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Nitrogen is a requirement for the photochemical induced 3-azabicyclo[3.3.1]nonane skeletal rearrangement!

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Abstract—Specific 3-azabicyclo[3.3.1]nonane derivatives undergo skeletal cleavage when subjected to light or Lewis acidic conditions affording novel heterotricycles, which is in stark contrast to 3-oxabicyclo[3.3.1]nonanes.

1. Introduction

The 3-azabicyclo[3.3.1]nonane (3-ABN) skeleton **1** is well known[1] to both natural product[2,3] and synthetic[4] chemists alike as it appears as the AE ring motif in the prolific C_{19}- (e.g., chasmanine **2**) and C_{20}- (e.g., atisine **3**) diterpene alkaloid series[5,6] (Fig. 1).

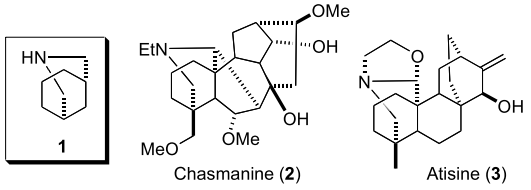
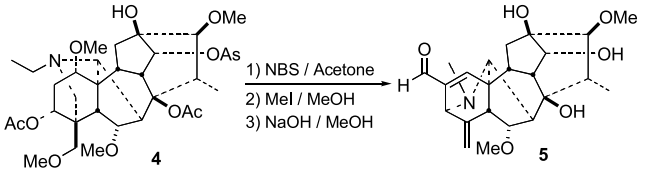


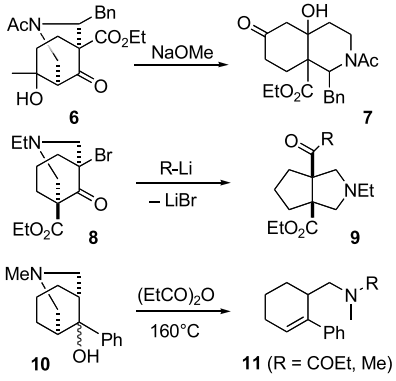
Figure 1.

In comparison, however, rearrangement of the 3-ABN skeleton is not so well known. For example, biosynthetic rearrangement is seldom observed (e.g., arcutin[7]), although, 3-acetylyunaconitine **4** affords AE ring rearranged products (e.g., **5**) when treated chemically (1. NBS; 2. MeI; 3. NaOH) (Scheme 1).[8]



Scheme 1.

Furthermore, synthetic 3-ABNs have been observed in only three instances to undergo rearrangement [i.e., retroaldol[9] (**6** to **7**), pinacol-type[10] (**8** to **9**) and thermal[11] (**10** to **11**)] (Scheme 2).



Scheme 2.

Recently, however, during the course of attempting to optimise our direct route to C_{19}- and C_{20}-diterpene alkaloid advanced intermediate **12**,[12] we discovered that certain 3-ABNs (e.g., **14**) undergo unprecedented photochemical rearrangement affording novel heterotricycles **15** (Scheme 3).[13] Unfortunately, however, photochemical rearrangement is not general and we herein disclose these results in full.

2. Results and discussion

Paramount to studying the photochemical rearrangement of

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† To whom correspondence should be made regarding X-ray crystal structure analysis.

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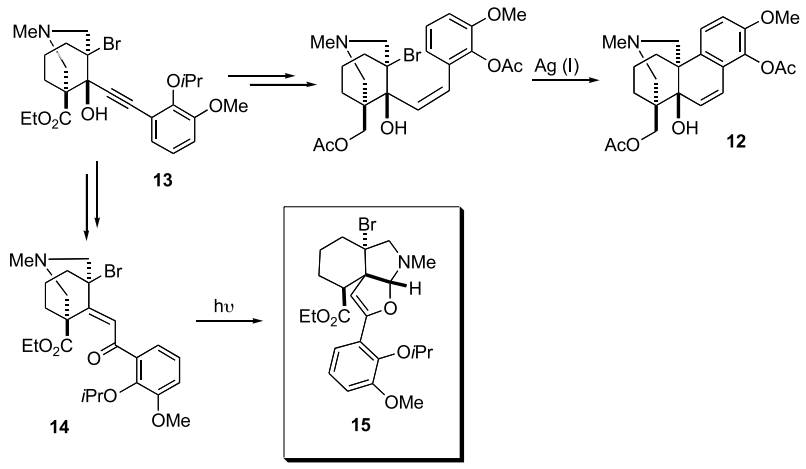
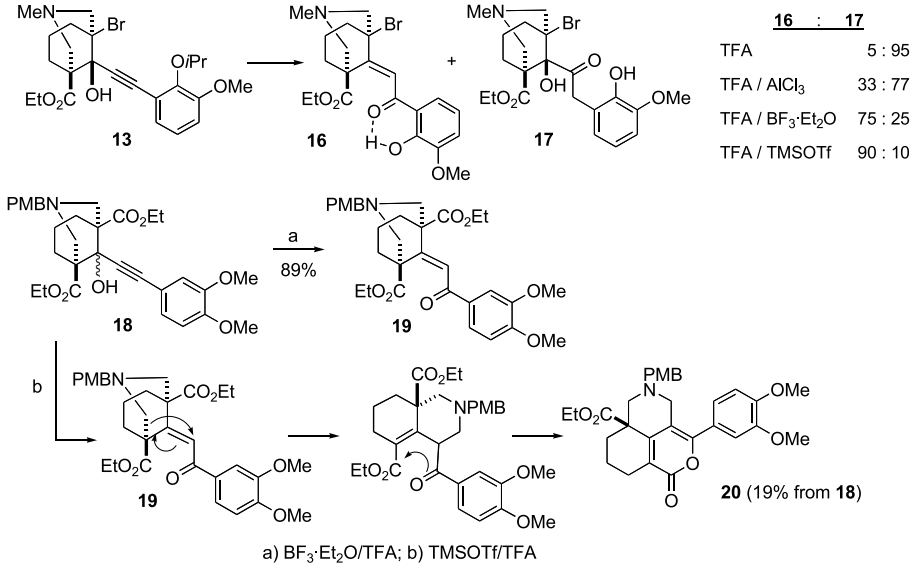


Scheme 3.



Scheme 4.

3-ABNs of type **14** was their synthesis and in this regard a Meyer–Schuster rearrangement[14] was found to be the method of choice. Treatment of the propargylic alcohol **13**[12] with a selection of Lewis acids in trifluoroacetic acid (TFA) gave the isopropyl deprotected enone **16** (Meyer–Schuster product) and the corresponding deprotected α-hydroxyketone **17** (triple bond hydration) in varying ratios (Scheme 4). Trimethylsilyl trifluorosulfonate (TMSOTf) in TFA was found to be the optimum conditions affording a 9:1 ratio in favour of the enone **16**. In stark contrast treatment of propargylic alcohol **18** using the successful conditions (TMSOTf/TFA) developed for **13**, gave the Meyer–Schuster product **19** only in low yield (13%) along with pyranone **20** (19%) [confirmed by X-ray crystal analysis (Fig. 2)], derived from a sequential [1,3]-sigmatropic shift followed by enolic ring closure. Changing the Lewis acid to borotrifluoride etherate, however, gave **19** in 89% (Scheme 4).

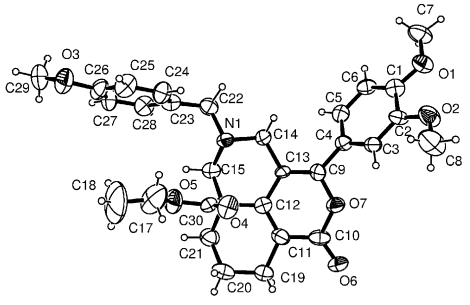
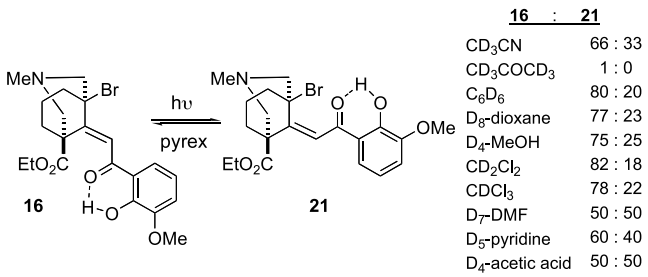


Figure 2.

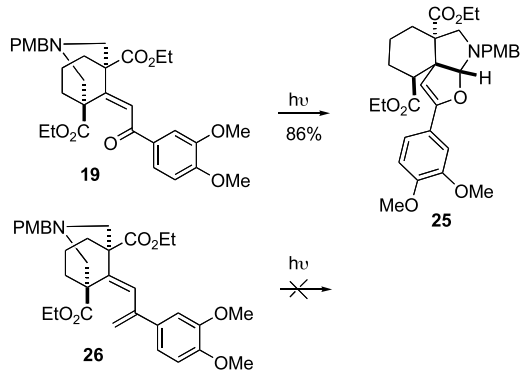
Photochemical rearrangement of 3-ABNs seem to be very functional group specific, for example, photolysis of **16** at 300 nm in various oxygen free deuterated solvents results in photochemical isomerization (*cis* to *trans*) of enone **16** to enone **21** without the formation of any rearranged product (Scheme 5). This is not easily explained, but maybe due to one of a number of processes, which prevent n to π* transitions, for example, nitrogen or oxygen protonation, or hydrogen bonding.[15]



Scheme 5.

Whereas conversion of the phenol to an isopropyl ether followed by photolysis afforded rearranged products (e.g., **14** to **15**). However, the etherfication procedure of Banwell[16] gave in addition to the isopropyl ether [i.e., **14** (48%)] pyranones **22** and **23** (29%) (Fig. 3), which was easily circumvented using the procedure of Sargent[17] in conjunction with a large excess of *iso*-propylbromide (93%) (Scheme 6). Pyranones **22** and **23** could be obtained in 26 and 61% yields, respectively, in the absence of isopropyl bromide. Irradiation of **14**, gave the rearranged product **15** (18%) along with a mixture (2:8) of **15** and **24** (51%) (Scheme 4). Unfortunately, conversion to **15** cannot be driven to completion, extended radiation leads to substantial decomposition mostly likely due to complications arising from the single electron susceptible bridgehead bromide function. A photochemical equilibrium between **14/24** and **15** was dismissed when pure **15** was irradiated affording slow decomposition.

In contrast, irradiation of **19** gave the rearranged product **25** in very high yield (86%) (Scheme 7). To evaluate the scope of this process the ketone functionality of **19** was replaced with CH_2 (e.g., **26**), in an attempt to emulate α-hydrogen abstraction reported by Grainger[18] and Reddy (Scheme 7)[19] and the ring *N* substituted with oxygen (**27**) (Scheme 8). Conversion to diene **26** via standard Wittig methodology (CH_2=PPh_3) proceeded smoothly (64%), however, photolysis at 254 and 300 nm resulted in decomposition.



Scheme 7.

Construction of **27**, confirmed by X-ray crystal structure analysis (Fig. 4), was achieved following similar protocols used to synthesise **19**, except starting from dimethyl 9-oxo-3-oxabicyclo[3.3.1]nonane-1,5-dicarboxylate.[20]

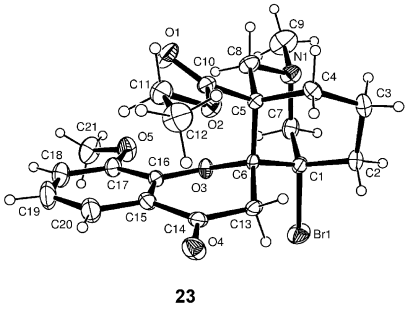


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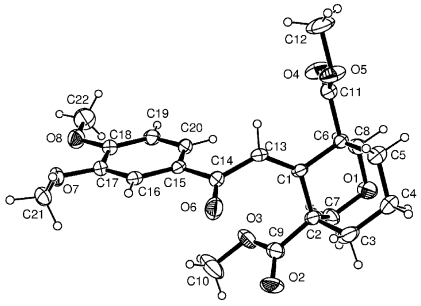
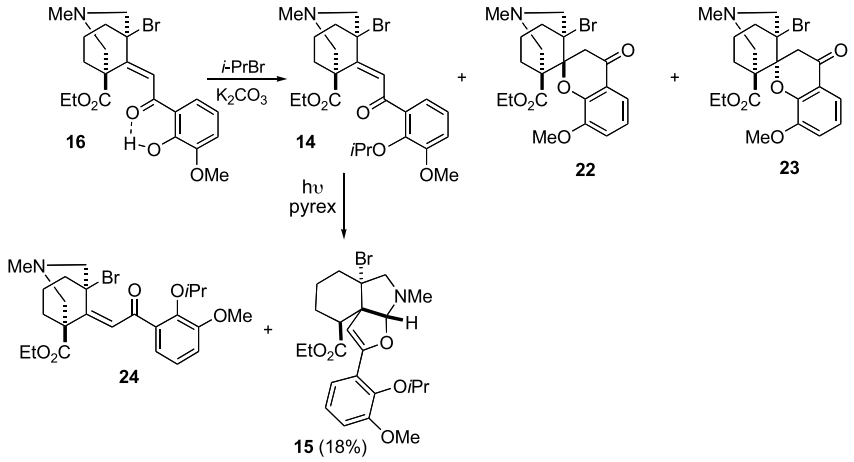
Figure 3.

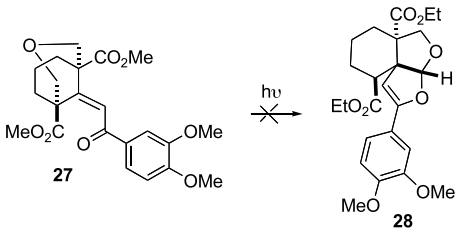


27

Figure 4.



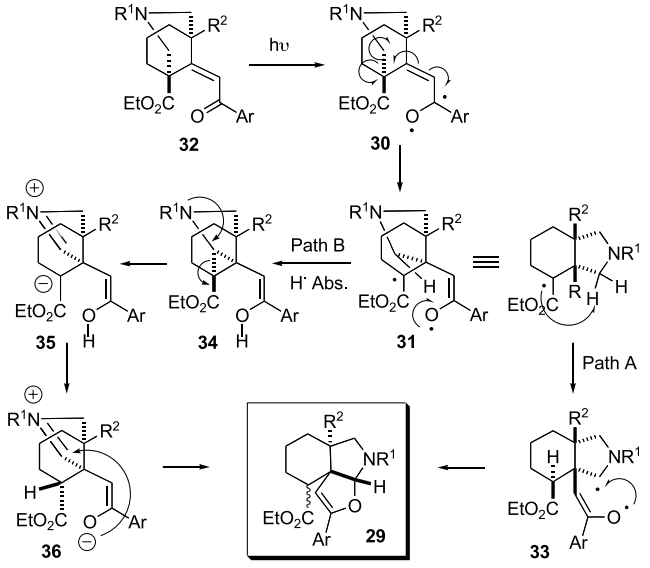
Scheme 6.



Scheme 8.

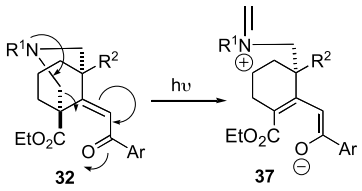
Unfortunately, however, photolysis of **27** at 300 nm returned starting material and irradiation at 254 nm resulted in slow decomposition (Scheme 8).

Two mechanistic pathways to **15** and **25** (e.g., **29**) are proposed of which only mechanistic pathway B arrives at the observed stereochemistry for the non-bridgehead ester group [**29** (β)] whereas pathway A would afford stereochemistry opposite [**29** (α)] to that seen in the X-ray crystal structures of **15** and **25** (Scheme 9). Both mechanisms involve a 1,2-sigmatropic shift (**30** to **31**) initiated by ketone **32** excitation (triple state). The subsequent formation of radical **33** (Path A) appears justified on the basis of recent data provided by Croft et al.[21] Ring closure of **33** leads to the final tricycle **29**. Alternatively, rearrangement of radical **31** (Path B) leads to the unstable cyclopropane intermediate **34**. Anionic ring opening of **34** would afford **35**, which undergoes immediate proton exchange on the less hindered face with concomitant ring closure, via the oxyanion **36**, affording **29**. An intermolecular pathway has been ruled out in this instance as deuterium atom abstraction from d_7-DMF was not observed.



Scheme 9.

The observation that oxabicyclo **27** does not undergo photochemical reaction suggests that the oxa substituent cannot suitably stabilise the 1,2-shift (i.e., **30** to **31**), which, if radical in nature would concur with recent calculations[22] (i.e., nitrogen has the greatest stabilisation of lone pair donor groups). It is also conceivable that photochemical induced heterolytic sigma bond cleavage may occur to give intermediate **37**, which would be favoured by aza more than oxa groups, however, it is difficult to transpose intermediate **37** into product (e.g., **15** and **25**) (Scheme 10).



Scheme 10.

3. Conclusion

We have discovered for the first time a photochemical rearrangement of the 3-ABN skeleton, which affords a unique heterotricyclic system. It should be noted that all attempts to ring open the aminal moiety of **15** and **25** so as to gain access to alkaloid type skeletons have failed.

4. Experimental

4.1. General experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV400 (400.13 MHz; 100.62 MHz) or a Bruker AC200 (200.13 MHz; 50.32 MHz) in deuteriochloroform ($CDCl_3$). Coupling constants are given in Hz and chemical shifts are expressed as δ values in ppm. High and low resolution EI mass spectral data were obtained on a KRATOS MS 25 RFA. Microanalyses were performed by the University of Queensland Microanalytical Service. Column chromatography was undertaken on silica gel (Flash Silica gel 230–400 mesh), with distilled solvents. Anhydrous solvents were prepared according to Perin and Armarego, 'Purification of laboratory solvents', 3rd Ed. Melting points were determined on a Fischer Johns Melting Point apparatus and are uncorrected. Methylmagnesium bromide and *n*-BuLi was purchased from the Aldrich Chem. Co.

4.2. X-ray crystallography

Data for all compounds were collected at 293 K on an Enraf-Nonius CAD4 diffractometer. Data reduction, direct methods structure solution and full least squares refinement (SHELX97[23]) were performed with the WINGX package.[24] Drawings of all molecules were created with ORTEP3.[25] Data in CIF format have been deposited with the Cambridge Crystallographic Data Centre (CCDC Deposition Nos. 248300–248302). Copies of the data can be obtained free of charge upon request to deposit@ccdc.cam.ac.uk

4.2.1. Ethyl 5-bromo-3-methyl-9-[2-oxo-2-(2-hydroxy-3-methoxyphenyl)-*E*-ethylidene]-3-azabicyclo[3.3.1]nonanecarboxylate 16. Ethyl 5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-isopropoxy)phenylethynyl]-3-azabicyclo[3.3.1]nonanecarboxylate[12] **13** (0.205 g, 0.041 mmol) was rapidly dissolved in trifluoroacetic acid (3 mL) at room temperature. The solution was cooled in an ice-bath and trimethylsilyltrifluorosulfonate (0.23 mL, 1.29 mmol)

added rapidly. After addition the flask was taken out of the bath and stirred at room temperature for 1 h. The reaction mixture was then transferred, via Pasteur pipette, to a separatory funnel containing a saturated solution of sodium hydrogen carbonate (50 mL) and extracted with dichloromethane (3×10 mL). The residue was dried under vacuum, redissolved in anhydrous THF (3 mL) and sodium hydride added until effervescence ceased. The mixture was quenched with saturated ammonium chloride solution and extracted with dichloromethane (3×10 mL). Column chromatography (ethyl acetate/dichloromethane, 5:95) afforded the title compound as a bright yellow viscous oil (0.13 g, 70%). ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.83 (t, J=7.1 Hz, 3H), 1.56–1.65 (m, 1H), 2.20 (s, 3H), 2.21–2.28 (m, 2H), 2.40–2.51 (m, 1H), 2.63 (d, J=11.1 Hz, 1H), 2.69–2.76 (m, 1H), 2.85 (dd, J=10.6, 2.4 Hz, 1H), 2.93–3.07 (m, 2H), 3.50 (dd, J=10.6, 1.3 Hz, 1H), 3.66–3.85 (m, 2H), 3.89 (s, 3H), 6.87 (t, J=8.1 Hz, 1H), 7.03–7.07 (m, 1H), 7.38 (s, 1H), 7.42 (dd, J=8.1, 1.4 Hz, 1H), 12.26 (s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 23.6, 36.3, 44.6, 47.3, 52.4, 56.2, 60.9, 64.1, 71.1, 71.5, 117.1, 118.4, 120.1, 122.6, 123.0, 148.7, 152.7, 153.0, 172.3, 199.5. MS *m/z* (EI) 453 ($M^{+\cdot}$, 4%), 451 ($M^{+\cdot}$, 5%), 408 (2), 406 (2), 372 (80), 326 (20), 302 (20), 300 (21), 298 (14), 286 (6), 283 (6), 279 (15), 256 (8), 222 (17), 220 (30), 206 (19), 167 (39), 151 (98), 149 (100), 129 (11), 113 (18). Anal. Calcd for $C_{21}H_{26}BrNO_5$: $M^{+\cdot}$ 451.0995. Found: 451.0989.

4.2.2. Photolysis of ethyl 5-bromo-3-methyl-9-[2-oxo-2-(2-hydroxy-3-methoxyphenyl)-*E*-ethylidene]-3-azabicyclo[3.3.1]nonanecarboxylate 16. Ethyl 5-bromo-3-methyl-9-[2-oxo-2-(2-hydroxy-3-methoxyphenyl)-*E*-ethylidene]-3-azabicyclo[3.3.1]nonanecarboxylate **16** (0.020 g, 0.044 mmol) was dissolved in oxygen free D_7-*N*,*N*-dimethylformamide (1 mL) in a 5 mm NMR tube (PP-528) and irradiated with a Hanovia high pressure mercury–xeon vapour lamp (1000 W). [*Note*. The light was passed through a ~5 °C water filter (30 cm long) and the sample placed 10 cm from the end of the cooling tube.] The isomerization was monitored by ^{1}H NMR every 15 min until a 1:1 mixture of **16** and **21** was evident. The solvent was removed and the residue subjected to column chromatography (dichloromethane) affording an inseparable 1:1 mixture of **16** and **21** (0.015 g, 75%).

The relevant ^{1}H NMR values for **21** are listed only and are a result from subtracting isolated peaks observed from a spectrum of pure **16**.

^{1}H NMR (200 MHz, $CHCl_3$) δ 1.27 (t, J=7.4 Hz, 3H), 3.32 (AB, 1H), 3.885 (s, 3H), 4.12–4.26 (m, 2H), 5.80 (s, 1H).

4.2.3. Ethyl 5-bromo-3-methyl-9-[2-oxo-2-(2-isopropoxy-3-methoxyphenyl)-*E*-ethylidene]-3-azabicyclo-[3.3.1]nonanecarboxylate 14. Ethyl 5-bromo-3-methyl-9-[2-oxo-2-(2-hydroxy-3-methoxyphenyl)-*E*-ethylidene]-3-azabicyclo[3.3.1]nonanecarboxylate **16** (0.156 g, 0.345 mmol) was dissolved in *N*,*N*-dimethylformamide (1.5 mL) followed by addition of 2-bromopropane (0.97 mL, 10.3 mmol) and potassium carbonate (0.095 g, 0.69 mmol). The mixture was then stirred at room temperature for 16 h. Excess 2-bromopropane and *N*,*N*-dimethylformamide were removed under high vacuum and the residue suspended in dichloromethane (5 mL) and passed through celite. Column chromatography (diethyl ether/light petroleum, ~1:4) of the residue on silica gel afforded the title compound (0.159 g, 93%) and **22** (0.004 g, 3%) both as pale yellow oils. ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.22–1.30 (m, 9H), 1.54–1.63 (m, 1H), 1.96–2.05 (m, 1H), 2.17 (s, 3H), 2.36–2.49 (m, 2H), 2.51–2.60 (m, 1H), 2.79 (dd, J=10.7, 2.4 Hz, 1H), 2.87 (dd, J=11.1, 2.4 Hz, 1H), 2.89–3.03 (m, 1H), 2.97 (dd, J=11.1, 1.3 Hz, 1H), 3.28 (dd, J=10.7, 1.3 Hz, 1H), 3.82 (s, 3H), 4.13–4.25 (m, 2H), 4.59 (sept, J=6.2 Hz, 1H), 6.99–7.07 (m, 2H), 7.42 (AB, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.3, 22.4, 23.6, 35.9, 44.8, 46.2, 54.9, 56.1, 61.2, 63.1, 65.4, 71.3, 76.1, 116.1, 122.8, 123.7, 125.7, 134.3, 142.4, 147.0, 153.5, 172.7, 195.3. Near IR (Nujol) ν (cm^{-1}) 1729, 1713, 1681, 1666. MS *m/z* (EI) 494 ($M^{+\cdot}$, 0.5%), 492 ($M^{+\cdot}$, 0.5%), 414 (77), 368 (7), 354 (7), 340 (2), 326 (9), 315 (1), 302 (11), 300 (12), 283 (2), 256 (2), 220 (27), 208 (5), 206 (8), 193 (49), 174 (2), 151 (100), 148 (6), 146 (5), 134 (6), 120 (4). Anal. Calcd for $C_{24}H_{32}BrNO_5$: $M^{+\cdot}$ 414.2280 (−HBr). Found: 414.2277.

4.2.4. Pyranones 22 and 23. Ethyl 5-bromo-3-methyl-9-[2-oxo-2-(2-hydroxy-3-methoxyphenyl)-*E*-ethylidene]-3-azabicyclo[3.3.1]nonanecarboxylate **16** (0.023 g, 0.051 mmol) was dissolved in *N*,*N*-dimethylformamide (2.0 mL) followed by addition of potassium carbonate (0.021 g, 0.15 mmol). The mixture was then heated at 80 °C for 15 min. On cooling *N*,*N*-dimethylformamide was removed under high vacuum and the residue suspended in dichloromethane (5 mL) and passed through celite. Column chromatography (dichloromethane/ethyl acetate, gradient) of the residue on silica gel afforded two fractions. Fraction one (**22**) (6 mg, 26%) was obtained as colourless crystals. Mp 116–118 °C (diethyl ether/dichloromethane) ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.89 (t, J=7.2 Hz, 3H), 1.63–1.78 (m, 2H), 2.22 (s, 3H), 2.31–2.38 (m, 1H), 2.67–2.97 (m, 5H), 3.15–3.27 (m, 2H), 3.34 (d, J=14.7 Hz, 1H), 3.52–3.73 (m, 3H), 3.88 (s, 3H), 6.86 (t, J=8.0 Hz, 1H), 7.03 (dd, J=8.0, 1.6 Hz, 1H), 7.37 (dd, J=8.0, 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 23.2, 29.4, 39.0, 41.3, 44.7, 52.8, 56.7, 59.7, 61.3, 65.5, 74.6, 83.1, 117.2, 117.9, 120.1, 120.4, 149.3, 150.7, 172.2, 189.8. MS *m/z* (EI) 453 ($M^{+\cdot}$, 30%), 451 ($M^{+\cdot}$, 32%), 408 (8), 372 (74), 328 (46), 315 (7), 298 (34), 283 (14), 270 (4), 255 (27), 220 (27), 151 (57), 138 (17), 136 (21), 122 (21), 105 (13). Anal. Calcd for $C_{21}H_{26}BrNO_5$: $M^{+\cdot}$ 451.0995. Found: 451.0992. Fraction two (**23**) (14 mg, 61%) was obtained as colourless needles. Mp 131–133 °C (diethyl ether/dichloromethane) ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.94 (t, J=7.2 Hz, 3H), 1.48–1.58 (m, 1H), 1.84 (dd, J=14.9 Hz, 6.5, 1H), 2.26 (s, 3H), 2.32–2.48 (m, 3H), 2.72 (d, J=11.6 Hz, 1H), 2.85–3.02 (m, 1H), 3.16 (d, J=10.8 Hz, 1H), 3.32 (dd, J=11.6, 2.6 Hz, 1H), 3.47–3.65 (m, 5H), 3.88 (s, 3H), 6.86 (t, J=7.9 Hz, 1H), 7.01 (dd, J=7.9, 1.5 Hz, 1H), 7.38 (dd, J=7.9, 1.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 22.7, 32.1, 39.8, 40.5, 45.1, 52.3, 56.8, 57.7, 61.2, 64.4, 74.8, 83.1, 117.1, 117.9, 120.2, 120.6, 149.3, 149.9, 172.3, 189.9. MS *m/z* (EI) 453 ($M^{+\cdot}$, 30%), 451 ($M^{+\cdot}$, 29%), 372 (43), 328 (27), 298 (14), 283 (10), 255 (13), 227 (4), 220 (7), 194 (6), 151 (32), 138 (10), 136 (9), 122 (11), 105 (6). Anal. Calcd for $C_{21}H_{26}BrNO_5$: C, 55.76; H, 5.79; N, 3.10; $M^{+\cdot}$ 451.0995. Found: C, 55.53; H, 5.76; N, 3.07; $M^{+\cdot}$ 451.0986.

4.2.5. Photolysis of ethyl 5-bromo-3-methyl-9-[2-oxo-2-(2-isopropoxy-3-methoxyphenyl)-*E*-ethylidene]-3-azabicyclo[3.3.1]nonanecarboxylate 14. Ethyl 5-bromo-3-methyl-9-[2-oxo-2-(2-isopropoxy-3-methoxyphenyl)-*E*-ethylidene]-3-azabicyclo[3.3.1]nonanecarboxylate **14** (0.171 g, 0.346 mmol) was dissolved in oxygen free *N*,*N*-dimethylformamide (150 mL) and irradiated through pyrex in a 1 L Hanovia photochemical reactor using a 4 W arc lamp for 10 days. The solvent was then removed under high vacuum using an in-line trap and the residue subjected to column chromatography (diethyl ether/light petroleum, 3:7–6:4), which afforded tricycle **15** (0.030 g, 18%) in fraction one and a mixture of **14** and **24** (1:1) (0.088 g, 51%) in fraction two.

Ethyl 3a-bromo-2-methyl-1,3,3a,4,5,6,7,7a-octahydro-9-(2-isopropoxy-3-methoxyphenyl)-isoindolo[1,7a-b]furan-7-carboxylate **15**. ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.00 (t, J=7.1 Hz, 3H), 1.23 (d, J=6.2 Hz, 3H), 1.29 (d, J=6.2 Hz, 3H), 1.54–1.82 (m, 3H), 1.84–1.91 (m, 1H), 2.19–2.26 (m, 1H), 2.34–2.44 (m, 1H), 2.51 (s, 3H), 2.83–2.92 (m, 2H), 3.35 (d, J=8.0 Hz, 1H), 3.81 (s, 3H), 3.84–4.00 (m, 2H), 4.67 (sept, J=6.2 Hz, 1H), 5.63 (s, 1H), 5.67 (s, 1H), 6.80–6.84 (m, 1H), 6.96 (t, J=16 Hz, 1H), 7.22–7.27 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.3, 22.2, 22.5, 26.3, 34.3, 40.0, 45.9, 55.9, 60.4, 65.18, 65.25, 69.5, 74.2, 94.4, 107.4, 112.7, 119.6, 122.9, 125.2, 144.7, 152.95, 153.04, 173.8. Near IR (Nujol) ν (cm^{-1}) 1731. MS *m*/*z* (EI) 494 ($M^{+\cdot}$, 0.5%), 492 ($M^{+\cdot}$, 0.5%), 414 (100), 368 (29), 326 (6), 298 (5), 282 (2), 270 (2), 256 (2), 220 (63), 208 (10), 193 (87), 175 (2), 151 (89), 148 (6), 146 (8), 134 (22), 120 (8). Anal. Calcd for $C_{24}H_{32}BrNO_5$: $M^{+\cdot}$ 414.2280 (−HBr). Found: 414.2279.

4.2.6. Diethyl 3-(4-methoxyphenylmethyl)-9-[2-oxo-2-(3,4-dimethoxyphenyl)ethylidene]-3-azabicyclo[3.3.1]-nonane-1,5-dicarboxylate 19. Following the procedure of Fukumoto.[4g,h] Diethyl cyclohexanone-2,6-dicarboxylate (3.20 g, 13.2 mmol) was dissolved in distilled ethanol (120 mL) and *p*-methoxybenzylamine (2.16 mL, 16.5 mmol) added followed by formaldehyde (4.8 mL, 54.2 mmol, 37% in water). After stirring the solution in the dark at room temperature for 48 h the solvent was removed in vacuo and the residue subjected to column chromatography (diethyl ether/light petroleum, ~1:4) affording diethyl 3-(4-methoxyphenylmethyl)-9-oxo-3-azabicyclo[3.3.1]nonane-1,5-dicarboxylate as a viscous colourless oil (4.67 g, 88%). ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.24 (t, J=7.2 Hz, 6H), 1.58–1.67 (m, 1H), 2.16–2.24 (m, 2H), 2.53–2.62 (m, 2H), 2.83–2.99 (m, 1H), 2.98–3.03 (m, 2H), 3.11–3.17 (m, 2H), 3.48 (s, 2H), 3.79 (s, 3H), 4.10–4.21 (m, 4H), 6.81–6.90 (m, 2H), 7.18–7.27 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 20.2, 36.3, 55.2, 58.4, 61.2, 61.4, 61.7, 113.8, 129.9, 130.0, 158.9, 170.4, 207.3. Near IR (film) ν (cm^{-1}) 1730, 1611, 1510. MS *m*/*z* (EI) 403 ($M^{+\cdot}$, 5%), 398 (1), 386 (2), 358 (2), 330 (4), 302 (1), 282 (2), 272 (1), 254 (2), 242 (8), 226 (2), 209 (7), 196 (25), 168 (30), 140 (19), 135 (17), 121 (100). Anal. Calcd for $C_{22}H_{29}NO_6$: $M^{+\cdot}$ 403.1995. Found: 403.1986.

3,4-Dimethoxyphenylacetylene[26] (0.442 g, 2.73 mmol) was dissolved in anhydrous tetrahydrofuran (3 mL) and placed in an ice-bath under argon. Methylmagnesium bromide (2 mL, 2.86 mmol, 1.4 M, tetrahydrofuran/toluene) was then added and the flask taken out of the bath and stirred at room temperature for 1.3 h. In a separate flask diethyl 3-(4-methoxyphenylmethyl)-9-oxo-3-azabicyclo[3.3.1]nonane-1,5-dicarboxylate (1.0 g, 2.48 mmol) was dissolved in anhydrous tetrahydrofuran (30 mL) and cooled to −78 °C (dry-ice/acetone bath) under argon. To this was added the above solution dropwise via cannular over 5 min. The reaction mixture was then allowed to reach 15–20 °C over 1.5 h and was stirred at room temperature for 1 h, before quenching with saturated ammonium chloride solution. The phases were partitioned and the aqueous washed with diethyl ether (2×20 mL). The combined organic layers were evaporated and the residue subjected to column chromatography (diethyl ether/light petroleum, gradient) affording diethyl 3-(4-methoxyphenylmethyl)-9-*exo*-hydroxy-9-[2-(3,4-dimethoxy)phenylethynyl]-3-azabicyclo[3.3.1]nonane-1,5-dicarboxylate (1.0 g, 71%) (pale yellow oil) as a mixture of diastereomers [7(*exo*):3(*endo*)]. Near IR (film) ν (cm^{-1}) 3468, 3272, 1725, 1511. MS {mixture of diastereomers [7(*exo*):3(*endo*)]} *m*/*z* (EI) 565 ($M^{+\cdot}$, 31%), 547 (1), 536 (2), 519 (3), 492 (10), 474 (6), 464 (1), 444 (4), 424 (3), 416 (3), 398 (4), 378 (3), 370 (4), 342 (1), 324 (4), 309 (1), 296 (2), 282 (2), 269 (1), 256 (2), 248 (4), 232 (1), 218 (2), 204 (1), 189 (8), 175 (3), 162 (5), 154 (9), 149 (3), 136 (3), 121 (100). Anal. Calcd for $C_{32}H_{39}NO_8$: $M^{+\cdot}$ 565.2676. Found: 565.2674.

Method A. To diethyl 3-(4-methoxyphenylmethyl)-9-*exo*-hydroxy-9-[2-(3,4-dimethoxy)phenylethynyl]-3-azabicyclo[3.3.1]nonane-1,5-dicarboxylate [7(*exo*):3(*endo*)] (0.430 g, 0.76 mmol) at room temperature was added a mixture of trifluoroacetic acid (0.5 mL) and borontriflouride diethyl etherate (0.3 mL, 2.36 mmol). After stirring at room temperature for 1 h the reaction mixture was then transferred, via Pasteur pipette, to a separatory funnel containing a saturated solution of sodium hydrogen carbonate (50 mL) and extracted with dichloromethane (3×10 mL). The residue was subjected to column chromatography (diethyl ether/dichloromethane/light petroleum, gradient) afforded diethyl 3-(4-methoxyphenylmethyl)-9-[2-oxo-2-(3,4-dimethoxyphenyl)ethylidene]-3-azabicyclo-[3.3.1]nonane-1,5-dicarboxylate **19** (0.381 g, 89%), as a colourless crystals, mp 168–170 °C. ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.74 (t, J=7.2 Hz, 3H), 1.29 (t, J=7.1 Hz, 3H), 1.60–1.71 (m, 1H), 1.99–2.08 (m, 1H), 2.13–2.22 (m, 1H), 2.24–2.42 (m, 2H), 2.66 (dd, J=11.1, 1.6 Hz, 1H), 2.82 (dd, J=11.1, 1.6 Hz, 1H), 2.90–3.07 (m, 3H), 3.41 (AB, 2H), 3.57–3.74 (m, 2H), 3.79 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 4.14–4.26 (m, 2H), 6.24 (s, 1H), 6.82–6.87 (m, 3H), 7.19–7.22 (m, 2H), 7.46 (d, J=1.9 Hz, 1H), 7.54 (dd, J=8.3 Hz, 1.9, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 14.3, 20.9, 36.6, 36.9, 49.9, 53.2, 55.22, 55.97, 55.05, 60.3, 61.0, 61.9, 62.0, 62.5, 109.9, 110.2, 113.8, 119.7, 123.9, 129.8, 130.3, 130.6, 149.1, 152.4, 153.3, 158.7, 173.0, 173.7, 191.5. MS *m*/*z* (EI) 565 ($M^{+\cdot}$, 13%), 536 (2), 520 (3), 492 (10), 474 (2), 444 (4), 429 (2), 416 (2), 400 (16), 385 (2), 370 (3), 354 (4), 343 (2), 330 (1), 312 (3), 297 (1), 278 (1), 263 (2), 206 (1), 191 (1), 180 (2), 165 (26), 121 (100). Anal. Calcd for $C_{32}H_{39}NO_8$: C, 67.95; H, 6.95; N, 2.48; $M^{+\cdot}$ 565.2676. Found: C, 68.05; H, 7.07; N, 2.34; 565.2676.

Method B. Diethyl 3-(4-methoxyphenylmethyl)-9-*exo*-hydroxy-9-[2-(3,4-dimethoxy)phenylethynyl]-3-azabicyclo[3.3.1]nonane-1,5-dicarboxylate [7(*exo*):3(*endo*)] (0.069 g, 0.122 mmol) was rapidly dissolved in trifluoroacetic acid (1 mL) at 0 °C (ice-bath) under argon. Trimethylsilyltrifluorosulfonate (0.07 mL, 0.378 mmol) was added rapidly and the flask then taken out of the bath and stirred at room temperature for 1 h. The reaction mixture was then transferred, via Pasture pipette, to a separatory funnel containing a saturated solution of sodium hydrogen carbonate (50 mL) and extracted with dichloromethane (3×10 mL). The residue was dried under vacuum and subjected to column chromatography (ethyl acetate/dichloromethane, 1:9) affording two fractions. Fraction one contained the title compound **19** (0.009 g, 13%) and fraction two afforded ethyl 1-(3,4-dimethoxyphenyl)-8-(4-methoxyphenylmethyl)-4,5,6,6a,7,9-hexahydro-3*H*-pyrano[4,4*a*,5,*d*-*e*]isoquinolin-3-on-6a-carboxylate **20** (0.012 g, 19%) as a yellow amorphous solid. ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.15 (t, J=7.1 Hz, 3H), 1.40–1.65 (m, 2H), 1.87–1.98 (m, 1H), 2.06–2.14 (m, 1H), 2.18 (d, J=11.2 Hz, 1H), 2.42–2.55 (m, 1H), 2.63–2.74 (m, 1H), 3.17 (d, J=14.6 Hz, 1H), 3.28–3.35 (m, 1H), 3.42–3.55 (AB, 2H), 3.76 (s, 3H), 3.79 (s, 3H), 3.89 (s, 3H), 3.91–3.98 (m, 1H), 4.00–4.21 (m, 2H), 6.76–6.87 (m, 3H), 6.97 (d, J=2.0 Hz, 1H), 7.03 (dd, J=8.4, 2.0 Hz, 1H), 7.08–7.13 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 18.1, 23.1, 29.3, 49.8, 53.0, 55.2, 55.89, 55.93, 58.1, 61.3, 61.8, 110.4, 110.5, 111.4, 113.6, 121.0, 121.6, 125.0, 129.3, 130.0, 148.7, 148.9, 150.0, 152.3, 158.9, 163.0, 173.4. MS *m*/*z* (EI) 519 ($M^{+\cdot}$, 5%), 504 (1), 490 (2), 474 (1), 446 (1), 398 (100), 370 (4), 354 (4), 324 (4), 297 (2), 269 (1), 165 (6), 121 (55). Anal. Calcd for $C_{30}H_{33}NO_7$: $M^{+\cdot}$ 519.2257. Found: 519.2261.

4.2.7. Diethyl 2-(4-methoxyphenylmethyl)-1,3,3a,4,5,6,7,7a-octahydro-9-(3,4-dimethoxyphenyl)-isoindolo-[1,7*a*-*b*]furan-3a,7-dicarboxylate 25. Diethyl 3-(4-methoxyphenylmethyl)-9-[2-oxo-2-(3,4-dimethoxyphenyl)ethylidene]-3-azabicyclo[3.3.1]nonane-1,5-dicarboxylate **19** (0.100 g, 0.177 mmol) was dissolved in oxygen free *N*,*N*-dimethylformamide (10 mL) under argon in a 10 mm NMR tube (PP-528) and irradiated for 1 h with a Hanovia high pressure mercury–xeon vapour lamp (1000 W). [*Note*. The light was passed through a water filter (30 cm long) at ~5 °C and the sample placed 10 cm from the end of the cooling tube.] The solvent was then removed under high vacuum using an in-line trap and the residue subjected to column chromatography (diethyl ether/dichloromethane/light petroleum, gradient), which afforded the title compound **25** (0.076 g, 76%), as a pale yellow solid, and recovered starting material **19** (0.012 g, 12%) in that order. Yield based on recovered starting material 86%, mp 109–111 °C (partial), 115–116 °C. ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.99 (t, J=7.1 Hz, 3H), 1.23 (t, J=7.1 Hz, 3H), 1.55–1.73 (m, 3H), 1.78–1.91 (m, 2H), 2.01–2.11 (m, 1H), 2.52 (d, J=8.7 Hz, 1H), 3.10 (d, J=8.7 Hz, 1H), 3.14–3.20 (m, 1H), 3.72 (d, J=13.6 Hz, 1H), 3.78 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 3.88–4.03 (m, 2H), 4.09–4.17 (m, 2H), 4.16 (d, J=13.6 Hz, 1H), 4.90 (s, 1H), 5.90 (s, 1H), 6.78–6.88 (m, 3H), 7.03 (d, J=2.0 Hz, 1H), 7.14 (dd, J=2.0, 8.3 Hz, 1H), 7.23–7.28 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.2, 21.4, 25.6, 33.1, 46.8, 51.2, 54.4, 55.2, 55.90, 55.93, 56.3, 60.1, 60.3, 60.8, 96.7, 97.9, 108.6, 110.7, 113.7, 118.4, 123.4, 129.6, 131.1, 148.6, 149.5, 157.1, 158.6, 173.9, 174.5. Near IR (Nujol) ν (cm^{-1}) 1729, 1715. MS *m*/*z* (EI) 565 ($M^{+\cdot}$, 13%), 520 (11), 492 (10), 474 (5), 444 (4), 424 (2), 416 (3), 400 (16), 165 (26), 121 (100). Anal. Calcd for $C_{32}H_{39}NO_8$: C, 67.95; H, 6.95; N, 2.48; $M^{+\cdot}$ 565.2676. Found: C, 67.79; H, 6.90; N, 2.41; 565.2674.

4.2.8. Diethyl 3-(4-methoxyphenylmethyl)-9-[2-methylene-2-(3,4-dimethoxyphenyl)ethylidene]-3-azabicyclo-[3.3.1]nonane-1,5-dicarboxylate 26. Methylphosphonium bromide (0.047 g, 0.133 mmol) was predried under high vacuum and suspended in anhydrous THF (0.5 mL) under argon. The flask was placed in an ice-bath and *n*-BuLi (0.08 mL, 1.5 M in hexanes) added. After 15 min diethyl 3-(4-methoxyphenylmethyl)-9-[2-oxo-2-(3,4-dimethoxyphenyl)ethylidene]-3-azabicyclo[3.3.1]nonane-1,5-dicarboxylate **19** (0.050 g, 0.088 mmol) was introduced, via cannular, to the flask as a solution in THF (0.5 mL). The mixture was stirred at room temperature for 1.5 h followed by addition of saturated ammonium chloride solution (20 drops). The solvent was then removed under vacuum and the residue extracted with dichloromethane (10 mL). Evaporation of the organic layer and column chromatography (dichloromethane/ethyl acetate, gradient) afforded the title compound **26** (0.023 g, 46%) and recovered starting material **19** (0.014 g, 28%) in that order. The yield based on recovered starting material is 64%. ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.68 (t, J=7.1 Hz, 3H), 1.22 (t, J=7.2 Hz, 3H), 1.62–1.74 (m, 1H), 1.94–2.10 (bm, 2H), 2.17–2.28 (m, 1H), 2.31–2.43 (m, 1H), 2.61–2.67 (m, 1H), 2.80 (bd, J=10.6 Hz, 1H), 2.87–3.09 (m, 3H), 3.32–3.66 (vbm, 2H), 3.41 (s, 2H), 3.79 (s, 3H), 3.867 (s, 3H), 3.875 (s, 3H), 4.04–4.21 (m, 2H), 4.80 (s, 1H), 5.34 (s, 1H), 5.67 (s, 1H), 6.78–6.88 (m, 3H), 7.00–7.06 (m, 2H), 7.18–7.25 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 14.2, 21.0, 37.0, 48.7, 52.6, 55.2, 55.81, 55.88, 60.1, 60.8, 62.3, 62.5, 63.4, 109.5, 110.7, 111.3, 113.7, 119.5, 122.2, 126.4, 129.8, 130.6, 131.2, 141.6, 142.2, 148.5, 148.9, 158.7, 174.3, 174.4. MS *m*/*z* (EI) 563 ($M^{+\cdot}$, 30%), 518 (1), 490 (4), 471 (1), 442 (17), 414 (1), 414 (1), 396 (2), 368 (3), 340 (2), 324 (1), 294 (2), 267 (3), 253 (1), 165 (6), 151 (2), 135 (1), 121 (100). Anal. Calcd for $C_{33}H_{41}NO_7$: $M^{+\cdot}$ 563.2883. Found: 563.2878.

4.2.9. Dimethyl 9-[2-oxo-2-(3,4-dimethoxyphenyl)ethylidene]-3-oxabicyclo[3.3.1]nonane-1,5-dicarboxylate 27. 3,4-Dimethoxyphenylacetylene[26] (0.211 g, 1.30 mmol) was dissolved in anhydrous THF (4 mL) and cooled to −78 °C (dry-ice/acetone bath) under argon. To this solution was added *n*-butyllithium (1.0 mL, 1.40 mmol, 1.4 M solution in *n*-hexane) via syringe during 2 min and the mixture was stirred at −78 °C for 1 h. After removing the cooling-bath the mixture was allowed to reach 20 °C over 2 h and was stirred at room temperature for 1 h. After cooling this mixture to −78 °C a solution of dimethyl 9-oxo-3-oxabicyclo[3.3.1]nonane-1,5-dicarboxylate[20] (0.308 g, 1.20 mmol) in anhydrous THF (3 mL) was quickly added (1 s) and stirred at −78 °C. After 1 h at −78 °C the reaction mixture was allowed to reach room temperature over 2–3 h, before quenching with saturated ammonium chloride solution (25 mL). The phases were partitioned and the aqueous washed with diethyl ether (5×25 mL). The combined organic layers were washed with distilled water (2×20 mL) and brine (1×20 mL), dried (Na_2SO_4) and

evaporated. The residue was then purified by flash chromatography (light petroleum/ethyl acetate, 3:1) affording dimethyl 9-(3,4-dimethoxyphenylethynyl)-9-hydroxy-3-oxabicyclo[3.3.1]nonane-1,5-dicarboxylate (0.402 g 80%) (colourless oil) as a mixture of diastereomeres (*exo*/*endo*=94: 6, detected by ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59–1.65 (m, 1H), 1.81–1.85 (m, 2H), 2.35–2.55 (m, 3H), 3.72 (s, 6H), 3.84 (s, 3H), 3.86 (s, 3H), 4.08 (d, J= 12.2 Hz, 2H), 4.25 (dd, J=12.1, 2.3 Hz, 2H), 4.75 (s, 1H, OH), 6.77 (d, J=8.3 Hz, 1H), 6.84 (d, J=1.8 Hz, 1H), 6.97 (dd, J=8.3, 1.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 27.7, 31.3, 49.7, 51.8, 55.5, 70.4, 71.4, 85.9, 88.1, 110.6, 113.8, 113.9, 124.7, 148.2, 149.4, 173.1.

Cooled (−15 °C) trifluoroacetic acid (1.5 mL) was rapidly added, under argon at −15 °C via syringe, to dimethyl 9-(3,4-dimethoxyphenylethynyl)-9-hydroxy-3-oxabicyclo-[3.3.1]nonane-1,5-dicarboxylate (0.230 g, 0.55 mmol). The reaction mixture was vigorously stirred while warming to room temperature over 2 h. The reaction was quenched with saturated sodium hydrogen carbonate solution and extracted with dichloromethane (5×15 mL). After solvent evaporation, the residue (pale yellow oil) was crystallised by adding diethyl ether. Recrystallisation from anhydrous methanol afforded the titled compound (0.197 g, 86%) as colourless crystals, mp 169.5–170.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68–1.75 (m, 1H), 2.13–2.17 (m, 1H), 2.25–2.43 (m, 3H), 2.52–2.66 (m, 1H), 3.24 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 3.93 (s, 3H), 3.97–4.07 (m, 2H), 4.09–4.21 (m, 2H), 6.24 (s, 1H), 6.87 (d, J=8.0 Hz, 1H), 7.45 (d, J=1.9 Hz, 1H), 7.52 (dd, J=8.3 Hz, 1.9, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 36.2, 36.6, 50.1, 51.3, 52.2, 52.9, 56.0, 56.1, 75.3, 75.8, 110.1, 110.2, 120.0, 124.0, 130.3, 149.1, 150.2, 153.4, 172.0, 172.9, 191.4. Near IR (Nujol) ν (cm^{-1}) 1738, 1717. Anal. Calcd for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26. Found: C, 63.16; H, 6.31.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.02.013.

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