combinatorial synthesis is undisputed as an enabling tool to access the required small-molecule based compound collections. Although the benefit for drug discovery seems obvious, the actual hit rates for new drug candidates have decreased steadily over the past decade.[2] It has become clear that not only the number of molecules but also the structural diversity and molecular complexity of the chosen scaffolds are key issues to address in the design of a compound library.[3]

Rapid generation of diverse sets of complex molecules can be achieved by employing diversity-oriented synthetic strategies in combination with complexity-generating reactions.[4] Multicomponent reactions (MCRs), which combine in one pot at least three simple building blocks,[5,6] provide a most powerful platform to access diversity as well as complexity in a limited number of reaction steps. Here we describe modular reaction sequences based on our previously reported MCR chemistry[7,8] in combination with other common organic reactions or even with a second MCR.

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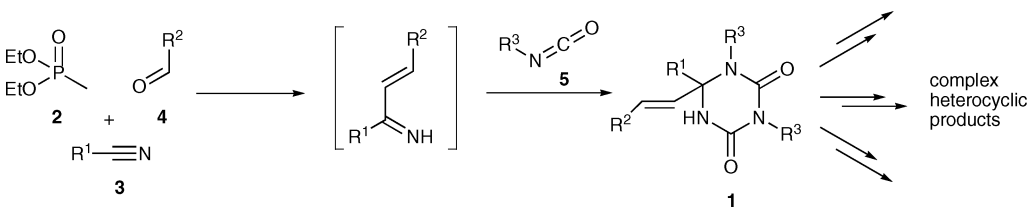
The MCR platform that we chose for this work is a one-pot synthetic protocol towards triazinane diones **1**, a rather unexplored class of heterocyclic scaffolds (Scheme 1).[7,8] The four-component reaction (4CR) combines phosphonate **2**, nitriles **3**, aldehydes **4** and isocyanates **5** and proceeds with remarkable efficiency and flexibility. Furthermore, subsequent alkylation of **5** proved successful and allows attachment of additional synthetic handles.

Combination of this 4CR with additional complexity-generating reactions, *e.g.*, ring-closing metathesis (RCM),[9] cycloaddition reactions (Huisgen[10] or Diels–Alder[11]), or isonitrile-based MCRs (I-MCR)[5] enables rapid access to highly complex (poly)heterocyclic scaffolds with pharmaceutically interesting cores.

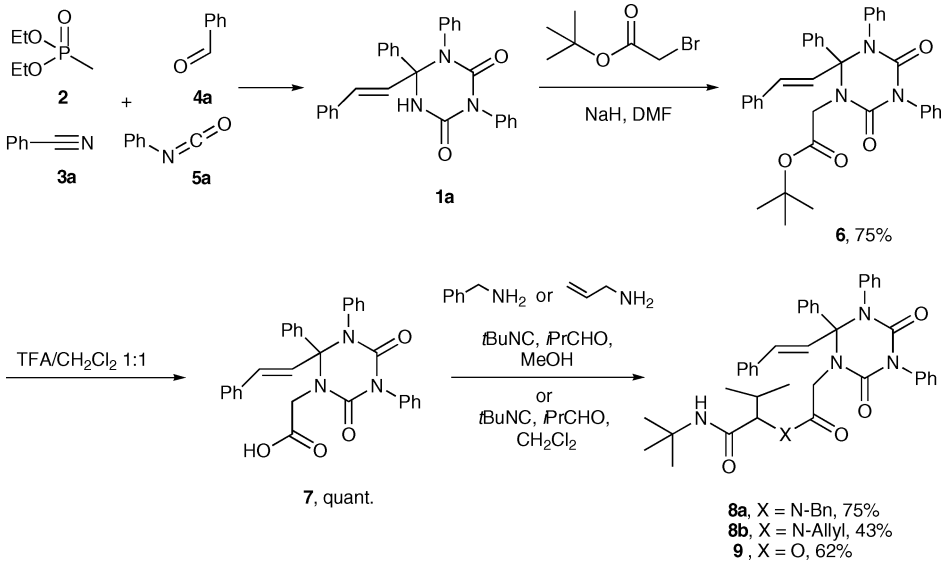
Results and discussion

The triazinane dione **1a** was chosen as the heterocyclic platform and our attention initially focused on the combination with additional MCRs. The isonitrile-based Ugi four-component (U-4CR)[5,6,12] and Passerini three-component (P-3CR)[13] reactions, widely used to generate complex peptide-like products, were considered as candidate reactions to achieve fast complexity generation. Thus, as described before,[7] the 4CR of **2**, **3a**, **4a** and **5a** gave the triazinane dione **1a** efficiently. The amide NH was alkylated (NaH, *tert*-butyl 2-bromoacetate, DMF) to give *tert*-butyl ester **6** in 75% yield. Subsequently, removal of the *tert*-butyl group with TFA in CH_2Cl_2 afforded carboxylic acid **7** in quantitative yield.

The acid **7** was employed in either an U-4CR or a P-3CR (Scheme 2). The U-4CR was performed in MeOH at room



Scheme 1 4CR for triazinane diones as versatile platform for complexity generation.

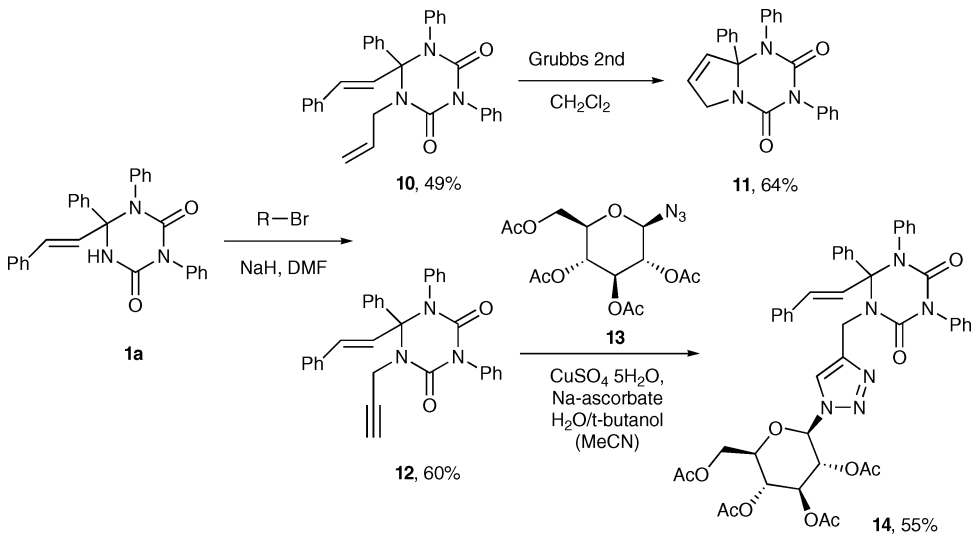


Scheme 2 Alkylation and then U-4CR or P-3CR reactions.

temperature using isobutyraldehyde, benzylamine or allylamine, the triazinane dione acid **7** and *tert*-butyl isocyanide. This indeed gave the expected peptide-derived triazinane diones **8a** and **8b**, respectively, in reasonable to good isolated yields. The P-3CR of isobutyraldehyde, acid **7** and *tert*-butyl isocyanide was performed in CH_2Cl_2 at room temperature and afforded the corresponding peptide-like **9** in 62% isolated yield. Thus, combination of our 4CR and these isonitrile-based MCRs in a short synthetic sequence (four steps) allows for rapid construction of rather complex, peptide-functionalized heterocycles. Both the initial 4CR, which generates the heterocyclic scaffold, as well as the U-4CR and the P-3CR are easy to perform and compatible with a large variety of differently functionalized inputs. This makes this four-step sequence amenable for a combinatorial set-up to generate libraries of peptidyl triazinane diones of type **8** or **9**.

Next, our attention focused on the construction of highly functionalized bi- or polycyclic ring systems. Combination of the initial triazinane dione-generating 4CR with RCM or cycloaddition reactions was envisioned as a powerful strategy to achieve this goal. Thus, allylation of **1a** to afford **10** and subsequent RCM using the 2nd generation Grubbs' catalyst[14] in CH_2Cl_2 resulted in the bicyclic triazinane dione **11** (64%, Scheme 3).

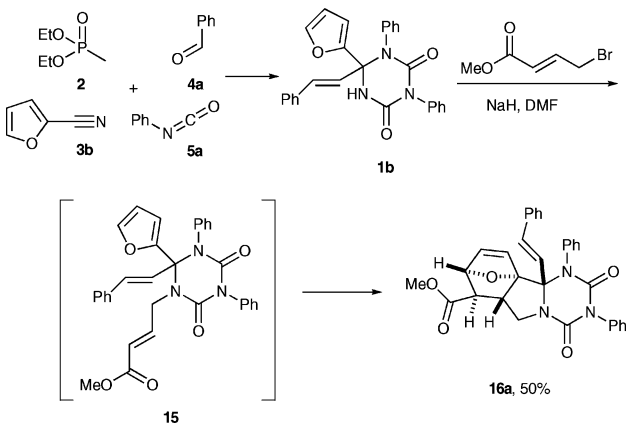
To further explore the potential of the triazinane dione scaffold as a versatile platform for additional cyclization reactions, a [2 + 3] Huisgen cycloaddition (click reaction)[15,16] was considered. Propargylation of the free NH in **1a** (NaH, propargyl bromide, DMF; Scheme 3) gave the desired product **12** in 60% isolated yield. Then, the click reaction of **12** and readily available β-glucosyl azide derivative **13** was performed in a H_2O–*t*-BuOH–MeCN mixture with $CuSO_4$ and sodium ascorbate as the catalyst



Scheme 3 Alkylation and then RCM or click reactions.

and co-catalyst, respectively.[15] The cycloaddition product **14** was obtained in a reasonable yield of 55%. Again, combination of our initial 4CR for triazinane diones and these cyclization protocols allow rapid complexity generation in a short synthetic sequence (three steps). The RCM and the [2 + 3] Huisgen cycloaddition are well established and robust reactions that are compatible with a wide variety of different functionalities. This opens the way for easy generation of diversified sets of xanthine-like[17] annelated bicyclic cores **11** or non-natural nucleoside mimics of type **14**.[18]

Furthermore, a strategy based on the 4CR for triazinane diones and an intramolecular Diels–Alder (IMDA) reaction was envisioned to access the desired diversity and complexity of functionalized polycyclic ring systems in a highly efficient manner.[19] For this purpose, we decided to introduce the required dienophile on a furan-functionalized triazinane dione (**1b**) platform. The four-component synthesis of **1b** proceeded smoothly following the general procedure reported by us earlier.[7] Next, reaction of **1b** with methyl *E*-4-bromo-2-butenoate in DMF after deprotonation with NaH would lead to **15**, which could then be subjected to heating to give the IMDA product. However, the anticipated IMDA reaction appears to proceed readily at room temperature and occurs immediately after alkylation of **1b** with the dienophile. The intermediate alkylation product **15** was not observed. Thus, the desired polycyclic IMDA product **16a** is formed in a very efficient one-pot domino process and could be isolated in 50% yield (Scheme 4). The structure of **16a** including the relative stereochemistry is predicted by orbital symmetry considerations and was unambiguously confirmed by NOESY and X-ray crystal structure determination (Fig. 1).



Scheme 4 A domino alkylation–IMDA reaction.

Other furan-functionalized triazinane diones underwent similar efficient spontaneous IMDA cyclization after alkylation with methyl *E*-4-bromo-2-butenoate. Thus, alkylation of **1c**, prepared efficiently *via* the 4CR of **2**, furonitrile **3b**, piperonal **4b** and **5a**, resulted in smooth *in situ* IMDA cyclization to give **16b** in high yield. Similarly, alkylation of **1d**, prepared *via* the 4CR of **2**, **3b**, **4a** and *p*-methoxyphenyl isocyanate **5b**, afforded **16c** (Scheme 5). The structures of **16b** and **16c** were assigned on the basis of NOE intensities between the hydrogens **A1**–**A2**, **A1**–**B**, **A2**–**C** and **B**–**C** (Fig. 1), which have a similar build-up rate as the NOE intensities

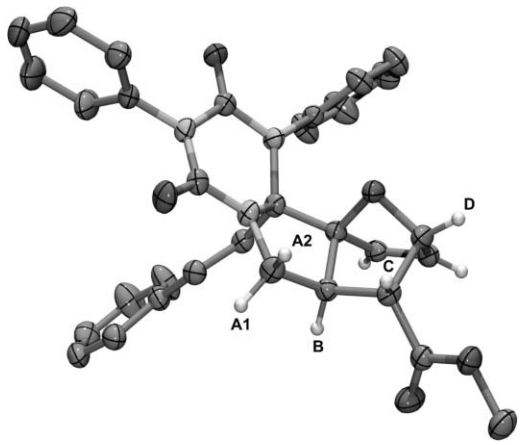


Fig. 1 Displacement ellipsoid plot of racemic **16a**, drawn at the 50% probability level, indicating the stereochemistry between hydrogens **A1**–**A2**, **A1**–**B**, **A2**–**C**, **B**–**C** and **C**–**D**. Other hydrogen atoms are omitted for clarity.

between the corresponding hydrogens in **16a**. Also, the coupling constants of the various hydrogens in **16a** (**A1**–**B** = 9.5 Hz; **A2**–**B** = 7.3 Hz; **B**–**C** = 2.9 Hz; **C**–**D** = 4.8 Hz) are comparable to those observed in **16b** and **16c**, indicating that the relative stereochemistry of all three compounds is the same.

Thus, combination of our 4CR with an alkylation–IMDA domino reaction yields a very efficient strategy to access highly functionalized polycyclic cores in only two reaction steps.

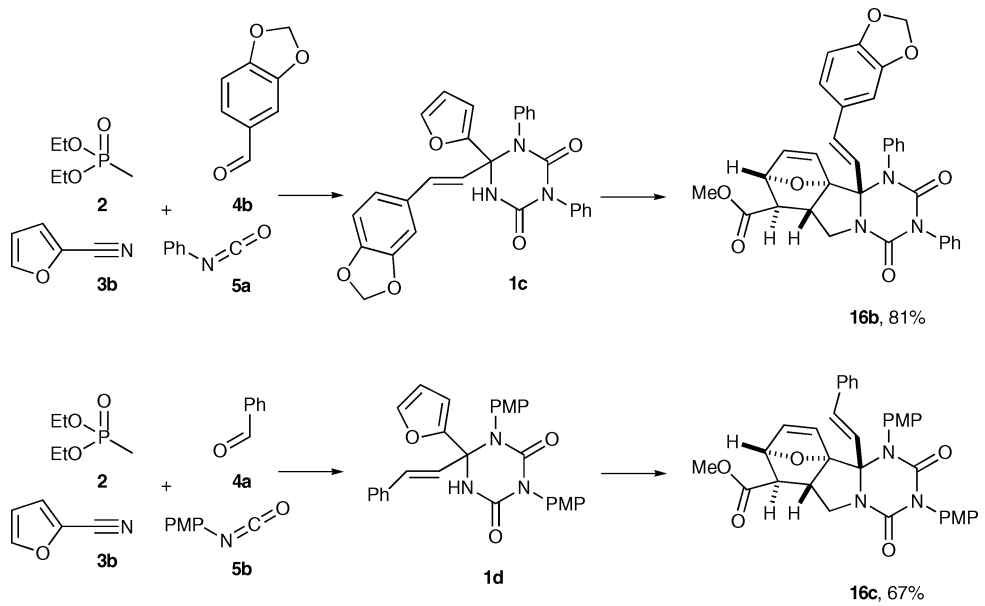
Conclusions

In summary, the 4CR for triazinane diones provides a versatile platform that can be applied in combination with additional MCRs, RCM, [2 + 3] cycloaddition and IMDA reactions. This results in very short reaction sequences (maximum of four) to generate both diversity and complexity. In some cases, diversification is based solely on the *N*-alkyl functionality, while in other cases various functional groups on the triazinane dione participate in the secondary reactions, thus leading to increased scaffold diversification. Combination of both approaches leads to higher overall diversity and therefore to a better coverage of chemical space. This strategy will prove useful in the design of combinatorial libraries based on highly functionalized heterocyclic small molecules.

Experimental

General information

All reactions were carried out under an inert atmosphere of dry nitrogen. THF was dried and distilled from sodium–benzophenone prior to use, CH_2Cl_2 was dried and distilled from $CaCl_2$ prior to use. Other commercially available chemicals were used as purchased. Thin layer chromatography (TLC) was performed using aluminium TLC sheets (silica gel 60 F_{254}) and compounds were visualized using UV-detection (254 nm) and colouring with an anisaldehyde solution (6 mL *p*-anisaldehyde, 7 mL acetic acid and 7 mL sulfuric acid in 120 mL of EtOH) or a CER-MOP solution (5 g molybdophosphoric acid, 2 g cerium(IV) sulfate and 16 mL sulfuric acid in 184 mL of H_2O). Column chromatography was performed using flash silica gel (40–63 μm) and mixtures of



Scheme 5 Two more examples of the domino alkylation–IMDA reaction. PMP = *p*-methoxyphenyl.

cyclohexane and EtOAc. Melting points are uncorrected. Infrared (IR) spectra were obtained from pure samples and wavelengths (ν) are reported in cm^{-1}. ^1H nuclear magnetic resonance (NMR) spectra were recorded at 400.13 MHz or 250.13 MHz and ^{13}C NMR spectra at 100.61 MHz or 62.90 MHz with chemical shifts (δ) reported in ppm downfield from tetramethylsilane. HRMS-FAB data were measured using a four sector mass spectrometer.

General procedure I: alkylation of triazinane diones

NaH (1.1 equivalent, 0.12 M) was added to a flame-dried Schlenk vessel and dry DMF was added. This suspension was cooled to 0 °C after which the triazinane dione (1.0 equivalent. 0.11 M) was added. The mixture was then stirred for 1.5 h at 0 °C after which the appropriate allylic or propargylic bromide was added (1.1 equivalent, 0.12 M). The reaction mixture was then allowed to warm to room temperature overnight, after which the reaction was worked up. DMF was removed by evaporation and the crude material was dissolved in EtOAc. This organic fraction was washed twice with water, then with brine, dried (Na_2SO_4), filtrated and concentrated by evaporation of the solvent under reduced pressure. The crude product was purified by column chromatography (cyclohexane–EtOAc).

tert-Butyl ester 6

Following general procedure I, reaction between triazinane dione **1a** (1.00 g, 2.20 mmol) and *tert*-butyl 2-bromoacetate (340 mg, 2.40 mmol) followed by column chromatography (cyclohexane–EtOAc = 2 : 1), afforded **6** (945 mg, 75%) as a white foam. ^1H NMR (400 MHz, $CDCl_3$): 7.45–7.58 (m, 2H), 7.09–7.36 (m, 18H), 6.61 (s, 2H), 4.03 (s, 2H), 1.39 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): 167.7, 153.2, 152.5, 138.6, 138.2, 135.4, 135.1, 135.0, 129.9 (2C), 129.5, 129.2 (2C), 129.0, 128.9 (2C), 128.7 (2C), 128.7 (2C), 128.6 (2C), 128.3 (2C), 128.1, 127.5, 127.0 (2C), 126.4, 81.9, 81.2, 48.2, 27.9 (3C). HRMS (FAB) calculated for $C_{35}H_{34}N_3O_4$ (MH^+) 560.2549, found 560.2543. IR (neat): 2978 (w), 1713 (s), 1676 (s), 1493 (m), 1433 (s), 1321 (m), 1229 (m), 1148 (s), 752 (s), 692 (s).

Triazinane dione acid 7

tert-Butyl ester **6** (900 mg, 1.6 mmol) was dissolved in CH_2Cl_2 (2 mL) and trifluoroacetic acid (2 mL) was added. This mixture was stirred for 45 minutes after which the solvent and excess trifluoroacetic acid were removed by evaporation under reduced pressure. This afforded crude **7** as a white solid (806 mg, quant.) without further purification being necessary. ^1H NMR (250 MHz, $CDCl_3$): 7.61–7.57 (m, 2H), 7.40–7.11 (m, 18H), 6.76 (d, J = 16.0 Hz, 1H), 6.62 (d, J = 15.9 Hz, 1H), 4.20 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): 169.5, 152.9, 152.2, 138.8, 138.5, 136.1, 135.5, 134.3, 130.1, 129.8, 129.6 (2C), 129.3, 129.3, 129.3 (2C), 129.0 (2C), 129.0 (2C), 128.9 (2C), 128.7, 128.4, 127.6, 127.6 (2C), 127.1, 125.8, 81.5, 47.8. HRMS (FAB) calculated for $C_{31}H_{26}N_3O_4$ (MH^+) 504.1923, found 504.1916. IR (neat): 2818 (w), 2567 (w), 1784 (m), 1705 (s), 1636 (s), 1491 (m), 1460 (m), 1445 (s), 1334 (m), 1253 (m), 1213 (s), 1146 (s), 756 (s), 692 (s), 590 (s). Melting point: 181.3–181.9 °C (decomp.).

Ugi product 8a

Benzylamine (107 mg, 1.0 mmol) and isobutyraldehyde (72 mg, 1.0 mmol) were dissolved in MeOH (5 mL) containing Na_2SO_4 (500 mg). This mixture was stirred for 2 h at room temperature, after which the acid **7** (252 mg, 0.5 mmol) was added. This mixture was then stirred for an additional 30 minutes after which *tert*-butyl isocyanide (42 mg, 0.5 mmol) was added. The reaction was stirred overnight and then worked up by addition of H_2O (25 mL) and extraction with EtOAc (3 × 25 mL). The combined organic fractions were washed with brine (25 mL), dried (Na_2SO_4),

filtered and concentrated by evaporation of the solvent under reduced pressure. The crude product was purified by column chromatography (cyclohexane–EtOAc 4 : 1, gradient) affording **8a** (281 mg, 75%) as a white foam as a 1 : 1 mixture of diastereomers and rotamers. NMR spectra were recorded at 403K to resolve the rotamers, but this did not have a good resolving effect on the NMR spectra. Therefore, quantification of the signals could not be achieved. ^{1}H NMR (400 MHz, DMSO-d_6, 403 K): 7.64 (bs), 7.57 (bs), 7.47–7.46 (m), 7.40 (bs), 7.38 (bs), 7.34–7.11 (m), 6.90–6.85 (m), 6.51 (d, J = 16.1 Hz), 6.40 (d, J = 15.6 Hz), 6.26 (d, J = 15.2 Hz), 6.23 (d, J = 16.0 Hz), 4.85 (bs), 4.81 (bs), 4.78 (bs), 4.74 (bs), 4.61 (bs), 4.57 (bs), 4.47 (bs), 4.44 (bs), 4.11 (bs), 2.27–2.22 (m, 1H), 1.18 (s), 1.09 (bs), 0.91 (d, J = 6.5 Hz), 0.88 (bs), 0.74 (d, J = 6.6 Hz), 0.65 (bs). ^{13}C NMR (101 MHz, DMSO-d_6, 403 K): 168.5, 168.4, 167.8, 151.8, 151.8, 151.4, 151.4, 139.5, 139.5, 137.9, 137.9, 135.5, 135.4, 135.3, 135.2, 134.4, 129.5, 129.5, 128.3, 128.3, 128.0, 127.9, 127.8, 127.8, 127.8, 127.7, 127.1, 127.0, 126.9, 126.9, 126.8, 126.5, 126.5, 126.1, 125.7, 80.2, 80.1, 65.3, 49.8, 49.7, 47.7, 47.6, 27.6, 27.5, 27.2, 27.1, 18.3, 18.1, 18.0. HRMS (FAB) calculated for $C_{47}H_{50}N_5O_4$ (MH^+) 748.3863, found 748.3862. IR (neat): 3341 (w), 3065 (w), 2965 (w), 1717 (m), 1653 (s), 1491 (m), 1437 (s), 1302 (m), 1219 (m), 756 (m), 711 (m), 692 (s), 590 (m).

Ugi product 8b

Allylamine (145 mg, 0.75 mmol) and isobutyraldehyde (53 mg, 0.75 mmol) were dissolved in MeOH (1 mL) containing Na_2SO_4 (50 mg). This mixture was stirred for 2 h at room temperature, after which the acid **7** (180 mg, 0.38 mmol) was added. This mixture was then stirred for an additional 30 minutes after which *tert*-butyl isocyanide (32 mg, 0.38 mmol) was added. The reaction was stirred overnight and then worked up by addition of H_2O (10 mL) and extraction with EtOAc (3 × 10 mL). The combined organic fractions were washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated by evaporation of the solvent under reduced pressure. The crude product was purified by column chromatography (cyclohexane–EtOAc 2 : 1, gradient) affording **8b** (112 mg, 43%) as a white foam as a 1 : 1 mixture of diastereomers and rotamers. NMR spectra were recorded at 403 K to resolve the rotamers, but this did not have a good resolving effect on the NMR spectra. Therefore, quantification of the signals could not be achieved. ^{1}H NMR (400 MHz, DMSO-d_6, 403 K): 7.68–7.65 (m), 7.52–7.39 (m), 7.33–7.28 (m), 7.24–7.16 (m), 7.08 (bs), 7.02 (bs), 6.89–6.87 (m), 6.53 (d, J = 16.1 Hz), 6.49 (d, J = 16.0 Hz), 6.32 (d, J = 16.0 Hz), 5.63 (bs), 5.09–5.04 (m), 4.93–4.86 (m), 4.66–4.62 (m), 4.38 (d, J = 17.2 Hz), 4.29 (d, J = 17.0 Hz), 4.04 (s), 4.02 (s), 2.19–2.14 (m), 1.23 (s), 1.19 (bs), 0.90 (d, J = 6.4 Hz), 0.71 (d, J = 6.7 Hz), 0.69 (bs). ^{13}C NMR (101 MHz, $CDCl_3$): 169.6, 169.5, 168.9, 168.8, 153.3, 153.2, 152.7, 152.7, 138.3, 138.2, 135.8, 135.4, 135.4, 135.1, 134.9, 133.6, 133.2, 130.0, 129.3, 129.1, 129.1, 129.0, 128.9, 128.8, 128.7, 128.7, 128.7, 128.6, 128.6, 128.1, 128.0, 127.5, 127.4, 127.2, 127.1, 126.9, 126.9, 126.8, 117.1, 116.9, 116.8, 81.2, 81.1, 51.3, 51.2, 47.9, 47.8, 28.5, 28.2, 26.8, 26.6, 19.5, 19.5, 18.7. HRMS (FAB) calculated for $C_{43}H_{48}N_5O_4$ (MH^+) 698.3706, found 698.3702. IR (neat): 2924 (m), 2853 (w), 1751 (s), 1709 (m), 1672 (m), 143 (m), 1441 (m), 1367 (m), 1221 (s), 1037 (s), 912 (m), 731 (m), 694 (m), 596 (w).

Passerini product 9

To a suspension of isobutyraldehyde (54 mg, 0.75 mmol) and **7** (252 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) was added *tert*-butyl isocyanide (62 mg, 0.75 mmol). Within a minute the reaction mixture became clear and it was then stirred overnight after which the solvent was removed by evaporation under reduced pressure. The crude product was purified by column chromatography yielding **9** (203 mg, 62%) as a white foam as a 1 : 1 mixture of diastereomers. *Diastereomer a:* ^{1}H NMR (400 MHz, $CDCl_3$): 7.62 (dd, J = 8.1, 1.9 Hz, 2H), 7.40–7.32 (m, 12H), 7.15–7.10 (m, 6H), 6.86 (d, J = 16.0 Hz, 1H), 6.60 (d, J = 16.0 Hz, 1H), 6.31 (s, 1H), 4.86 (d, J = 3.5 Hz, 1H), 4.16 (d, J = 16.2 Hz, 1H), 4.00 (d, J = 16.2 Hz, 1H), 2.34–2.27 (m, 1H), 1.37 (s, 9H), 0.89 (d, J = 7.6 Hz, 3H), 0.87 (d, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): 168.0, 167.6, 153.8, 152.0, 138.2, 137.4, 135.1, 135.1, 134.7, 129.9, 129.3, 129.2 (2C), 129.0 (2C), 129.0 (2C), 128.9 (2C), 128.8 (2C), 128.7 (2C), 128.6 (2C), 128.4, 127.5, 127.1 (2C), 125.7, 81.6, 79.4, 51.4, 48.1, 30.2, 28.3 (3C), 18.9, 16.5. *Diastereomer b:* ^{1}H NMR (250 MHz, $CDCl_3$): 7.58–7.09 (m, 20H), 6.95 (d, J = 16.0 Hz, 1H), 6.81 (d, J = 15.9 Hz, 1H), 6.46 (s, 1H), 4.93 (d, J = 3.2 Hz, 1H), 4.12 (d, J = 16.6 Hz, 1H), 3.94 (d, J = 16.6 Hz, 1H), 2.48–2.35 (m, 1H) 1.15 (s, 9H), 0.99 (d, J = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): 168.0, 167.7, 153.7, 152.0, 138.2, 137.3, 135.1, 134.8, 134.4, 129.9, 129.2, 129.1 (2C), 129.0 (2C), 128.9 (2C), 128.8 (2C), 128.8 (2C), 128.6 (2C), 128.5 (2C), 128.4, 127.4, 127.2 (2C), 125.8, 81.6, 79.4, 51.4, 48.5, 30.1, 28.2 (3C), 19.1, 16.4. HRMS (FAB) calculated for $C_{40}H_{43}N_4O_5$ (MH^+) 659.3233, found 659.3237. IR (neat): 3349 (w), 2967 (w), 1716 (s), 1663 (s), 1437 (s), 1319 (m), 1192 (m), 756 (s), 692 (s), 588 (m).

***N*-Allyltriazinane dione 10**

Following general procedure I, reaction between triazinane dione **1a** (500 mg, 1.12 mmol) and allyl bromide (150 mg, 1.24 mmol) followed by column chromatography (cyclohexane–EtOAc = 2 : 1), afforded **10** (267 mg, 49%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): 7.57–7.55 (m, 2H), 7.38–7.06 (m, 18H), 6.61 (s, 2H), 5.96–5.89 (m, 1H), 5.14 (ddt, J = 10.2, 1.4, 1.4 Hz, 1H), 5.05 (ddt, J = 17.1, 1.4, 1.4 Hz, 1H), 4.20 (ddt, J = 15.7, 5.2, 1.6 Hz, 1H), 3.98 (ddt, J = 15.6, 6.3, 1.3 Hz, 1H) ^{13}C NMR (101 MHz, $CDCl_3$): 153.4, 152.7, 138.7, 138.3, 135.5, 135.1, 135.0, 134.0, 129.6 (2C), 129.4, 129.2 (2C), 129.0, 128.9 (2C), 128.7 (2C), 128.6 (4C), 128.5 (2C), 128.1, 127.3, 127.0 (2C), 126.5, 117.2, 81.7, 49.0.

HRMS (FAB) calculated for $C_{32}H_{28}N_3O_2$ (MH^+) 486.2182, found 486.2176. IR (neat): 3061 (w), 1716 (s), 1670 (s), 1491 (m), 1420 (s), 1314 (m), 1281 (m), 754 (s), 692 (s), 588 (m).

RCM product 11

Grubbs' 2nd generation catalyst (22 mg, 0.026 mmol) was added to a solution of **10** (125 mg, 0.26 mmol) in CH_2Cl_2 (4.5 mL, dry) and this mixture was heated to reflux for 2 h. Then the solvent was removed by evaporation under reduced pressure. The crude product was purified by column chromatography (cyclohexane–EtOAc = 2 : 1) affording **11** (63 mg, 64%) as a grey solid. ^{1}H NMR (250 MHz, $CDCl_3$): 7.49–7.28 (m, 13H), 7.15–7.12 (m, 2H), 6.25 (d, J = 6.3 Hz, 1H), 5.83 (d, J = 6.3 Hz, 1H), 4.77 (d, J = 16.2 Hz, 1H), 4.53 (d, J = 16.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): 152.5, 150.6, 141.1, 137.5, 135.3, 130.2, 129.3 (2C), 129.0, 129.0

(4C), 128.7 (2C), 128.7 (2C), 128.3, 128.2, 127.8, 125.6 (2C), 84.7, 54.0. HRMS (FAB) calculated for $C_{24}H_{20}N_3O_2$ (MH^+) 382.1556, found 382.1560. IR (neat): 3067 (w), 2872 (w), 1717 (s), 1684 (s), 1443 (s), 1319 (m), 1194 (w), 760 (m), 731 (m), 694 (m). Melting point: 199.5–200.1 °C (decomp.).

N-Propargyltriazinane dione 12

Following general procedure I, reaction between triazinane dione **1a** (500 mg, 1.12 mmol) and propargyl bromide (148 mg, 1.24 mmol) followed by column chromatography (cyclohexane–EtOAc = 2 : 1), afforded **12** (326 mg, 60%) as a yellow foam. ^{1}H NMR (250 MHz, $CDCl_3$): 7.61–7.57 (m, 2H), 7.44–7.32 (m, 13H), 7.19–7.12 (m, 5H), 6.99 (d, J = 15.9 Hz, 1H), 6.82 (d, J = 16.0 Hz, 1H), 4.43 (dd, J = 17.5, 2.4 Hz, 1H), 3.96 (dd, J = 17.5, 2.4 Hz, 1H), 2.30 (t, J = 2.4 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$): 153.0, 152.6, 138.4, 137.5, 135.3, 135.1, 134.5, 129.7, 129.4 (HSQC), 129.2 (2C), 129.1, 129.0 (2C), 129.0 (HSQC), 128.9 (2C), 128.8 (2C), 128.8 (2C), 128.6 (2C), 128.3, 127.3, 127.2 (2C), 126.1, 81.7, 79.8, 72.0, 35.4. HRMS (FAB) calculated for $C_{32}H_{26}N_3O_2$ (MH^+) 484.2025, found 484.2032. IR (neat): 3287 (w), 3061 (w), 1713 (s), 1674 (s), 1491 (m), 1431 (s), 1310 (m), 1281 (m), 752 (s), 691 (s), 586 (m).

Triazole 14

12 (100 mg, 0.21 mmol) and **13** (78 mg, 0.21 mmol) were added to a mixture of H_2O–*t*-BuOH (1 : 1, 400 µl : 400 µl). Sodium ascorbate (17 mg, 0.084 mmol) and $CuSO_4{\cdot}5H_2O$ (10 mg, 0.042 mmol) were added to the white suspension and this was stirred for 2.5 h. Then, acetonitrile (400 µl) was added and the mixture was stirred overnight. An additional batch of sodium ascorbate and $CuSO_4{\cdot}5H_2O$ were added to the clear yellow solution and the mixture was stirred for another 2 h. The reaction was worked up by adding H_2O (10 mL) and extraction with CH_2Cl_2 (2 × 20 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated by evaporation of the solvent under reduced pressure. The crude product was purified by column chromatography (cyclohexane–EtOAc = 2 : 1, gradient) affording **14** (99 mg, 55%) as a light yellow sticky oil as a 1 : 1 mixture of diastereomers. *Diastereomer a:* ^{1}H NMR (400 MHz, $CDCl_3$): 8.00 (s, 1H), 7.62–7.60 (m, 2H), 7.44–7.28 (m, 12H), 7.21–7.13 (m, 4H), 7.08–7.06 (m, 2H), 6.89 (d, J = 16.0 Hz, 1H), 6.51 (d, J = 15.9 Hz, 1H), 5.83–5.81 (m, 1H), 5.46–5.43 (m, 2H), 5.28–5.23 (m, 1H), 4.91 (d, J = 15.2 Hz, 1H), 4.69 (d, J = 15.0 Hz, 1H), 4.32 (dd, J = 12.6, 4.5 Hz, 1H), 4.26–4.15 (m, 1H), 4.02–3.98 (m, 1H), 2.10 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): 170.4, 169.9, 169.1, 168.3, 153.2, 152.4, 144.8, 139.0, 138.1, 135.7, 135.3, 135.0, 129.6 (2C), 129.3, 129.1 (2C), 128.8, 128.7 (2C), 128.6 (4C), 128.4 (2C), 128.1, 128.1 (2C), 127.3, 127.1 (2C), 127.0, 123.2, 85.7, 81.7, 75.0, 72.5, 70.3, 67.5, 61.4, 41.0, 20.6, 20.4 (2C), 19.8. *Diastereomer b:* ^{1}H NMR (400 MHz, $CDCl_3$): 7.89 (s, 1H), 7.63–7.56 (m, 2H), 7.44–7.28 (m, 12H), 7.21–7.20 (m, 4H), 7.15–7.08 (m, 2H), 6.96 (d, J = 16.0 Hz, 1H), 6.60 (d, J = 16.0 Hz, 1H), 5.85–5.82 (m, 1H), 5.46–5.42 (m, 2H), 5.27–5.24 (m, 1H), 4.82 (d, J = 15.2 Hz, 1H), 4.69 (d, J = 15.1 Hz, 1H), 4.32 (dd, J = 12.7, 4.7 Hz, 1H), 4.17–4.13 (m, 1H), 4.01–3.97 (m, 1H), 2.09 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): 170.4, 169.8, 169.1, 168.6, 153.4, 152.4, 144.7, 138.5, 138.1, 135.3, 135.3, 135.0, 129.6 (2C), 129.4, 129.0 (2C), 128.8, 128.7 (2C), 128.7 (2C), 128.6 (2C), 128.5 (2C), 128.3 (2C), 128.1, 127.3, 127.1 (2C), 126.9, 122.7, 85.7, 81.8, 75.0, 72.6, 70.3, 67.5, 61.3, 41.0, 20.6, 20.4 (2C), 20.0. HRMS (FAB) calculated for $C_{46}H_{45}N_6O_{11}$ (MH^+) 857.3146, found 857.3146. IR (neat): 3350 (w), 3067 (w), 2967 (w), 2247 (w), 1713 (s), 1655 (s), 1493 (m), 1441 (s), 1304 (m), 1223 (m), 1186 (m), 909 (s), 727 (s), 692 (s), 646 (m), 690 (m), 519 (m).

Diels–Alder product 16a

Following general procedure I, reaction between triazinane dione **1b** (250 mg, 0.57 mmol) and methyl *E*-4-bromo-2-butenoate (113 mg, 0.63 mmol) followed by column chromatography (cyclohexane–EtOAc = 2 : 1), afforded **16a** (144 mg, 47%) as a yellow solid. **16a** was crystallized by slow evaporation of an EtOAc-solution. ^{1}H NMR (400 MHz, $CDCl_3$): 7.51–7.32 (m, 12H), 7.26–7.23 (m, 3H), 6.98 (d, J = 15.7 Hz, 1H), 6.61 (d, J = 15.8 Hz, 1H), 6.10 (dd, J = 5.9, 1.6 Hz, 1H), 6.00 (d, J = 5.9 Hz, 1H), 5.33 (dd, J = 4.8, 1.6 Hz, 1H), 4.20 (dd, J = 11.3, 9.5 Hz, 1H), 3.75 (dd, J = 11.7, 7.3 Hz, 1H), 3.63 (s, 3H), 3.26 (dd, J = 4.8, 2.9 Hz, 1H), 2.61 (ddd, J = 9.4, 7.3, 2.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): 170.8, 152.7, 150.5, 136.3, 135.3, 134.7, 133.8, 133.2, 133.0 (2C), 129.3 (4C), 129.1 (3C), 128.8 (2C), 128.5, 128.2, 127.2 (3C), 132.2, 98.8, 80.4, 77.1, 52.9, 52.2, 50.2, 42.7. HRMS (FAB) calculated for $C_{32}H_{28}N_3O_5$ (MH^+) 534.2029, found 534.2031.

IR (neat): 3013 (w), 1717 (s), 1676 (s), 1449 (s), 1319 (m), 1213 (m), 754 (m), 694 (m). Melting point: 194.9–195.4 °C (decomp.).

Crystallographic data for 16a

$C_{32}H_{27}N_3O_5$, Fw = 533.57, yellow plate, 0.36 × 0.36 × 0.12 mm^3, monoclinic, $P2_1/c$ (no. 14), a = 9.8195(1), b = 25.2307(3), c = 11.4069(2) Å, β = 112.6460(5)°, V = 2608.20(6) Å^3, Z = 4, D_x = 1.359 g cm^{-3}, μ = 0.09 mm^{-1}. 28707 Reflections were measured on a Nonius Kappa CCD diffractometer with rotating anode (graphite monochromator, λ = 0.71073 Å) up to a resolution of $(\sin\theta/\lambda)_{max}$ = 0.65 Å^{-1} at a temperature of 150 K. The reflections were corrected for absorption and scaled on the basis of multiple measured reflections with the program SORTAV[20] (0.95–0.99 correction range). 5961 Reflections were unique (R_{int} = 0.0497). The structure was solved with Direct Methods (program SHELXS-97[21]) and refined with SHELXL-97[21] against F^2 of all reflections. Non hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were located in difference Fourier maps. Methyl and phenyl hydrogen atoms were refined with a riding model; all other hydrogen atoms were refined freely with isotropic displacement parameters. 398 Parameters were refined with no restraints. $R1/wR2$ [$I > 2\sigma(I)$]: 0.0464/0.1247. $R1/wR2$ [all refl.]: 0.0716/0.1416. S = 1.085. The maximum residual electron density peak has a height of 0.84 e Å^{-3} and a distance of 2.34 Å to the closest atom H33. Geometry calculations and checking for higher symmetry was performed with the PLATON program.[22]

Triazinane dione 1c

Triazinane dione **1c** was prepared by the method reported by Groenendaal *et al.*[7] Reaction between diethyl methylphosphonate

(730 mg, 5.0 mmol), furonitrile (510 mg, 5.5 mmol), piperonal (826 mg, 5.5 mmol) and phenyl isocyanate (1.31 g, 11.0 mmol), followed by column chromatography (cyclohexane–EtOAc 4 : 1) afforded **1c** (1.47 g, 61%) as a brown solid. ^{1}H NMR (250 MHz, $CDCl_3$): 7.52–7.51 (m, 1H), 7.45–7.27 (m, 8H), 7.52–7.13 (m, 2H), 6.83 (d, $J = 15.9$ Hz, 1H), 6.76 (s, 3H), 6.46 (dd, $J = 3.4$, 0.8 Hz, 1H), 6.40 (dd, $J = 3.4$, 1.9 Hz, 1H), 6.11 (d, $J = 15.8$ Hz, 1H), 6.10 (s, 1H), 5.97 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): 152.7, 152.0, 151.7, 148.4, 148.1, 143.5, 136.8, 134.8, 133.4, 129.9 (2C), 129.1, 129.1 (2C), 128.7 (4C), 128.2, 128.1, 123.3, 122.4, 110.7, 110.0, 108.4, 105.8, 101.3, 71.0. HRMS (FAB) calculated for $C_{28}H_{22}N_3O_5$ (MH^+) 480.1559, found 480.1562. IR (neat): 3160 (w), 3069 (w), 2899 (w), 1709 (s), 1667 (s), 1489 (m), 1444 (s), 1325 (m), 1251 (s), 1036 (s), 929 (m), 748 (m), 692 (s), 560 (s). Melting point: 205.8–206.4 °C (decomp.).

Triazinane dione 1d

Triazinane dione **1d** was prepared by the method reported by Groenendaal *et al.*[7] Reaction between diethyl methylphosphonate (730 mg, 5.0 mmol), furonitrile (510 mg, 5.5 mmol), benzaldehyde (585 mg, 5.5 mmol) and *p*-methoxyphenyl isocyanate (1.64 g, 11.0 mmol), afforded **1d** (1.30 g, 52%) as a light brown solid. The crude product precipitated out of the reaction mixture after evaporation of half of the solvent and addition of water (10 mL). Subsequent washing of the crude product with cold Et_2O gave **1d** as a light brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): 9.16 (s, 1H), 7.82 (dd, $J = 1.6$, 0.6 Hz, 1H), 7.46 (d, $J = 7.2$ Hz, 2H), 7.39–7.32 (m, 3H), 7.07 (d, $J = 8.9$ Hz, 2H), 7.01 (d, $J = 8.8$ Hz, 2H), 6.95 (d, $J = 8.9$ Hz, 2H), 6.85 (d, $J = 15.9$ Hz, 1H), 6.83 (d, $J = 9.0$ Hz, 2H), 6.56 (dd, $J = 3.3$, 0.8 Hz, 1H), 6.49 (dd, $J = 3.2$, 1.8 Hz, 1H), 6.45 (d, $J = 16.0$ Hz, 1H), 3.77 (s, 3H), 3.70 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): 158.9, 158.7, 152.7, 152.4, 152.1, 144.3, 135.6, 133.1, 131.6 (2C), 130.8 (2C), 130.2, 129.1 (2C), 129.0, 128.7, 127.4 (2C), 126.6, 114.1 (4C), 111.1, 110.6, 71.0, 55.6, 55.5. HRMS (FAB) calculated for $C_{29}H_{26}N_3O_5$ (MH^+) 496.1872, found 496.1868. IR (neat): 3215 (w), 3065 (w), 2905 (w), 1717 (s), 1670 (s), 1508 (s), 1437 (m), 1296 (m), 1240 (s), 1028 (m), 826 (m), 743 (m), 554 (m). Melting point: 195.6–196.3 °C (decomp.).

Diels–Alder product 16b

Following general procedure I, reaction between triazinane dione **1c** (250 mg, 0.52 mmol) and methyl *E*-4-bromo-2-butenoate (140 mg, 0.78 mmol) followed by column chromatography (cyclohexane–EtOAc = 2 : 1), afforded **16b** (150 mg, 81%, based on recovered starting material) as an orange solid. ^{1}H NMR (400 MHz, $CDCl_3$): 7.47–7.29 (m, 8H), 7.23–7.20 (m, 2H), 6.98 (d, $J = 1.5$ Hz, 1H), 6.93 (dd, $J = 8.0$, 1.5 Hz, 1H), 6.86 (d, $J = 16.1$ Hz, 1H), 6.84 (d, $J = 7.7$ Hz, 1H), 6.41 (d, $J = 15.6$ Hz, 1H), 6.09 (dd, $J = 5.9$, 1.6 Hz, 1H), 6.02 (s, 2H), 5.97 (d, $J = 5.9$ Hz, 1H), 5.32 (dd, $J = 4.8$, 1.5 Hz, 1H), 4.16 (dd, $J = 11.3$, 9.6 Hz, 1H), 3.72 (dd, $J = 11.5$, 7.4 Hz, 1H), 3.62 (s, 3H), 3.25 (dd, $J = 4.8$, 2.9 Hz, 1H), 2.58 (ddd, $J = 9.8$, 7.3, 2.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): 170.7, 152.6, 150.4, 148.6, 148.3, 136.2, 135.2, 133.7, 133.1, 132.4 (2C), 129.2 (4C), 128.9, 128.7 (4C), 128.4, 128.0, 122.6, 121.1, 108.6, 105.8, 101.4, 98.4, 80.2, 52.8, 52.0, 50.0, 42.6. HRMS (FAB) calculated for $C_{33}H_{28}N_3O_7$ (MH^+) 578.1972, found 578.1932. IR (neat): 2955 (w), 2899 (w), 1713 (s), 1676 (s), 1449 (s), 1319 (m), 1254 (m), 1036 (m), 912 (m), 760 (m), 729 (m), 696 (m). Melting point: 161.8–162.5 °C (decomp.)

Diels–Alder product 16c

Following general procedure I, reaction between triazinane dione **1d** (250 mg, 0.50 mmol) and methyl *E*-4-bromo-2-butenoate (135 mg, 0.76 mmol) followed by column chromatography (cyclohexane–EtOAc = 2 : 1), afforded **16c** (125 mg, 67%, based on recovered starting material) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): 7.47–7.37 (m, 6H), 7.13 (d, $J = 8.9$ Hz, 2H), 6.93 (d, $J = 15.8$ Hz, 1H), 6.88 (d, $J = 9.0$ Hz, 2H), 6.58 (d, $J = 15.7$ Hz, 1H), 6.11 (dd, $J = 5.9$, 1.6 Hz, 1H), 5.99 (d, $J = 5.9$ Hz, 1H), 5.33 (dd, $J = 4.9$, 1.6 Hz, 1H), 4.17 (dd, $J = 11.2$, 9.5 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.73 (dd, $J = 11.3$, 7.5 Hz, 1H), 3.62 (s, 3H), 3.25 (dd, $J = 4.8$, 2.9 Hz, 1H), 2.56 (ddd, $J = 9.5$, 7.2, 2.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): 170.7, 159.2, 159.0, 153.0, 150.7, 134.7, 133.8, 133.1, 132.7 (2C), 130.1 (3C), 129.2, 128.9 (3C), 128.8, 127.9, 127.1 (3C), 123.1, 114.0 (2C), 113.5 (2C), 98.4, 80.2, 55.3, 52.8, 52.0, 50.2, 42.4. HRMS (FAB) calculated for $C_{34}H_{32}N_3O_7$ (MH^+) 594.2240, found 594.2242. IR (neat): 2955 (w), 2837 (w), 1713 (s), 1676 (s), 1510 (s), 1456 (s), 1296 (m), 1248 (s), 1169 (m), 1032 (m), 829 (m), 731 (m). Melting point: 198.7–199.3 °C (decomp.).

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