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Investigating direct routes to an advanced intermediate for the synthesis of C-20 diterpene alkaloids

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Abstract—Rapid access to the ABCE ring system of the C-20 diterpene alkaloids was achieved by silver (I) promoted intramolecular Friedel–Crafts arylation of a functional group specific 5-bromo-3-azabicyclo[3.3.1]nonane derivative.

1. Introduction

Diterpene alkaloids have been isolated from a range of plants including *Aconitum*, *Delphinium*, *Consolida*, *Thalictrum* and *Spiraea* species.[1,2] There has been some interest in their biological activity,[3] but it is their complex highly functionalised skeletons that have attracted the attention of numerous synthetic[4] chemists. Of particular note is the work of the Wiesner,[5] Masamune,[6] Fukumoto,[7] and Nagata groups[8] all of whom have shown enormous creativity and ingenuity in their efforts to assemble these complex structures. The construction of the highly bridged structures of the kobusine[9] (**1**)–hetisine[10] (**2**) family[11] (Fig. 1) of alkaloids, however, has remained elusive. Some progress has been made[12–14] and these reports prompt us to disclose our own endeavours in the field.

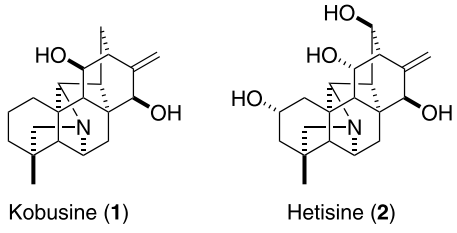
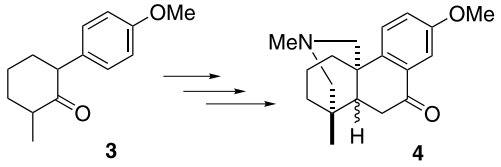


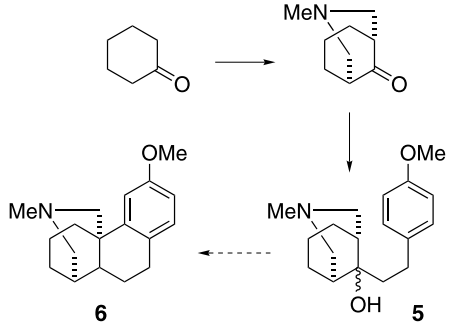
Figure 1.

In designing our approach, we were mindful of the formidable logistical challenges that were likely to develop in pursuing a target possessing such a complex skeleton and were consequently drawn to the double Mannich strategy developed by Shimizu et al.[15] The rapid assembly of 3-azabicyclo[3.3.1]nonan-7-ones on cyclohexanone based starting materials,[16] provides a particularly direct and efficient method for assembling the E-ring of these alkaloids and when applied to the aryl substituted cyclohexanone **3**, afforded a particularly direct synthesis of the tetracyclic intermediate **4**, although with poor stereochemical control (Scheme 1).[17]



Scheme 1.

Shimizu et al. also prepared 3-methyl-9-(4-methoxyphenyl-ethyl)-3-azabicyclo[3.3.1]nonan-9-ol **5** by a similar approach, but were unable to convert it into the target phenanthrene derivative **6** (Scheme 2).[15]



Scheme 2.

Keywords: Diterpene alkaloids; Silver (I); Intramolecular Friedel–Crafts arylation; 3-Azabicyclo[3.3.1]nonane.
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Although equivalent arene carbinols have been cyclised to give hydrophenanthrenes this must occur *via* alkene formation or a 1,2-hydride shift to give cation **7** (Fig. 2).[18] With the azabicyclononane, however, the formation of the necessary bridgehead alkene or cation would constitute a violation of Bredt's rule.[19]

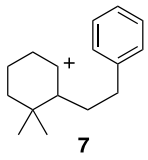


Figure 2.

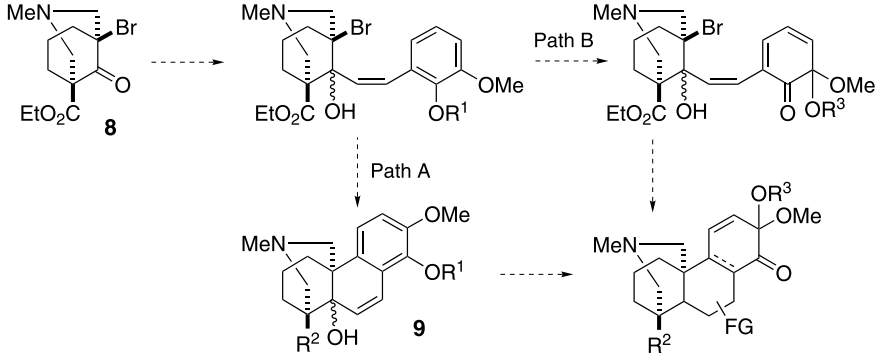
To address the problem, we elected to begin with the bromo-3-azabicyclo[3.3.1]nonanone **8** (the *N*-methyl analogue of an intermediate that had been prepared previously by Kraus and Shi[20]) in the knowledge that intermolecular bridgehead arylation had been achieved with 1-bromoadamantane using palladium (Pd/C) at high temperature (de Meijere[21]) and with 1-bromobicyclo[2.2.2]octane using silver (I) salts at room temperature (Kraus[22]). As an alternative coupling strategy, we could also envisage a free radical based approach initiated by loss of a bromine radical.[23] For the elaboration of the C- and D-rings, we planned to utilise an aromatic C-ring that would serve as a precursor to an *ortho*-quinonoid moiety in anticipation of the addition of the D-ring by means of a [4+2] cycloaddition, a tactic that has been used so effectively by Wiesner.[24] If we could combine these various elements into a viable strategy, then there was a reasonable expectation of restricting the complete sequence to a manageable length. Thus, we arrived at the synthetic plan outlined in Scheme 3 and now describe in full our investigations, which have culminated in an exceptionally direct approach to the advanced intermediate **9**.[25]

2. Results and discussion

Attempts were made to prepare **10** either by treating **8** with the metalated *cis*-styrene[26] **11**, derived from the telluride **12**, or the less sterically demanding alkyne analogue **13**[27] followed by reduction. It was hoped that the *cis* stereochemistry of the alkene bond in **10** would reduce the degrees of freedom relative to the saturated analogue and maximize the chances of the planned cyclisation. Both reagents were synthesised from *ortho*-vanillin in good overall yield, using Comasseto–Marino[26] and Corey–Fuchs methodology,[28] respectively. The robust isopropylether masking function as developed by Banwell[29] had been chosen for both of these approaches so as to allow for selective de-alkylation at the appropriate juncture without the risk of premature deprotection. In the event, only small amounts of the rearranged product **14** were obtained when **11** was employed (Fig. 3).

We therefore deprotonated arylacetylene **13** with methylmagnesium bromide (i.e., **15**) and added it to bicycle **8** dissolved in toluene, thereby affording a 3:2 mixture of diastereomers **16** and **17**, respectively, in 94% yield. With THF as solvent, however, mainly the desired epimer[30] **16** (64% yield) was obtained, accompanied this time by the by-product **18** from rearrangement of **17** (Scheme 4). This kind of rearrangement had also been observed by Kraus and put to good effect in the synthesis of epi-modhephene.[20]

Catalytic hydrogenation of the alkyne bond in **16** without hydrogenolysis of the bridgehead bromo substitutent proved, not surprisingly, to be unattainable, but could be achieved with diimide, generated in situ from 1,3,5-triisopropylbenzenesulfonylhydrazide,[31] to afford the *cis*-alkene **10** in 74% yield as the sole product (Fig. 3). With this intermediate in hand we embarked upon the cyclisation



Scheme 3.

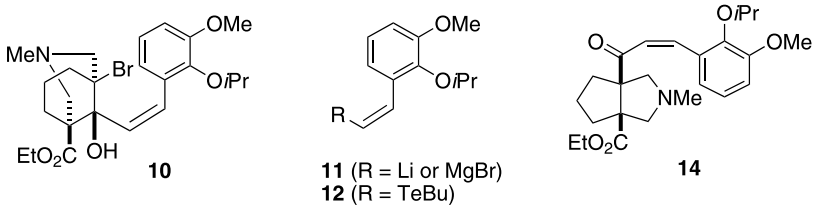
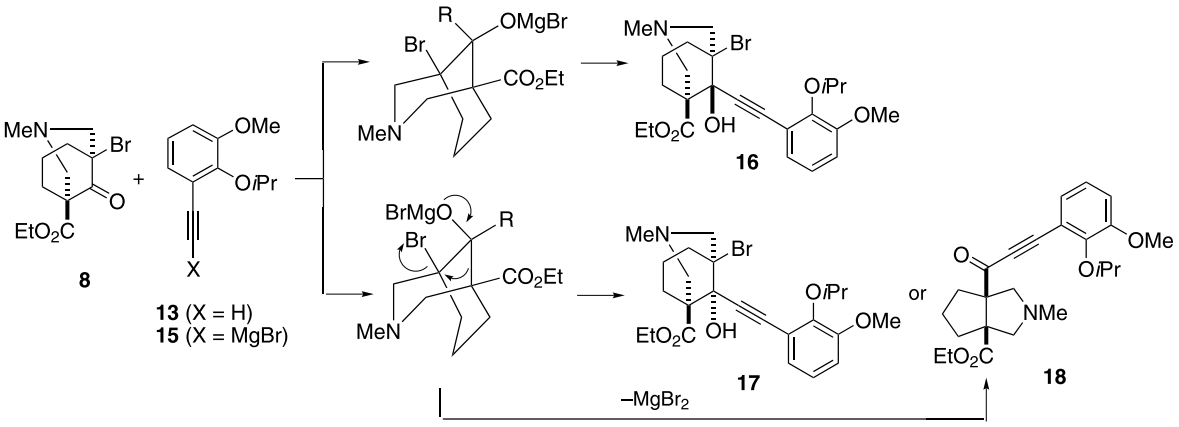
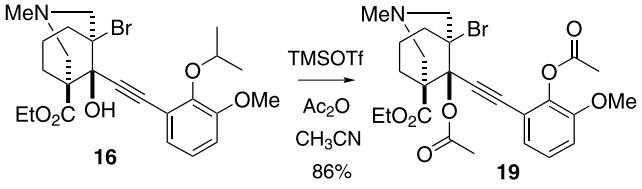


Figure 3.



Scheme 4.

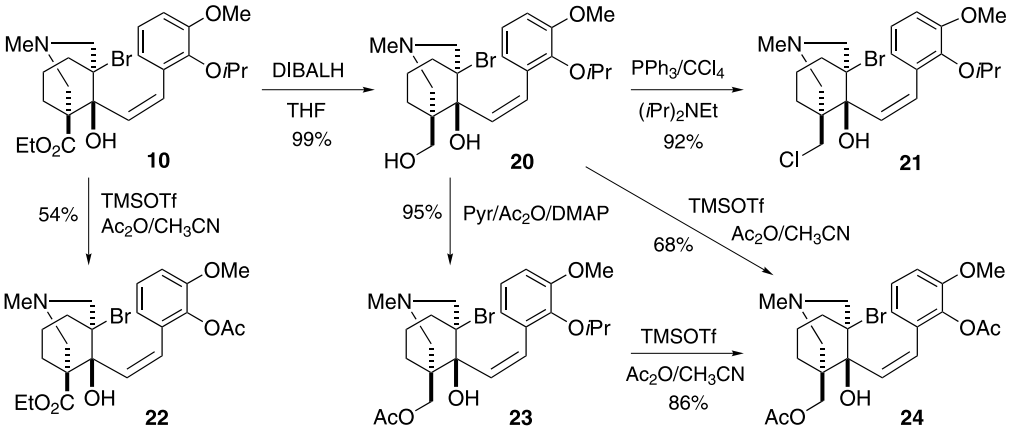
studies. Treatment of **10** with silver trifluoroacetate at various temperatures or with palladium (Pd/C), however, resulted in rearrangement[32] to ketone **14** (Fig. 3). Although, acylation of the hydroxyl could be expected to retard the rearrangement, this deceptively simple step proved to be surprisingly difficult.[33] Nevertheless, when **16** was treated with acetic anhydride and trimethylsilyl triflate, the desired acylation was achieved (i.e., **19**). While replacement of the isopropyloxy function by acetate also occurred[34] (Scheme 5), it was considered to be of no significance as the acetylene was resistant to hydrogenation.



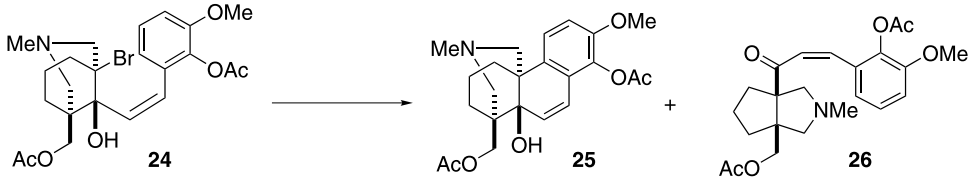
Scheme 5.

Further modification of the functionality in these intermediates by routine procedures to afford substrates **20–23** (Scheme 6) and subsequent treatment with silver trifluoroacetate still failed to result in cyclisation, affording only rearranged products.

However, when both ester and isopropyl functionality were modified, that is, as in diacetate **24**, intramolecular arylation induced by treatment with silver trifluoroacetate was at last observed, producing **25**, albeit in only 18% yield, the remainder consisting of the rearranged product **26** (Scheme 7). Then, after extensive small scale experimentation with different solvents and silver salts [e.g., $AgOCOCF_3$, $AgBF_4$, $AgB(C_6F_5)_4$[35]] we found that the yield of cyclisation could be increased to 53% using silver 2,4,6-trinitrobenzenesulfonate[36] in nitromethane. Changing the solvent system and investigating solvent mixtures gave no improvement on nitromethane. Although it is not entirely clear as to why silver 2,4,6-trinitrobenzenesulfonate



Scheme 6.



Scheme 7.

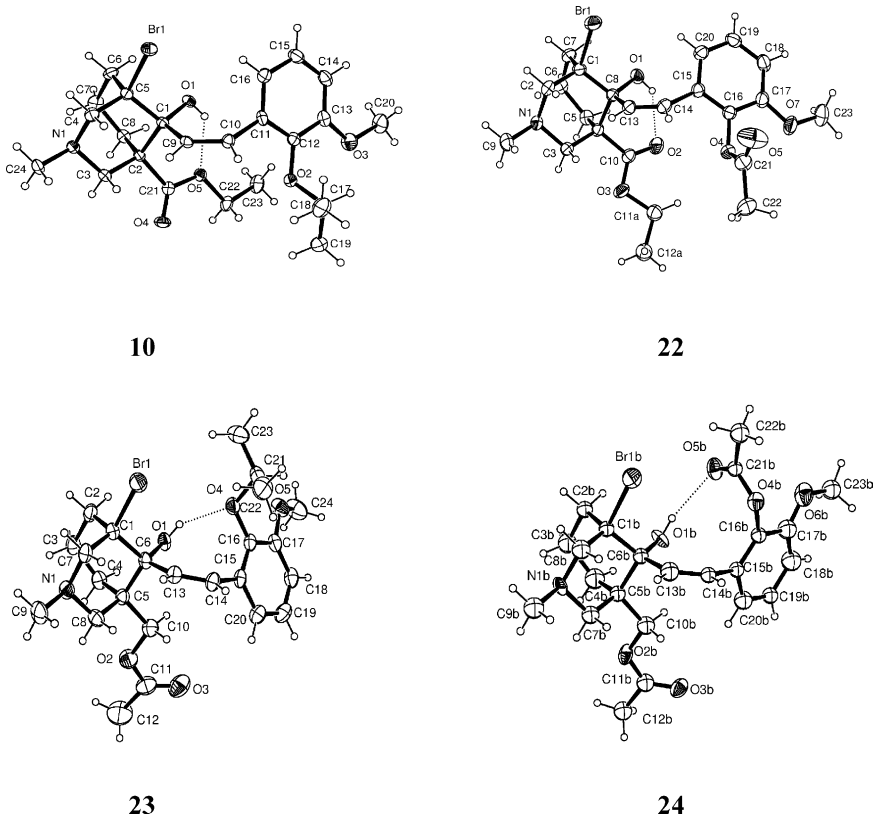


Figure 4. X-ray crystal structure diagrams for compounds **10**, **22**, **23** and **24**. In the case of **24** only one of the two crystallographically independent molecules is shown for this structure.

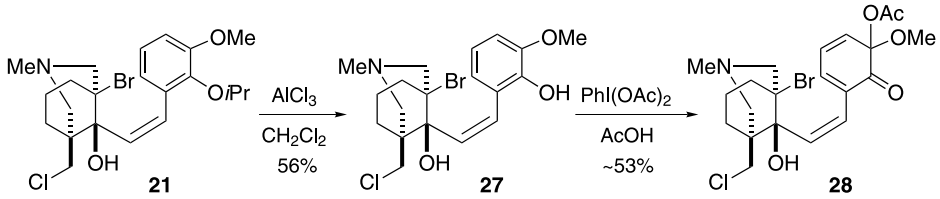
provides such a dramatic improvement in yield it is conceivable, however, that the 2,4,6-trinitrobenzenesulfonate counter ion provides increased silver(I) solubility.

In an attempt to understand why **24** is amenable to cyclisation while derivatives **10** and **20**–**23** fail to bridgehead arylate X-ray crystal structure analysis was performed and data obtained for compounds **10**, **22**, **23** and **24** (Fig. 4).

On close inspection of the ^{1}H NMR spectrum, sharp O*H* singlets are observed for the hydroxyl proton [**10** (5.01 ppm), **20** (4.26 ppm), **21** (4.05 ppm), **22** (3.63 ppm) and **23** (4.46 ppm)] suggesting strong intramolecular hydrogen bonding interactions have formed, but for compound **24** the OH peak is not observed. In the solid state hydrogen bonding is seen for all compounds **10**, **22**, **23** and **24**, but, **24** maintains the longest non-covalent hydrogen–oxygen bond length (2.14–2.19 Å). In the case of strong intramolecular hydrogen bonding (e.g., **10**, **20**, **21**, **22** and **23**) this has two implications: restricted aryl rotation and increasing electron density on the hydroxyl oxygen both favouring the undesired pinacol-type rearrangement.

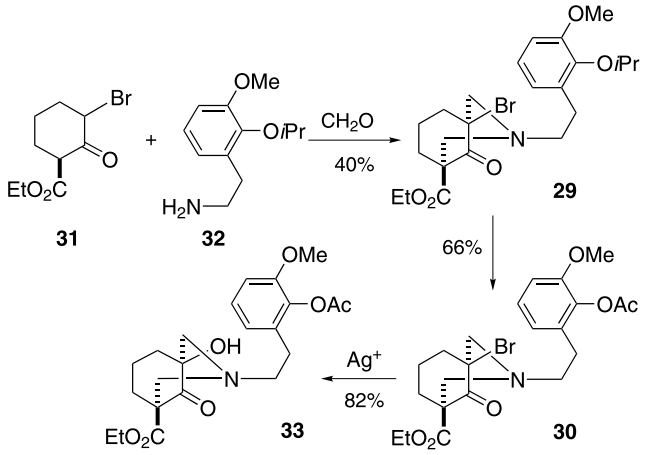
Attempts were made to circumvent the medium yielding silver (I) induced cyclisation by investigating radical based processes. As aromatic rings are generally not amenable to radical mediated substitution (addition/elimination) reactions the aryl ring was firstly dearomatised. Treatment of **21** with aluminium trichloride[29] removed the isopropyl protecting group affording the phenol **27** (56%), which underwent oxidation to the unstable *ortho*-quinone acetal **28** (~53%) with phenyliododiacetate[37] (Scheme 8). Using radical inducing conditions applicable to the azabicyclo-[3.3.1]nonane system[23] (Vitamin B_{12}) resulted in rapid decomposition. Tin based procedures gave similar results.

Finally, in view of the results above *N*-phenethyl derivatives **29** and **30** were synthesised to further probe silver (I) mediated bridgehead arylation. Derivative **29**, obtained in 40% yield from a double Mannich reaction of bromide **31** and amine **32** in the presence of formaldehyde, afforded no



Scheme 8.

cyclised products when subjected to a variety of silver (I) salts. Conversion of **29** into **30** proceeded smoothly (66%) using the TMSOTf/Ac_2O/CH_3CN protocol developed above. Treatment with silver (I) 2,4,6-trinitrobenzenesulfonate[36] in nitromethane, did not lead to a cyclised product but gave instead, alcohol **33** (82%) (Scheme 9).



Scheme 9.

3. Conclusion

We have demonstrated that intramolecular bridgehead arylation of a functional group specific 5-bromo-3-azabicyclo[3.3.1]nonane derivative (**24**) affords a viable route to a highly functionalized, advanced intermediate (**25**), the brevity of the route (the longest linear sequence is only 8 steps) compensating for the modest yield of cyclization. While the kobusine family of alkaloids (>100 in number[11]) remain our main objective, we note that **25** and its analogues may also have the potential to serve as an intermediate for the synthesis of denudatine[38] and dictysine[39] type alkaloids (Fig. 5).

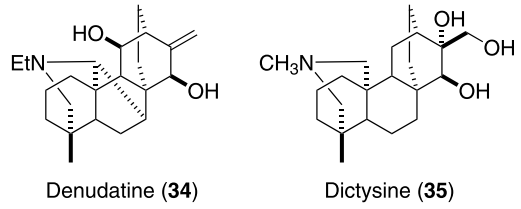


Figure 5.

4. Experimental

4.1. General experimental

^1H 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 was purchased from the Aldrich Chem. Co.

4.2. X-ray crystallography

Data for compounds **22**, **23** and **24** were collected at 293 K on an Enraf-Nonius CAD4 diffractometer. Data reduction, structure solution and refinement (SHELX97[40]) were performed with the WINGX package.[41] For compound **10** data were collected at 200 K on a Nonius Kappa CCD diffractometer. Structure solution and refinement of this structure was carried out with the teXsan package.[42] Drawings of all molecules were created with ORTEP3.[43] Data in CIF format have been deposited with the Cambridge Crystallographic Data Centre (CCDC Deposition Nos. 247761–247764). 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-oxo-3-azabicyclo-[3.3.1]nonanecarboxylate 8. To a solution of ethyl 6-bromocyclohexanone-2-carboxylate[44] **31** (10 g, 0.040 mol) and formaldehyde (39.1 mL, 0.482 mol, 37% in water) in methanol (160 mL) at 0 °C was added a solution of methylamine (9.35 mL, 0.120 mol, 40% in water) in methanol (90 mL) dropwise over 3 h. The solution was then allowed to warm to room temperature over 20 h followed by refluxing for 30 min. On cooling the volatiles were removed in vacco and the residue diluted with water (100 mL) and extracted with diethyl ether (3×50 mL). The ether layers were dried (Na_2SO_4) and evaporated affording an oil which was passed through a plug of alumina. The residue was then purified by distillation (116°/0.01 mmHg) affording a pale yellow solid (8.30 g, 68%) on cooling, mp 49–51 °C. Five fold scale-up afforded ethyl 5-bromo-3-methyl-9-oxo-3-azabicyclo[3.3.1]nonanecarboxylate in 50% yield. ^1H NMR (400 MHz, $CHCl_3$) δ 1.27 (t, 3H, J=7.2 Hz), 1.56–1.63 (m, 1H), 2.21–2.27 (m, 1H), 2.27 (s, 3H), 2.54–2.60 (m, 2H), 2.72–2.82 (m, 1H), 2.96 (dd, 1H, J=11.1, 2.3 Hz), 3.03–3.17 (m, 3H), 3.50 (dd, 1H, J=11.1, 2.3 Hz), 4.20 (q, 2H, J=7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 36.4, 44.3, 46.3, 59.9, 61.5, 63.7, 68.9, 71.2, 169.7, 201.9. Near IR (Nujol) υ (cm^{-1}) 1747, 1736. MS m/z (EI) 305 ($M^{+\cdot}$, 20%), 303 ($M^{+\cdot}$, 20%), 288 (13), 286 (13), 260 (19), 258 (16), 232 (8), 224 (100), 206 (8), 197 (15), 178 (74), 150 (37), 135 (11), 125 (15), 122 (14), 108 (10), 94 (10), 86 (43), 84 (68), 79 (27). Anal. Calcd for $C_{12}H_{18}BrNO_3$: C, 47.38; H, 5.96; N, 4.60; $M^{+\cdot}$ 305.0451. Found: C, 47.26; H, 6.00; N, 4.47; 305.0451.

4.2.2. 2-Isopropoxy-3-methoxyphenylacetylene 13.[27] The procedure of Banwell[29] was used. To a suspension of *o*-vanillin (20 g, 131 mmol) and potassium carbonate (63.6 g, 460 mmol) in *N*,*N*-dimethylformamide (200 mL) was added isopropyl bromide (15.4 mL, 164 mmol). The mixture was then heated at 100 °C for 4 h. On cooling the reaction mixture was diluted with water (~500 mL) and washed with diethyl ether (3×100 mL). The ether layers were combined, dried (Na_2SO_4) and evaporated. The residue (>90% yield) was dried under high vacuum and used in the next step without purification. Spectral data was

in agreement with that reported.[45] ^{1}H NMR (400 MHz, TMS) δ 1.30 (d, J=6.4 Hz, 6H), 3.86 (s, 3H), 4.61 (sep, J=6.4 Hz, 1H), 7.05–7.12 (m, 2H), 7.38–7.41 (m, 1H), 7.43 (s, 1H). ^{13}C NMR (400 MHz, $CHCl_3$) δ 22.3, 56.0, 76.2, 117.8, 118.9, 123.6, 130.9, 150.6, 153.2, 190.9. MS *m/z* (EI) 194 ($M^{+\cdot}$, 11%), 152 (100), 122 (12), 106 (47), 84 (6), 62 (18), 51 (6), 45 (38). Anal. Calcd for $C_{11}H_{14}O_3$: $M^{+\cdot}$ 194.0943. Found: 194.0942.

Following the method of Corey and Fuchs[28] triphenylphosphine (108.0 g, 412 mmol) was dissolved in dichloromethane (400 mL) at 0 °C and to this was added carbontetrabromide (68.3 g, 206 mmol) portionwise. After 15 min the aldehyde above was added to the mixture portionwise over 10 min and allowed to stir for a further 10 min at 0 °C followed by stirring at room temperature for 30 min. The mixture was then preabsorbed onto silica gel (~400 g) and the pure product eluted from the silica gel plug (diethyl ether/light petroleum; 1:1) (600–700 mL). Evaporation of the eluent afforded a pale yellow oily residue (22 g, 61%) after distillation (105°/0.01 mm). ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.27 (d, J=6.2 Hz, 6H), 3.82 (s, 3H), 4.37 (sep, J=6.2 Hz, 1H), 6.89 (dd, J=8.15, 1.4 Hz, 1H), 7.02 (t, J=8.15 Hz, 1H), 7.25–7.27 (m, 1H), 7.63 (s, 1H). ^{13}C NMR (400 MHz, $CHCl_3$) δ 22.5, 55.8, 76.0, 89.9, 112.6, 120.9, 123.2, 130.8, 134.1, 144.9, 152.9. Near IR (film) υ (cm^{-1}) 1577. MS *m/z* (EI) 350 ($M^{+\cdot}$, 9%), 308 (26), 228 (5), 226 (5), 214 (8), 212 (9), 199 (1), 185 (4), 183 (5), 170 (1), 155 (1), 148 (100), 133 (2), 105 (9), 89 (5), 76 (10), 63 (2). Anal. Calcd for $C_{12}H_{14}Br_2O_2$: C, 41.17; H, 4.03; $M^{+\cdot}$ 347.9361. Found: C, 41.08; H, 4.01; 347.9363.

The above material (20 g, 57.1 mmol) was dissolved in anhydrous tetrahydrofuran (450 mL) and cooled to −78 °C under nitrogen. To this was added *n*-BuLi (82 mL, 123 mmol, 1.5 M in hexanes) dropwise over 15 min. The reaction mixture was stirred at −78 °C for 1 h and then removed from the cold bath and stirred for 2 h. The flask was then placed in an ice-bath and the reaction quenched with saturated ammonium chloride solution (200 mL). The phases were partitioned and the aqueous phase washed with diethyl ether (100 mL). The combined ether phases were dried (Na_2SO_4) and evaporated affording the product, which was purified by distillation (75°/0.1 mm) giving the pure product (8.30 g, 76%) as a colourless oil. The oil slowly solidified on refrigeration as a colourless solid, mp 48–50 °C. ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.31 (d, J=6.2 Hz, 6H), 3.20 (s, 1H), 3.81 (s, 3H), 4.56 (sep, J=6.2 Hz, 1H), 6.88 (dd, J=8.2, 1.7 Hz, 1H), 6.94 (t, J=8.2 Hz, 1H), 7.03 (dd, J=8.2, 1.7 Hz, 1H). ^{13}C NMR (400 MHz, $CHCl_3$) δ 22.6, 55.9, 76.2, 80.6, 80.8, 113.3, 117.9, 123.4, 125.6, 149.3, 153.2. Near IR (Nujol) υ (cm^{-1}) 1917, 1836. MS *m/z* (EI) 190 ($M^{+\cdot}$, 24%), 148 (100), 133 (10), 118 (8), 105 (14), 91 (8), 84 (8), 77 (15). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42; $M^{+\cdot}$ 190.0994. Found: C, 76.06; H, 7.61; 190.0997.

4.2.3. Ethyl 5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-isopropoxy)phenylethynyl]-3-azabicyclo-[3.3.1]nonanecarboxylate 16. *Method A*. Phenylacetylene **13** (5.16 g, 27.1 mmol) was dissolved in anhydrous tetrahydrofuran (40 mL) and placed in an ice-bath under nitrogen. Methylmagnesium bromide (21 mL, 24.4 mmol, 1.16 M, tetrahydrofuran/toluene) was then added and the flask taken out of the bath and stirred at room temperature for 2.5 h. In a separate flask azabicyclo[3.3.1]nonane **8** (3.91 g, 12.9 mmol) was dissolved in anhydrous tetrahydrofuran (130 mL) and cooled to −78 °C (dry-ice/acetone bath) under nitrogen. To this was added the above solution dropwise over 5 min. The reaction mixture was then allowed to reach 15–20 °C over 80 min in the bath before being quenched with acetic acid (1 mL) in tetrahydrofuran (16 mL). After 5 min saturated sodium hydrogencarbonate solution (5 mL) was added followed by extraction into diethyl ether, drying (Na_2SO_4) and evaporation in vacco. The residue was subjected to column chromatography (*t*-butylmethylether/light petroleum; 3:7), which firstly eluted recovered excess phenyl acetylene **13** followed by the titled compound (4.54 g, 71%) as a mixture of diasteroisomers [9(**16**):1(**17**)]. Flushing the column with ethyl acetate afforded ethyl 3-methyl-5-[2-(3-methoxy-2-isoproxy)phenylethynyl]-oxo-3-azabicyclo[3.3.0]octane-carboxylate **18**.

Method B. Phenylacetylene **13** (0.136 g, 0.714 mmol) was reacted with methylmagnesium bromide (0.47 mL, 0.655 mmol, 1.4 M, THF) as above in toluene (2 mL). This was added to azabicyclo[3.3.1]nonane **8** (0.181 g, 0.595 mmol) as above in toluene (7 mL) and quenched with acetic acid (0.6 mL) in tetrahydrofuran (2 mL) followed by saturated sodium hydrogencarbonate solution (1 mL). Work up as above gave **16** and **17** (3:2) (0.275 mg, 94%).

Ethyl 5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-isopropoxy)phenylethynyl]-3-azabicyclo[3.3.1]nonane-carboxylate **16** (major diasteromer reported only). ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.22 (t, J=7.1 Hz, 3H), 1.29 (d, J=6.2 Hz, 6H), 1.47–1.62 (m, 1H), 1.72–1.83 (m, 1H), 2.22 (s, 3H), 2.21–2.36 (m, 2H), 2.72–2.90 (m, 2H), 2.98 (dd, J=12.0, 2.5 Hz, 1H), 3.13 (d, J=12 Hz, 1H), 3.19 (d, J=11.1 Hz, 1H), 3.28 (dd, J=11.1, 12.0 Hz, 1H), 3.79 (s, 3H), 4.13–4.23 (m, 2H), 4.67 (sep, J=6.2 Hz, 1H), 5.04 (s, 1H, OH), 6.83 (dd, J=8.1, 1.7 Hz, 1H), 6.91 (t, J=8.1 Hz, 1H), 6.97 (dd, J=8.1, 1.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.50, 22.54, 23.1, 29.1, 36.8, 44.8, 53.2, 55.8, 59.2, 61.5, 67.1, 69.1, 74.8, 75.3, 85.1, 92.5, 112.8, 118.2, 123.2, 125.6, 148.0, 153.2, 175.1. MS *m/z* (EI) 495 ($M^{+\cdot}$, 2%), 493 ($M^{+\cdot}$, 2%), 478 (6), 476 (6), 458 (1), 452 (2), 450 (2), 436 (1), 414 (100), 370 (11), 368 (10), 340 (18), 326 (10), 324 (7), 298 (17), 190 (14), 177 (64), 161 (10), 148 (30), 134 (9), 122 (36), 105 (9). Anal. Calcd for $C_{24}H_{32}BrNO_5$: $M^{+\cdot}$ 495.1444. Found: 495.1432.

Ethyl 3-methyl-5-[2-(3-methoxy-2-isoproxy)phenylethynyl]-oxo-3-azabicyclo[3.3.0]octanecarboxylate **18** was obtained as a pale yellow oil. ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.16 (t, J=7.1 Hz, 3H), 1.30 (d, J=6.2 Hz, 6H), 1.80–1.94 (m, 4H), 2.29–2.39 (m, 1H), 2.33 (s, 3H), 2.49–2.57 (m, 1H), 2.79 (d, J=6.0 Hz, 1H), 2.81 (d, J=6.0 Hz, 1H), 2.91 (d, J=9.4 Hz, 1H), 3.00 (d, J=9.4 Hz, 1H), 3.82 (s, 3H), 4.05 (q, J=7.1 Hz, 2H), 4.59 (sep, J=6.2 Hz, 1H), 6.94 (m, 3H), 7.00–7.09 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.8, 22.5, 26.0, 38.0, 39.5, 42.0, 55.9, 60.9, 64.1, 66.5, 67.3, 70.3, 76.4, 90.0, 90.1, 115.0, 116.0, 123.7, 126.0, 149.9, 153.1, 174.5, 188.3. Near IR (film) υ (cm^{-1}) 2192, 1729, 1664, 1572. MS *m/z* (EI) 413 ($M^{+\cdot}$, 12%), 398 (2),

370 (14), 354 (6), 340 (13), 324 (2), 312 (2), 298 (10), 281 (3), 260 (3), 242 (2), 224 (6), 209 (8), 196 (8), 182 (9), 175 (15), 161 (27), 142 (18), 122 (44), 110 (14), 94 (15), 84 (45), 72 (100). Anal. Calcd for $C_{24}H_{31}NO_5$: $M^{+\cdot}$ 413.2202. Found: 413.2189.

4.2.4. Ethyl 5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-isopropoxy)phenyl-*Z*-ethenyl]-3-azabicyclo-[3.3.1]nonanecarboxylate 10. *Method A*. Acetylene **16** (213 mg, 0.14 mmol) was dissolved in distilled methanol (9 mL) and to this was added pyridine (9 drops) and palladium on carbon (21 mg, 10%). The mixture was degassed/gassed three times with hydrogen and stirred under a hydrogen atmosphere for 24–27 h. Filtration of the reaction mixture through celite followed by evaporation afforded an oily residue which was subjected to column chromatography (*t*-butylmethylether/light petroleum; 1:17) affording recovered starting material (~50 mg), ethyl 5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-isopropoxy)phenyl-*Z*-ethenyl]-3-azabicyclo[3.3.1]nonanecarboxylate (100 mg, 47%) and a mixture of unidentified products (20 mg).

Method B. Acetylene **16** (4.32 g, 8.74 mmol) was dissolved in anhydrous tetrahydrofuran (200 mL) and to this was 1,3,5-triisopropylbenzenesulfonohydrazide[31] (5.48 g, 18.4 mmol). The mixture was refluxed for 2 h. To the hot mixture was added a solution of sodium acetate (1 M, 18.5 mL) and reflux continued for 5 min. Tetrahydrofuran was evaporated and the residue diluted with saturated sodium hydrogen carbonate (100 mL) and extracted with diethyl ether (3×50 mL). The organic layer was dried (Na_2SO_4), and evaporated in vacco afforded an oily residue, which was dried under high vacuum for 30 min. The above procedure was repeated two more times and the resulting residue subjected to column chromatography (*t*-butylmethylether/ethyl acetate/light petroleum; 2:1:7) affording recovered starting material (0.786 g, 18%) and ethyl 5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-isopropoxy)phenyl-*Z*-ethenyl]-3-azabicyclo[3.3.1]nonanecarboxylate (3.21 g, 74%) (91% based on starting material recovery). Mp 123–125 (diethyl ether). ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.98 (t, J=7.1 Hz, 3H), 1.21 (d, J=6.2 Hz, 3H), 1.27 (d, J=6.2 Hz, 3H), 1.66–1.77 (m, 2H), 2.10–2.21 (m, 1H), 2.21–2.27 (m, 1H), 2.58–2.63 (m, 1H), 2.93–3.03 (m, 1H), 2.96 (s, 3H), 3.60 (dd, J=13.6, 2.4 Hz, 1H), 3.67 (dd, J=13.6, 2.4 Hz, 1H), 3.72 (dq, J=10.7, 7.1 Hz, 1H), 3.81 (s, 3H), 3.99 (d, J=13.5 Hz, 1H), 4.01 (dq, J=10.7, 7.1 Hz, 1H), 4.42 (d, J=13.5 Hz, 1H), 4.51 (sep, J=6.2 Hz, 1H), 5.01 (s, 1H), 5.87 (d, J=13.1 Hz, 1H), 6.72 (d, J=13.1 Hz, 1H), 6.79–6.85 (m, 1H), 6.96–7.01 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.6, 20.0, 22.4, 22.6, 27.1, 35.8, 47.0, 52.3, 55.6, 57.5, 61.5, 62.3, 67.3, 75.6, 75.8, 77.3, 111.8, 122.3, 123.0, 126.7, 130.8, 132.2, 152.4, 170.4. MS *m/z* (EI) 497 ($M^{+\cdot}$, 15%), 495 ($M^{+\cdot}$, 12%), 454 (2), 452 (2), 438 (1), 436 (1), 416 (51), 398 (11), 372 (16), 370 (13), 356 (7), 354 (5), 342 (17), 340 (9), 313 (7), 300 (9), 288 (6), 286 (7), 284 (5), 282 (7), 238 (20), 224 (37), 195 (25), 177 (47), 162 (10), 150 (40), 142 (14), 122 (100), 94 (20). Anal. Calcd for $C_{24}H_{34}BrNO_5$: $M^{+\cdot}$ 495.1620. Found: 495.1612.

4.2.5. Ethyl 5-bromo-3-methyl-9-*exo*-acetoxy-9-[2-(3-methoxy-2-acetoxy)phenylethynyl]-3-azabicyclo[3.3.1]-nonanecarboxylate 19. Acetylene **16** (63 mg, 0.127 mmol) was dissolved in anhydrous acetonitrile (0.2 mL) and anhydrous acetic anhydride (0.2 mL) under a nitrogen atmosphere. To this solution was added one half portion of trimethylsilyltrifluoromethanesulfonate (0.1 mL, 0.51 mmol) dropwise over 1 min. After 10 min the remaining half portion was added and the reaction mixture stirred for 10 min. The reaction flask was placed in an ice-bath and the reaction quenched with saturated sodium hydrogen carbonate solution (1–2 mL) followed by solid sodium hydrogen carbonate (~300 mg) and dilution with water (3 mL). Extraction with diethyl ether (3×5 mL), drying (Na_2SO_4), and evaporation in vacco afforded a residue which was subjected to column chromatography (diethyl ether/light petroleum; 7:3) affording ethyl 5-bromo-3-methyl-9-*exo*-acetoxy-9-[2-(3-methoxy-2-acetoxy)phenylethynyl]-3-azabicyclo[3.3.1]nonanecarboxylate as a colourless glass (59 mg, 87%) and trace amounts of a triacetylated derivative. Compound **19** was crystallised by slow evaporation from chloroform, mp 98–100 °C (white crystals). ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.21 (t, J=7.2 Hz, 3H), 1.47–1.62 (bm, 1H), 1.78 (bdd, J=14.0, 5.2 Hz, 1H), 2.11 (s, 3H), 2.20 (bs, 3H), 2.29–2.50 (m, 2H), 2.35 (s, 3H), 2.68–2.90 (m, 3H), 3.10–3.40 (bm, 3H), 3.79 (s, 3H), 4.04–4.18 (m, 2H), 6.89–6.95 (m, 1H), 7.10–7.15 (m, 2H). Near IR (Nujol) υ (cm^{-1}) 1764, 1756, 1716. MS *m/z* (EI) 537 ($M^{+\cdot}$, 15%), 535 ($M^{+\cdot}$, 12%), 478 (56), 476 (54), 456 (93), 414 (40), 396 (100), 382 (13), 368 (16), 354 (17), 340 (12), 324 (21), 308 (14), 280 (25), 246 (12), 206 (16), 175 (23), 161 (14), 148 (24), 122 (22), 94 (12). Anal. Calcd for $C_{25}H_{30}Br_1N_1O_7$: C, 55.98; H, 5.64; N, 2.61; $M^{+\cdot}$ 535.1206. Found: C, 55.72; H, 5.65; N, 2.52; $M^{+\cdot}$ 535.1206.

4.2.6. 5-Bromo-1-hydroxymethyl-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-isopropoxy)phenyl-*Z*-ethenyl]-3-azabicyclo[3.3.1]nonane 20. Alkene **10** (3.21 g, 6.48 mmol) was dissolved in anhydrous tetrahydrofuran (120 mL) under nitrogen and the flask placed in an ice-bath. Diisobutylaluminium hydride (31.1 mL, 31.1 mmol, 1 M solution in hexanes) was added dropwise over 5 min. The reaction was stirred for 1 h and then at room temperature for 1 h before quenching with saturated ammonium chloride solution (50 mL). Tetrahydrofuran was evaporated in vacco and the aqueous extracted with diethyl ether (3×50 mL). The organic layer was partitioned, dried (Na_2SO_4), and evaporation in vacco afforded a residue which was subjected to column chromatography (*t*-butylmethylether/light petroleum; 6:4) on silica gel affording a white solid (2.92 g, 99%), mp 134–136 °C. ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.19 (d, J=6.1 Hz, 3H), 1.34 (d, J=6.1 Hz, 3H), 1.41–1.50 (bm, 1H), 1.66–1.84 (m, 2H), 2.07–2.15 (m, 1H), 2.23 (bs, 3H), 2.32 (bd, J=11.4 Hz, 1H), 2.6–2.75 (bm, 1H), 2.77–2.87 (m, 1H), 2.96 (bd, J=11.4 Hz, 1H), 3.18 (bd, J=11.2 Hz, 1H), 3.31 (bd, J=11.2 Hz, 1H), 3.40 (AB, J=11.1 Hz, 2H), 3.81 (s, 3H), 4.45 (bs, 1H), 4.48 (sep, J=6.1 Hz, 1H), 6.17 (d, J=13.0 Hz, 1H), 6.54 (d, J=13.0 Hz, 1H), 6.69 (d, J=7.7 Hz, 1H), 6.79 (d, J=7.7 Hz, 1H), 7.00 (t, J=7.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 22.7, 23.1, 27.5, 38.8, 45.0, 47.1, 52.8, 55.6, 60.2, 66.5, 75.9, 77.5, 78.4, 111.0, 120.9, 123.7, 128.5, 131.6, 133.5, 142.7, 153.0. Near IR (Nujol) υ (cm^{-1}) 3447, 3381, 1569. MS *m/z* (EI) 455 ($M^{+\cdot}$, 12%), 453 ($M^{+\cdot}$, 13%), 412 (2), 410 (2), 396 (10), 394 (10), 374 (100), 356 (12), 332 (10), 314 (48), 282 (5),

244 (9), 196 (8), 177 (28), 164 (25), 150 (12), 137 (18), 122 (25), 91 (8). Anal. Calcd for $C_{22}H_{32}BrNO_4$: C, 58.15; H, 7.09; N, 3.08; $M^{+\cdot}$ 453.1515. Found: C, 58.35; H, 7.20; N, 3.14; 453.1526.

4.2.7. 5-Bromo-1-chloromethyl-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-isopropoxy)phenyl-*Z*-ethenyl]-3-azabicyclo[3.3.1]nonane 21. Diol **20** (1.0 g, 2.20 mmol) from above and triphenylphosphine (2.31 g, 8.80 mmol) were dissolved in anhydrous carbon tetrachloride (50 mL) under a nitrogen atmosphere and to this was added *N*,*N*-diisopropylethylamine (6.13 mL, 35.2 mmol). The mixture was then refluxed for 14 h. On cooling the solvent was removed and the residue dissolved in dichloromethane (50 mL) and washed with saturated sodium hydrogen carbonate solution (100 mL). The organic layer was then partitioned, dried (Na_2SO_4), and evaporation in vacco afforded a white solid residue which was subjected to column chromatography (dichloromethane) affording a white amorphous solid (960 mg, 92%), mp 168–170 °C. ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.16–1.22 (m, 1H), 1.27 (d, J=6.2 Hz, 6H), 1.4–1.54 (m, 1H), 2.04–2.14 (m, 1H), 2.15–2.25 (m, 1H), 2.22 (bs, 3H), 2.39 (AB, J=11.7 Hz, 2H), 2.65–2.85 (m, 3H), 3.07 (AB, J=8.2 Hz, 1H), 3.23 (AB, J=11.4 Hz, 2H), 3.52–3.57 (m, 1H), 3.80 (s, 3H), 4.05 (s, 1H), 4.53 (sep, J=6.2 Hz, 1H), 6.24 (d, J=12.8 Hz, 1H), 6.56 (d, J=12.8 Hz, 1H), 6.79 (d, J=8.0 Hz, 1H), 6.88–6.91 (m, 1H), 7.02 (t, J=8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 22.6, 23.2, 27.9, 38.9, 45.0, 46.2, 55.6, 60.2, 66.3, 68.4, 75.8, 80.2, 111.1, 121.2, 123.9, 127.8, 132.2, 133.6, 142.1, 152.6. Near IR (Nujol) υ (cm^{-1}) 3400, 1569. MS *m*/*z* (EI) 473 ($M^{+\cdot}$, 37%), 471 ($M^{+\cdot}$, 26%), 438 (58), 436 (56), 394 (38), 392 (100), 374 (5), 350 (18), 314 (21), 262 (22), 246 (93), 244 (92), 214 (24), 200 (19), 183 (5), 177 (39), 164 (56), 150 (18), 137 (38), 122 (30), 91 (14). Anal. Calcd for $C_{22}H_{31}BrClNO_3$: C, 55.88; H, 6.61; N, 2.96; $M^{+\cdot}$ 471.1176. Found: C, 55.73; H, 6.59; N, 2.70; $M^{+\cdot}$ 471.1184.

4.2.8. Ethyl 5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-acetoxy)phenyl-*Z*-ethenyl]-3-azabicyclo-[3.3.1]nonanecarboxylate 22. Alcohol **10** (104 mg, 0.209 mmol) was dissolved in anhydrous acetonitrile (0.7 mL), anhydrous dichloromethane (0.35 mL) and acetic anhydride (0.35 mL) under a nitrogen atmosphere. To this solution was added trimethylsilyltrifluoromethanesulfonate (0.14 mL, 0.733 mmol) dropwise over 1 min. The reaction mixture was stirred for 15 min then quenched with saturated sodium hydrogen carbonate solution (1–2 mL) followed by solid sodium hydrogen carbonate (~300 mg) and dilution with water (3 mL). Extraction with diethyl ether (3×5 mL), drying (Na_2SO_4), and evaporation in vacco afforded a residue which was subjected to column chromatography (dichloromethane/ethyl acetate; 24:1) on silica gel affording a colourless glass which was crystallised from diethyl ether as transparent prisms (56 mg, 54%), mp 169–171 °C. ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.13 (t, J=7.2 Hz, 3H), 1.44–1.64 (m, 2H), 2.10–2.20 (m, 1H), 2.25 (s, 3H), 2.28 (bs, 3H), 2.33–2.44 (m, 1H), 2.70–2.83 (bm, 1H), 2.84–3.40 (m, 3H), 3.12–3.35 (bm, 2), 3.63 (bs, 1H), 3.79 (s, 3H), 4.04 (dq, J=10.8, 7.2 Hz, 1H), 4.17 (dq, J=10.8, 7.2 Hz, 1H), 6.18 (bd, J=12.6 Hz, 1H), 6.39 (bd, J=12.6 Hz, 1H), 6.85 (bd, J=8.0 Hz, 1H), 7.12 (t, J=8.0 Hz, 1H), 7.38 (bd, J=8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 20.6, 23.0, 30.4, 38.2, 44.9, 53.4, 55.9, 58.8, 61.3, 66.2, 71.7, 78.3, 111.1, 123.0, 125.4, 127.0, 130.8, 131.1, 137.5, 150.6, 168.4, 174.0. Near IR (Nujol) υ (cm^{-1}) 3447, 1752, 1701. MS *m*/*z* (EI) 497 ($M^{+\cdot}$, 43%), 495 ($M^{+\cdot}$, 44%), 454 (1), 434 (1), 424 (1), 416 (83), 398 (17), 374 (17), 356 (9), 342 (11), 324 (8), 314 (9), 305 (15), 303 (15), 288 (21), 286 (21), 257 (7), 248 (18), 238 (23), 232 (6), 224 (100), 206 (8), 195 (28), 177 (43), 162 (10), 150 (36), 137 (12), 122 (67), 94 (13), 84 (66). Anal. Calcd for $C_{23}H_{30}BrNO_6$: C, 55.65; H, 6.09; N, 2.82; $M^{+\cdot}$ 495.1256. Found: C, 55.56; H, 6.14; N, 2.77; $M^{+\cdot}$ 495.1259.

4.2.9. 1-Acetoxymethyl-5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-isopropoxy)phenyl-*Z*-ethenyl]-3-azabicyclo[3.3.1]nonane 23. Diol **20** (201 mg, 0.442 mmol) was dissolved in anhydrous dichloromethane (3 mL) under an argon atmosphere. The solution was cooled in an ice-bath and acetic anhydride (0.33 mL, 3.54 mmol), pyridine (0.11 mL, 1.37 mmol) and 4-(dimethylamino)pyridine (10 mg) were added. After 2 h at room temperature the reaction was heated at 40 °C for 3 h. Solvents were then removed and the residue subjected to column chromatography (diethyl ether/light petroleum, 1:1) affording 1-acetoxymethyl-5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-isopropoxy)phenyl-*Z*-ethenyl]-3-azabicyclo-[3.3.1]nonane (210 mg, 95%) which solidified on standing, mp 117–118 °C. ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.19 (d, J=6.1 Hz, 3H), 1.33 (d, J=6.1 Hz, 3H), 1.39–1.48 (m, 1H), 1.51–1.58 (m, 1H), 1.77–1.90 (m, 1H), 1.92 (s, 3H), 2.06–2.15 (m, 1H), 2.21 (s, 3H), 2.36 (dd, J=11.6, 2.5 Hz, 1H), 2.59–2.79 (m, 1H), 2.70 (d, J=12.1 Hz, 1H), 2.78–2.89 (m, 1H), 3.17 (dd, J=11.6, 2.5 Hz, 1H), 3.31 (d, J=11.8 Hz, 1H), 3.59 (d, J=11.1 Hz, 1H), 3.79 (s, 3H), 4.03 (d, J=11.1 Hz, 1H), 4.46 (s, OH), 4.46 (sep, J=6.1 Hz, 1H), 6.17 (d, J=13.0 Hz, 1H), 6.53 (d, J=13.0 Hz, 1H), 6.76–6.84 (m, 2H), 7.01 (t, J=8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 22.2, 22.7, 23.1, 27.5, 38.9, 45.0, 46.2, 55.5, 60.3, 66.5, 69.9, 75.9, 77.2, 77.5, 110.9, 121.6, 123.5, 128.3, 131.6, 133.5, 142.6, 152.7, 170.9. MS *m*/*z* (EI) 497 ($M^{+\cdot}$, 7%), 495 ($M^{+\cdot}$, 9%), 454 (4), 452 (2), 438 (4), 436 (4), 415 (5), 372 (8), 356 (17), 342 (35), 314 (8), 312 (13), 300 (15), 282 (12), 270 (10), 240 (15), 195 (29), 177 (54), 164 (25), 150 (38), 137 (28), 122 (100). Anal. Calcd for $C_{24}H_{34}BrNO_5$: C, 58.07; H, 6.90; N, 2.82; $M^{+\cdot}$ 495.1621. Found: C, 58.00; H, 7.15; N, 2.64; $M^{+\cdot}$ 495.1614.

4.2.10. 1-Acetoxymethyl-5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-acetoxy)phenyl-*Z*-ethenyl]-3-azabicyclo[3.3.1]nonane 24. *Method A*. The diol **20** (86 mg, 0.189 mmol) was dissolved in anhydrous acetonitrile (0.35 mL), and acetic anhydride (0.35 mL) under a nitrogen atmosphere. To this solution was added one half portion of trimethylsilyltrifluoromethanesulfonate (0.22 mL, 1.15 mmol) dropwise over 30 s. After 10 min the remaining half portion was added and the reaction mixture stirred for 10 min. The reaction flask was placed in an ice-bath and the reaction quenched with saturated sodium hydrogen carbonate solution (2–3 mL) followed by solid sodium hydrogen carbonate (~400 mg) and dilution with water (5 mL). Extraction with diethyl ether (3×5 mL), drying (Na_2SO_4), and evaporation in vacco afforded a residue which was subjected to column chromatography

(diethyl ether/light petroleum; 6:4) affording 1-acetoxymethyl-5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-acetoxy)phenyl-*Z*-ethenyl]-3-azabicyclo[3.3.1]nonane as a white solid (64 mg, 68%) and triacetylated material (8 mg, 8%).

Method B. Compound **23** (56 mg, 0.113 mmol) was reacted, as above in method A, with acetic anhydride (0.3 mL), anhydrous acetonitrile (0.3 mL) and trimethylsilyltrifluoromethanesulfonate (0.14 mL, 0.677 mmol). Column chromatography as above afforded 1-acetoxymethyl-5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-acetoxy)phenyl-*Z*-ethenyl]-3-azabicyclo[3.3.1]nonane (48 mg, 86%) as a white solid, mp 127–129 °C. ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.45–1.63 (m, 1H), 1.84–1.94 (m, 1H), 1.98 (s, 3H), 2.10–2.17 (m, 1H), 2.23 (s, 3H), 2.28 (s, 3H), 2.43–2.48 (m, 1H), 2.44 (s, OH), 2.62–2.79 (m, 1H), 2.77 (d, J=11.8 Hz, 1H), 3.16 (dd, J=11.5 Hz, 1H), 3.28 (d, J=11.5 Hz, 1H), 3.79 (s, 3H), 3.93 (bd, J=11.0 Hz, 1H), 4.13 (d, J=11.0 Hz, 1H), 6.22 (d, J=12.8 Hz, 1H), 6.50 (d, J=12.8 Hz, 1H), 6.86 (d, J=8.0 Hz, 1H), 7.06 (d, J=8.0 Hz, 1H), 7.16 (t, J=8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 20.8, 23.1, 27.6, 39.0, 44.9, 45.2, 55.8, 60.2, 66.4, 69.9, 76.6, 78.9, 110.96, 121.0, 126.2, 126.8, 131.9, 132.7, 136.6, 150.9, 169.6, 170.9. Near IR (Nujol) υ (cm^{-1}) 3452, 1745, 1731, 1725. MS *m/z* (EI) 497 ($M^{+\cdot}$, 14%), 495 ($M^{+\cdot}$, 14%), 454 (2), 452 (2), 438 (3), 436 (2), 416 (92), 398 (10), 374 (14), 356 (26), 342 (15), 328 (5), 314 (4), 300 (9), 286 (17), 272 (5), 246 (16), 195 (25), 177 (56), 164 (70), 150 (19), 136 (19), 134 (17), 122 (90), 105 (22). Anal. Calcd for $C_{23}H_{30}Br_1N_1O_6$: C, 55.65; H, 6.09; N, 2.82; $M^{+\cdot}$ 495.1257. Found: C, 55.75; H, 6.23; N, 2.68; $M^{+\cdot}$ 495.1257.

4.2.11. 7-Acetoxy-4a-*exo*-hydroxy-8-methoxy-2-methyl-4-acetoxymethyl-2,3,4,4a-tetrahydro-1*H*-4,10b-propanobenz[h]isoquinoline 25. *Method A*. Diacetate **24** (33 mg, 0.066 mmol) was dissolved in anhydrous dichloromethane (2 mL) under a nitrogen atmosphere and the reaction flask covered with aluminium foil. The reaction flask was cooled in an ice-bath and solid silver trifluoroacetate (31 mg, 0.140 mmol) added to the vigorously stirring solution. After 1 h the reaction was quenched with concd ammonia solution (15 drops) followed by addition of solid sodium sulfate. Filtration through glass wool and evaporation of the filtrate afforded an oily residue which was subjected to column chromatography (*t*-butyl methyl ether). The 7-acetoxy-4a-*exo*-hydroxy-8-methoxy-2-methyl-4-acetoxymethyl-2,3,4,4a-tetrahydro-1*H*-4,10b-propanobenz[h]isoquinoline **25** (5 mg, 18%) was eluted first followed by the more polar by-product **26**, which underwent significant isomerization on the column (ethyl acetate/methanol).

Method B. Diacetate **24** (10 mg, 0.020 mmol) was dissolved in anhydrous nitromethane (2 mL) under an argon atmosphere and the reaction flask covered with aluminium foil. The reaction flask was cooled in an ice-bath and solid silver 2,4,6-trinitrobenzenesulfonate[36] (24 mg, 0.060 mmol) added to the vigorously stirring solution. The reaction was allowed to reach room temperature over 14 h. The solvent was removed under high vacuum, the residue redissolved in dichloromethane (~ 2–3 mL) and concd ammonia solution (20 drops) added followed by addition of solid sodium sulfate. The dichloromethane layer was removed (Pastuer Pipette) and the solid residue washed three times with dichloromethane. The combined dichloromethane extracts were passed through glass wool and evaporated. Column chromatography (dichloromethane/ethyl acetate, 3:1) afforded 7-acetoxy-4a-*exo*-hydroxy-8-methoxy-2-methyl-4-acetoxymethyl-2,3,4,4a-tetrahydro-1*H*−4,10b-propanobenz[h]isoquinoline **25** (4.5 mg, 54%) ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.56 (bs, 1H), 1.57–1.72 (m, 2H), 1.89–2.31 (m, 5H), 2.02 (s, 3H), 2.07 (s, 3H), 2.33 (s, 3H), 2.57 (d, J=11.3 Hz, 1H), 2.73 (d, 11.3, 1H), 2.77 (m, 1H), 3.79 (s, 3H), 4.18 (AB, 2H), 6.38 (d, J=10.1 Hz, 1H), 6.64 (d, J=10.1 Hz, 1H), 6.84 (d, J=8.6 Hz, 1H), 7.21 (d, J=8.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.40, 20.43, 21.0, 28.8, 28.9, 40.2, 42.6, 45.5, 56.0, 61.0, 66.2, 67.7, 71.5, 111.5, 122.1, 123.6, 124.7, 130.9, 133.2, 135.9, 149.8, 168.8, 171.0. Near IR (Nujol) υ (cm^{-1}) 3463, 1743. MS *m/z* (EI) 415 ($M^{+\cdot}$, 22%), 372 (17), 356 (8), 330 (42), 282 (11), 240 (31), 203 (12), 71 (11), 43 (100). Anal. Calcd for $C_{23}H_{29}NO_6$: $M^{+\cdot}$ 415.1995. Found: $M^{+\cdot}$ 415.1989.

4.2.12. *o*-Quinone acetal 28. To a solution of **21** (20 mg, 0.042 mmol) in anhydrous dichloromethane (2 mL) under a nitrogen atmosphere was added solid aluminium chloride (7 mg, 0.055 mmol) in one portion. The mixture was then stirred at room temperature for 16 h. The reaction was quenched with saturated sodium hydrogencarbonate solution (2 mL) and extracted with dichloromethane/diether ether (1:1) (5 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was subjected to column chromatography (*t*-butyl methyl ether/light petroleum, 3:7), which afforded two fractions. The first (8 mg) was recovered starting material and the second was 5-bromo-1-chloromethyl-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-hydroxy)phenyl-*Z*-ethenyl]-3-azabicyclo[3.3.1]-nonane **27** (10 mg, 56%) as an orange oil. ^{1}H NMR (300 MHz, $CHCl_3$) δ 1.45–1.60 (m, 1H), 1.74–1.97 (m, 3H), 2.16–2.25 (m, 1H), 2.32 (s, 3H), 2.50 (dd, 1H), 2.69–2.87 (m, 2H), 3.07 (d, J=12 Hz, 1H), 3.24–3.39 (m, 2H), 3.65 (AB, 2H), 3.95 (s, 3H), 5.96 (bs, OH), 6.31 (d, J=13 Hz, 1H), 6.68 (d, J=13 Hz, 1H), 6.78–6.94 (m, 3H).

Phenol **27** (68 mg, 0.158 mmol) was dissolved in anhydrous dichloromethane (2 mL) under a nitrogen atmosphere and added dropwise to a solution of iodobenzene diacetate (51 mg, 0.158 mmol) in anhydrous dichloromethane (1.5 mL) and acetic acid (0.5 mL) all at room temperature. After 1.5 h the reaction was quenched with excess solid sodium hydrogen carbonate followed by saturated sodium hydrogen carbonate solution (5 mL). Extraction with dichloromethane, drying (Na_2SO_4) and evaporation afforded the crude product (~48 mg, 53%), which was found to decompose on silica gel and hence was used without further purification. ^{1}H NMR (300 MHz, $CHCl_3$) δ 1.46–1.60 (m, 1H), 1.85–1.95 (m, 2H), 2.14 (s, 3H), 2.10–2.30 (m, 1H), 2.28 (s, 3H), 2.46 (dd, 1H), 2.65 (d, 1H), 2.67–2.85 (m, 2H), 3.00–3.10 (bdd, 1H), 3.12–3.50 (m, 2H), 3.53 (s, 3H), 3.64 (s, 1H), 3.39 (d, 1H), 6.20–6.50 (m, 3H), 6.80–6.88 (m, 1H), 7.07–7.14 (m, 1H).

4.2.13. Ethyl 5-bromo-3-[2-(3-methoxy-2-isopropoxy)-ethyl]-9-oxo-3-azabicyclo[3.3.1]nonanecarboxylate 29. To a solution of ethyl 6-bromocyclohexanone-2-carboxylate **31** (0.30 g, 1.20 mmol) and formaldehyde

(1.2 mL, 14.5 mmol, 37% in water) in methanol (2.0 mL) at 0 °C was added a solution of 2-(3-methoxy-2-isopropoxy)-ethylamine[46] **32** (0.756 mg, 3.61 mmol) in methanol (2.0 mL) dropwise over 1 h. The solution was then allowed to warm to room temperature over 22 h followed by refluxing for 10 min. On cooling the volatiles were removed in vacco and the residue subjected to column chromatography (dichloromethane) affording a colourless oil (231 mg, 40%). ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.15–1.34 (m, 9H), 1.34–1.44 (m, 1H), 2.10–2.18 (m, 1H), 2.41–2.53 (m, 1H), 2.60–2.76 (m, 2H), 2.78–2.87 (m, 1H), 2.98 (dd, J=11.0, 1.8 Hz, 1H), 3.07 (dd, J=11.5, 1.8 Hz, 1H), 3.30 (dd, J=11.5, 2.2 Hz, 1H), 3.65 (dd, J=11.0, 2.2 Hz, 1H), 3.80 (s, 3H), 4.16–4.24 (m, 2H), 4.50 (sep, J=6.2 Hz, 1H), 6.73–6.77 (m, 2H), 6.93 (t, J=7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.4, 22.63, 22.67, 28.1, 36.2, 46.2, 55.6, 56.6, 60.0, 61.2, 61.4, 68.7, 69.4, 74.4, 110.5, 121.9, 123.2, 134.1, 145.1, 152.9, 169.8, 202.2. MS *m/z* (EI) 483 ($M^{+\cdot}$, 5%), 481 ($M^{+\cdot}$, 5%), 466 (4), 438 (20), 436 (21), 402 (5), 304 (98), 302 (100), 226 (10), 224 (5), 222 (11), 194 (3), 164 (4), 150 (14), 137 (8), 122 (7), 107 (5). Anal. Calcd for $C_{23}H_{32}BrNO_5$: $M^{+\cdot}$ 483.1444. Found: $M^{+\cdot}$ 483.1431.

4.2.14. Ethyl 5-bromo-3-[2-(3-methoxy-2-acetoxy)ethyl]-9-oxo-3-azabicyclo[3.3.1]nonanecarboxylate 30. Ethyl 5-bromo-3-[2-(3-methoxy-2-isopropoxy)ethyl]-9-oxo-3-azabicyclo[3.3.1]nonanecarboxylate **29** (58 mg, 0.12 mmol) was dissolved in anhydrous acetonitrile (0.3 mL) and acetic anhydride (0.3 mL) under a argon atmosphere. To this solution was added one half portion of trimethylsilyltrifluoromethanesulfonate (0.13 mL, 0.733 mmol). After 5 min the remaining half portion was added and the reaction mixture stirred for 5 min. The reaction was then transferred to a separatory funnel containing saturated sodium hydrogen carbonate solution (10 mL). Extraction with diethyl ether (3×5 mL), drying (Na_2SO_4), and evaporation in vacco afforded a residue which was subjected to column chromatography (dichloromethane) affording the title compound as a pale yellow oil (38 mg, 66%). ^{1}H NMR (200 MHz, $CHCl_3$) δ 1.27 (t, J=7.1 Hz, 3H), 1.34–1.51 (m, 1H), 2.07–2.22 (m, 1H), 2.33 (s, 3H), 2.39–2.84 (m, 8H), 2.99 (dd, J=11.0, 1.6 Hz, 1H), 3.07 (dd, J=11.5, 2.2 Hz, 1H), 3.25 (dd, J=11.5, 2.2 Hz, 1H), 3.60 (dd, J=11.0, 2.2 Hz, 1H), 3.79 (s, 3H), 4.20 (q, J=7.1 Hz, 2H), 6.76–6.86 (m, 2H), 7.12 (dd, J=7.3, 8.5 Hz, 1H). MS *m/z* (EI) 483 ($M^{+\cdot}$, 5%), 481 ($M^{+\cdot}$, 5%), 438 (2), 436 (2), 402 (5), 356 (1), 342 (1), 330 (1), 328 (1), 304 (95), 302 (100), 222 (13), 210 (2), 164 (2), 162 (2), 150 (12), 137 (8), 122 (5), 107 (5), 91 (5). Anal. Calcd for $C_{22}H_{28}BrNO_6$: $M^{+\cdot}$ 483.1081. Found: $M^{+\cdot}$ 483.1069.

4.2.15. Ethyl 5-hydroxy-3-[2-(3-methoxy-2-acetoxy)-ethyl]-9-oxo-3-azabicyclo[3.3.1]nonanecarboxylate 33. Ethyl 5-bromo-3-[2-(3-methoxy-2-acetoxy)ethyl]-9-oxo-3-azabicyclo[3.3.1]nonanecarboxylate **30** (38 mg, 0.079 mmol) was dissolved in anhydrous nitromethane (2 mL) under an argon atmosphere and the flask covered with aluminium foil. The reaction flask was then placed in an ice-bath and solid silver 2,4,6-trinitrobenzenesulfonate[36] (95 mg, 0.236 mmol) added in one portion. The mixture was allowed to reach room temperature in the bath over 24 h. The solvent was then removed under high vacuum and the solid residue redissolved in dichlormethane (~2 mL) and concd ammonia solution (50 drops) added. After 5 min solid Na_2SO_4 was added and the dichloromethane removed (Pasteur Pipette) followed by multiple dichloromethane washes. The combined extracts were evaporated and the residue subjected to column chromatography [dichloromethane then dichloromethane/ethyl acetate (95:5)], which afforded recovery of starting material (~5 mg) and the titled compound as a pale yellow oil (27 mg, 82%). ^{1}H NMR (200 MHz, $CHCl_3$) δ 1.27 (t, J=7.3 Hz, 3H), 1.38–1.54 (m, 1H), 1.76–1.96 (m, 1H), 2.08–2.47 (m, 4H), 2.32 (s, 3H), 2.47–2.79 (m, 5H), 2.96–3.06 (m, 1H), 3.21–3.35 (m, 2H), 3.61 (s, OH), 3.80 (s, 3H), 4.21 (q, J=7.3 Hz, 2H), 6.78–6.87 (m, 2H), 7.11 (t, 7.9, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 19.8, 20.1, 20.5, 27.9, 36.6, 42.1, 55.9, 56.5, 58.6, 61.5, 61.8, 66.4, 75.0, 110.3, 121.9, 126.3, 133.1, 138.3, 151.2, 168.9, 169.9, 211.5. MS *m/z* (EI) 419 ($M^{+\cdot}$, 3%), 402 (1), 374 (2), 332 (1), 302 (1), 286 (1), 254 (1), 240 (100), 212 (1), 194 (1), 176 (5), 164 (1), 151 (2), 136 (1), 107 (1), 91 (1). Anal. Calcd for $C_{22}H_{29}NO_7$: $M^{+\cdot}$ 419.1944. Found: $M^{+\cdot}$ 419.1955.

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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.2005.02.014. Both ^{1}H and ^{13}C NMR spectra of compounds **8**, **10**, **13**, **16**, **18**, **20–25**, **29–30** and **33** are available.

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