

# Synthesis of benzocycloheptenones by 1,3-dipolar additions of 2-(1,3-benzodioxol-5-ylmethyl)-4-hydroxy-3-methoxycarbonylisoquinolin-2-ium chloride with dipolarophiles

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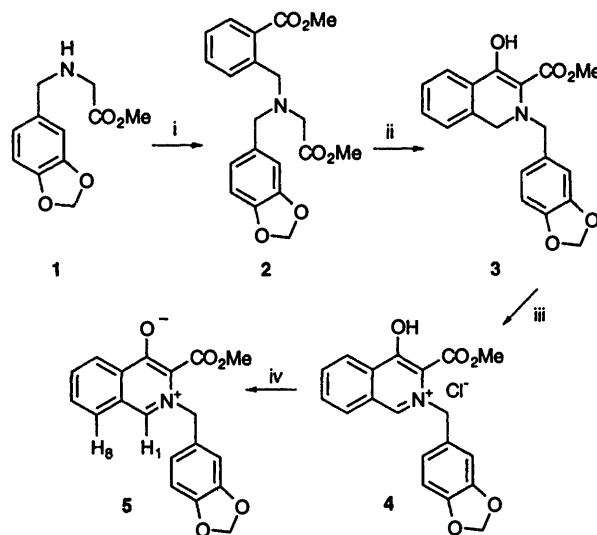
The addition of thionyl chloride to dihydroisoquinolines affords isoquinolinium chlorides which are readily converted to the corresponding ylides upon treatment with sodium hydrogen carbonate. These ylides undergo facile 1,3-dipolar additions with dimethyl acetylenedicarboxylate, maleic anhydride and acrylonitrile to afford the corresponding benzocycloheptenone cycloadduct.

As part of a programme directed towards the design of non-peptide endothelin antagonists,<sup>1</sup> we were interested in the synthesis of 4-aryl-3-carboxydihydroisoquinolines as isosteric replacements for 4-aryl-3-carboxybenzothiazine dioxides. We envisioned that conversion of the 4-hydroxy-3-methoxycarbonyldihydroisoquinolines to the corresponding vinyl chlorides would allow the introduction of 4-aryl substituents by organometallic cross coupling chemistry. However, during the attempted derivatisation of the 4-hydroxy-3-methoxycarbonyl-2-arylmethyldihydroisoquinoline **3** with thionyl chloride we unexpectedly isolated the salt **4**. This salt, upon treatment with aqueous sodium hydrogen carbonate, afforded the azomethine ylide **5**, which underwent the typical 1,3-dipolar additions with dipolarophiles as classically studied by Katritzky.<sup>2</sup> This study reports the synthesis of this ylide and the results obtained from the 1,3 dipolar cycloadditions with a variety of dipolarophiles.

## Results and discussion

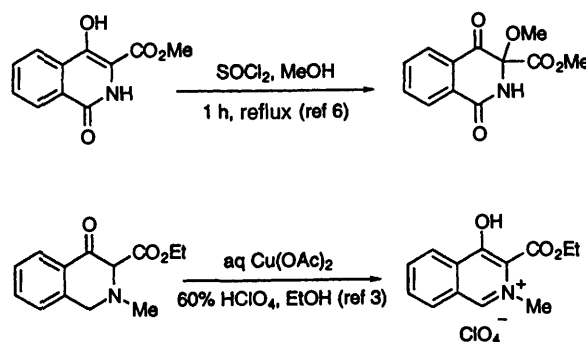
The synthesis of the dihydroisoquinoline precursor **3** followed a procedure that had previously been reported for the synthesis of 1,2,3,4-tetrahydro-2-methyl-4-oxoisoquinolines<sup>3</sup> and 1,2,3,4-tetrahydro-2-benzyl-4-oxoisoquinolines.<sup>4</sup> The only difference between this synthesis and those reported previously is the incorporation of a 1,3-benzodioxole ring. This pharmacophore has previously been demonstrated to be important for endothelin antagonist activity<sup>5</sup> and hence, with the initial objective of synthesising endothelin antagonists, we decided to incorporate this substituent at the 2 position of the resultant isoquinoline. Therefore, piperonal was condensed with glycine methyl ester and the resultant imine reduced with sodium borohydride to afford, in good yield, the reductive amination product **1**. Alkylation of this secondary amine with methyl 2-(bromomethyl)benzoate proceeded readily to afford the tertiary amine **2** (Scheme 1). Finally, base-induced cyclisation with sodium methoxide in methanol generated the dihydroisoquinoline **3**, which existed as a mixture of keto-enol tautomers (1 : 5). Simply treating a solution of this dihydroisoquinoline in methylene chloride with thionyl chloride readily afforded a precipitate. This precipitate, the isoquinolinium chloride **4**, could either be isolated or treated directly with aqueous sodium hydrogen carbonate to afford the ylide **5**.

The structure of this unexpected ylide **5**, and hence **4**, was rigorously established by a combination of heteroatom correlation (HETCOR), 2D proton-proton correlation (COSY) and NOE NMR experiments. Particularly characteristic was the downfield shift of the vinyl proton H-1 which showed NOEs to H-8 and the methylene of the *N*-benzyl substituent.



Scheme 1 Reagents and conditions: i, methyl 2-bromomethylbenzoate,  $K_2CO_3$ , PhMe, 16 h; ii, NaOMe, PhH, reflux, 1.5 h; iii,  $SOCl_2$ ,  $CH_2Cl_2$ , 16 h; iv, aq.  $NaHCO_3$ , 5 min

Interestingly, it has been reported that thionyl chloride reacts with methyl 1,4-dioxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate to presumably afford the 3-chloro derivative, which was isolated as the methyl ether upon treatment with methanol (Scheme 2).<sup>6</sup> Since it has also been observed that 3-ethoxycarbonyl-2-methyl-4-oxoisoquinolines may be dehydrogenated by the use of cold aqueous cupric acetate or by bromine in carbon tetrachloride, with undisclosed yields,<sup>3</sup> it is likely that isoquinolinium salt **4** is formed by 3-chlorination of the dihydroisoquinoline **3** with subsequent elimination and tautomerisation.

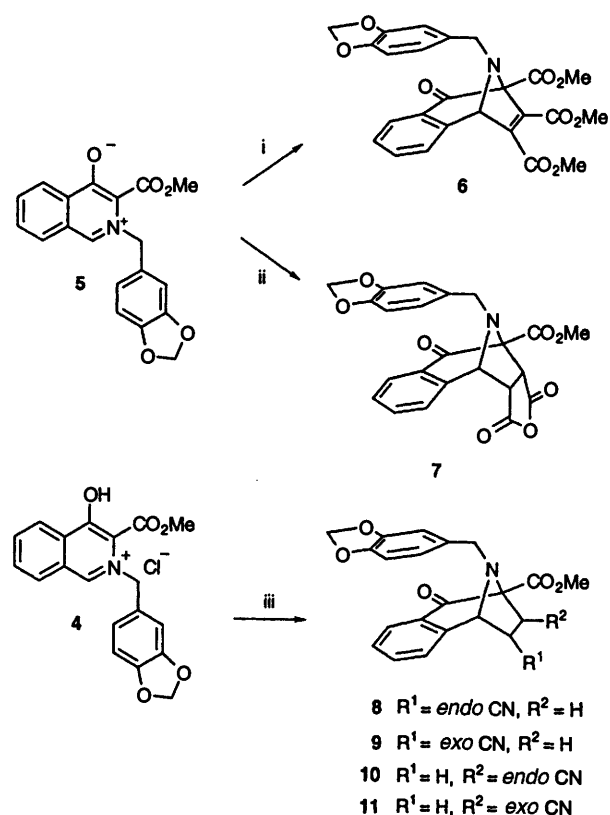


Scheme 2

An alternative mechanistic rationale that involves N-chlorination with subsequent elimination of HCl, or radical cation formation by single electron transfer to thionyl chloride followed by loss of HCl may also be considered.

Of the several reagents that were investigated to effect functionalisation of the tetrahydroisoquinoline **3**, thionyl chloride was unique in its ability to generate the betaine. The use of trifluoromethanesulfonic anhydride or oxalyl chloride led to extensive decomposition accompanied by N-dearylation.

The iminium salt **4**, in the presence of triethylamine, or the ylide **5** readily underwent the expected 1,3-dipolar cycloadditions with a number of dipolarophiles.<sup>7</sup> For example, warming the ylide **5** in dimethyl acetylenedicarboxylate afforded the cycloadduct **6** in excellent yield (Scheme 3).



**Scheme 3** Reagents and conditions: i, DMAD, 70 °C, 2 h; ii, maleic anhydride, PhCH<sub>3</sub>, reflux, 2 h; iii, acrylonitrile, Et<sub>3</sub>N, 70 °C, 1 h

Similarly, refluxing a mixture of the ylide and maleic anhydride in toluene afforded the *endo* product **7** as a crystalline solid upon cooling the reaction mixture. NMR studies revealed that this product was the expected *endo* adduct, as is evident from the characteristic bridgehead doublet that results from a <sup>3</sup>J coupling constant of 6.8 Hz. This coupling constant is commensurate with a dihedral angle of 35° as predicted from 3-21G\* geometry optimisation.<sup>8</sup> Not unexpectedly the cycloadducts generated from the reaction of acrylonitrile with the iminium salt **4** and base were more numerous. Potentially four different products may result from addition of the 1,3-dipole to acrylonitrile, namely **8**, **9**, **10** and **11**. In the event only three products **8** (29%), **9** (2%) and **10** (54%) were observed with the major adducts resulting from the expected *endo* addition of acrylonitrile.

While the regioselectivity of addition favours the addition product **10**, in accord with the regioselectivity observed during the related addition of acrylonitrile to 1-cyclohexyl-6-(cyclohexylimino)-1a-phenylindano[1,2-*b*]aziridine,<sup>9</sup> it has also been reported that addition of acrylonitrile to 4-hydroxy-N-methylisoquinolinium iodide affords significant amounts of

all four potential isomers.<sup>10</sup> The regioselectivity of addition of ylides is usually controlled by the electronic characteristics of the substituents carried by the dipolarophile, in this case acrylonitrile. However, the ylide **5** has a variety of resonance stabilised tautomers allowing the regioselectivity to be controlled, in part, by the electronic properties of the dipole resulting in the formation of both **8** and **10**. It is also expected that, similar to the work of Lown,<sup>9</sup> the 2-benzyl substituent exerts substantial steric hindrance to the approaching dipolarophile resulting in the preferential formation of the *endo* isomers. Furthermore, the HOMO and LUMO surfaces for **5**, as generated by semiempirical optimisation at the AM1 level,<sup>8</sup> confirm the experimentally observed preponderance for the *endo* isomers **8** and **10**.

## Conclusions

This report demonstrates a facile procedure for the preparation of 2-substituted 3-carboxyisoquinolinium salts by chlorination and elimination. The corresponding ylide undergoes stereospecific 1,3-dipolar additions with dipolarophiles providing access to a number of substituted benzocycloheptenones. The stereochemistry of addition favors the *endo* isomers, as rationalised by HOMO and LUMO interaction, whereas the regiochemistry favours the 10-substituted product.

## Experimental

### General details

Microanalyses were performed on a CEC Model 240 elemental analyser. Mps were determined on a Thomas-Hoover capillary melting point apparatus. Flash chromatography was performed on E. Merck Silica Gel 60 (230–400 mesh). Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel 60F<sub>254</sub> precoated glass plates and were visualised with UV light or iodine. <sup>1</sup>H NMR spectra were measured with a Varian Gemini 2000 (300 MHz) or Varian Unity 400 MHz instrument with tetramethylsilane as an internal standard. *J* Values are given in Hz. Mass spectra were obtained from a Finnigan 4500 or a VG analytical 7070 E/HF spectrometer.

### Preparation of methyl 1,3-benzodioxol-5-ylmethylaminoacetate **1**

A mixture of methyl glycinate hydrochloride (10.00 g, 79.6 mmol), piperonal (11.96 g, 79.6 mmol) and triethylamine (24.4 cm<sup>3</sup>, 175 mmol) in toluene (250 cm<sup>3</sup>) was heated to reflux for 24 h in a Dean–Stark apparatus, allowing for the azeotropic removal of water. After cooling to room temperature the yellow solid was collected. A portion of this solid (4.00 g, 55.3 mmol) was dissolved in methanol (20 cm<sup>3</sup>) and then sodium borohydride (2.10 g, 55.3 mmol) was added in portions. The mixture was refluxed for 2 h, evaporated and then suspended in water. Extraction with ethyl acetate (3 × 70 cm<sup>3</sup>), followed by drying over MgSO<sub>4</sub> and concentration *in vacuo* afforded an oil. This oil was purified by chromatography, eluting with 35% ethyl acetate in hexane, to provide the desired product as a colourless oil (3.25 g, 81%) (Found: C, 58.9; H, 5.9; N, 6.1. C<sub>11</sub>H<sub>13</sub>N<sub>1</sub>O<sub>4</sub> requires C, 59.2; H, 5.9; N, 6.3%); δ<sub>H</sub>(400 MHz; CDCl<sub>3</sub>) 2.42 (1 H, br s, NH), 3.27 (2 H, s, ArCH<sub>2</sub>N), 3.60 (2 H, s, NCH<sub>2</sub>CO<sub>2</sub>Me), 3.61 (3 H, s, CO<sub>2</sub>Me), 5.97 (2 H, s, OCH<sub>2</sub>O), 6.74 (1 H, dd, *J* 1.4, 8.0, ArH), 6.82 (1 H, d, *J* 8.0, ArH), 6.88 (1 H, d, *J* 1.4, ArH); *m/z* (CI): 223 (M<sup>+</sup>, 5%), 192 (4), 164 (7), 150 (27), 135 (100).

### Preparation of methyl 2-[(1,3-benzodioxol-5-ylmethyl)(methoxycarbonylmethyl)amino]benzoate **2**

To a solution of methyl 2-bromomethylbenzoate (1.50 g, 6.6 mmol) and **1** (1.46 g, 6.6 mmol) in toluene (25 cm<sup>3</sup>) was added potassium carbonate (1.81 g, 13.1 mmol). The suspension was refluxed for 16 h, filtered and the filtrate evaporated *in vacuo*.

Chromatography of the residue eluting with 10% ethyl acetate in hexane afforded the required compound as a viscous oil (2.33 g, 96%) (Found: C, 64.5; H, 5.7; N, 3.7.  $C_{20}H_{21}N_1O_6$  requires C, 64.7; H, 5.7; N, 3.8%;  $\delta_H$ (400 MHz;  $CDCl_3$ ), 3.25 (2 H, s,  $ArCH_2N$ ), 3.67 (3 H, s,  $CO_2Me$ ), 3.69 (2 H, s,  $NCH_2CO_2Me$ ), 3.89 (3 H, s,  $CO_2Me$ ), 4.16 (2 H, s,  $ArCH_2N$ ), 5.92 (2 H, s,  $OCH_2O$ ), 6.70 (2 H, s,  $ArH$ ), 6.81 (1 H, s,  $ArH$ ), 7.30 (1 H, dt,  $J$  1.2, 7.5,  $ArH$ ), 7.44 (1 H, dt,  $J$  1.4, 7.7,  $ArH$ ), 7.57 (1 H, m,  $ArH$ ), 7.74 (1 H, dd,  $J$  1.2, 7.7,  $ArH$ );  $m/z$  (CI): 372 ( $M + 1$ , 84%), 312 (30), 250 (12), 236 (96), 135 (100).

#### Preparation of methyl 2-(1,3-benzodioxol-5-ylmethyl)-4-hydroxy-1,2-dihydroisoquinoline-3-carboxylate 3

Sodium hydride (2.45 g; 60% in oil) was cautiously added to methanol (15  $cm^3$ ), and then a solution of **2** (11.36 g, 30.6 mmol) in benzene (50  $cm^3$ ) was added. The clear solution was refluxed for 1.5 h. The cooled suspension was diluted with ethyl acetate (100  $cm^3$ ) and water (50  $cm^3$ ). The ethyl acetate extract was dried over  $MgSO_4$ , evaporated *in vacuo* and purified by chromatography eluting with 8% ethyl acetate in hexane, to afford the product as a viscous yellow oil which solidified upon standing (6.08 g, 59%) (Found: C, 66.9; H, 5.1; N, 4.0.  $C_{19}H_{17}N_1O_5$  requires C, 67.3; H, 5.1; N, 4.1%;  $\delta_H$ (300 MHz;  $CDCl_3$ ) apparent as a mixture of tautomers. Major tautomer: 3.56 (2 H, s,  $NCH_2$ ), 3.92 (2 H, s,  $NCH_2$ ), 3.93 (3 H, s,  $CO_2Me$ ), 5.95 (2 H, s,  $OCH_2O$ ), 6.69 (1 H, dd,  $J$  8.0, 1.7,  $ArH$ ), 6.75 (1 H, d,  $J$  8.0,  $ArH$ ), 6.89 (1 H, d,  $J$  1.5,  $ArH$ ), 7.08 (1 H, dd,  $J$  6.3, 0.7,  $ArH$ ), 7.37–7.40 (2 H, m,  $ArH$ ), 7.77 (1 H, dd,  $J$  7.5, 0.8,  $ArH$ ), 11.56 (1 H, s, OH);  $m/z$  339 (20%), 280 (10), 204 (40), 172 (10), 135 (100).

#### Preparation of 2-(1,3-benzodioxol-5-ylmethyl)-4-hydroxy-3-methoxycarbonylisoquinolin-2-ium chloride 4

To a solution of **3** (0.346 g, 1.02 mmol) in methylene chloride (9  $cm^3$ ) was added thionyl chloride (0.11  $cm^3$ , 1.51 mmol) dropwise over 5 min. The mixture was filtered after stirring at room temperature for 16 h. The precipitate was washed with methylene chloride (5  $cm^3$ ) and then dried under high vacuum to afford the product **4** (0.305 g, 80%). Crystallisation from MeOH and diethyl ether afforded colourless needles, mp 155–156 °C (Found: C, 60.8; H, 4.3; N, 3.7; Cl, 9.8.  $C_{19}H_{16}N_1O_5Cl_1$  requires C, 61.1; H, 4.3; N, 3.8; Cl, 9.5%;  $\delta_H$ (400 MHz;  $[^2H_6]DMSO$ ) 3.78 (3 H, s,  $CO_2Me$ ), 5.83 (2 H, s,  $NCH_2Ar$ ), 6.02 (2 H, s,  $OCH_2O$ ), 6.82 (1 H, dd,  $J$  7.9, 1.7,  $ArH$ ), 6.93 (1 H, d,  $J$  7.8,  $ArH$ ), 6.95 (1 H, s,  $ArH$ ), 8.08 (1 H, t,  $J$  8.0,  $ArH$ ), 8.20 (1 H, t,  $J$  8.3,  $ArH$ ), 8.43 (1 H, d,  $J$  7.9,  $ArH$ ), 8.62 (1 H, d,  $J$  8.2,  $ArH$ ), 9.74 [1 H, s, C(1)H], (4-OH exchanged with residual water in DMSO);  $m/z$  338 (94%), 204 (20), 172 (17), 135 (100).

#### Preparation of 2-(1,3-benzodioxol-5-ylmethyl)-3-methoxycarbonylisoquinolin-2-ium-5-olate 5

To a solution of **3** (1.50 g, 4.4 mmol) in methylene chloride (40  $cm^3$ ) was added thionyl chloride (0.49  $cm^3$ , 6.7 mmol) dropwise over 5 min. After stirring for 16 h at room temperature ethyl acetate (100  $cm^3$ ) and saturated aqueous sodium hydrogen carbonate (50  $cm^3$ ) were added and the mixture vigorously stirred for 5 min. The ethyl acetate extract was dried over  $MgSO_4$ , filtered and then concentrated until the product began to crystallise. After standing for 1 h the yellow crystalline solid was collected and washed with hexane (10  $cm^3$ ). This process afforded the product **5** (0.99 g, 66%), mp 209–210 °C (Found: C, 67.4; H, 4.5; N, 4.0.  $C_{19}H_{15}N_1O_5$  requires C, 67.7; H, 4.5; N, 4.2%;  $\delta_H$ (400 MHz;  $[^2H_6]DMSO$ ) 3.68 (3 H, s,  $CO_2Me$ ), 5.58 (2 H, s,  $NCH_2$ ), 5.99 (2 H, s,  $OCH_2O$ ), 6.76 (1 H, dd,  $J$  8.0, 1.8,  $ArH$ ), 6.86 (1 H, d,  $J$  1.8,  $ArH$ ), 6.89 (1 H, d,  $J$  8.0,  $ArH$ ), 7.73 (2 H, m,  $ArH$ ), 8.08 (1 H, m,  $ArH$ ), 8.21 (1 H, m,  $ArH$ ), 8.46 [1 H, s, C(1)H];  $m/z$  [ES (20:80) MeOH–MeCN] 338.3 ( $M + H$ )<sup>+</sup>.

#### Preparation of trimethyl 12-(1,3-benzodioxol-5-ylmethyl)-8-oxo-12-azatricyclo[7.2.1.0<sup>2,7</sup>]dodeca-2(7),3,5,10-tetraene-9,10,11-tricarboxylate 6

To **5** (0.125 g, 0.371 mmol) was added dimethyl acetylenedicarboxylate (0.5  $cm^3$ ) and the yellow suspension transferred to an oil bath at 70 °C. Over 2 h the yellow suspension faded to a faint yellow solution. The solution was cooled and applied directly to a silica gel column. Eluting with hexane–ethyl acetate (3:1) afforded the required product **6** (0.146 g, 82%). Crystallisation from diisopropyl ether, methylene chloride, and hexane afforded analytically pure material, mp 143–144 °C (Found: C, 62.5; H, 4.5; N, 2.9.  $C_{25}H_{20}N_1O_9$ , requires C, 62.8; H, 4.2; N, 2.9%;  $\delta_H$ (300 MHz;  $CDCl_3$ ) 3.59 (3 H, s,  $CO_2Me$ ), 3.61 (3 H, s,  $CO_2Me$ ), 3.79 (3 H, s,  $CO_2Me$ ), 4.13 (1 H, d,  $J$  14.3,  $NCH_2$ ), 5.58 (1 H, d,  $J$  14.5,  $NCH_2$ ), 5.94 (2 H, s,  $OCH_2O$ ), 6.68 (1 H, d,  $J$  7.8,  $ArH$ ), 6.80 (1 H, dd,  $J$  7.8, 1.5,  $ArH$ ), 6.84 (1 H, d,  $J$  1.5,  $ArH$ ), 7.42–7.46 (2 H, m,  $ArH$ ), 7.50 (1 H, m,  $ArH$ ), 7.93 (1 H, s, CH-bridgehead);  $m/z$  (CI) 479 ( $M + 1$ , 2%), 448 (2), 271 (4), 232 (5), 163 (3), 135 (100).

#### Preparation of methyl 11-(1,3-benzodioxol-5-ylmethyl)-1,3,9-trioxo-1,3,3a,9,10,10a-hexahydro-4H-4,10-epiminobenzo-[4,5]cyclohepta[1,2-c]furan-10-carboxylate 7

To **5** (0.250 g, 0.742 mmol) was added toluene (5  $cm^3$ ) and then maleic anhydride (0.080 g, 0.81 mmol). The mixture was heated at reflux for 2 h. After cooling to room temperature the crystalline solid was collected and washed with diethyl ether (10  $cm^3$ ). This process afforded **7** (0.151 g, 47%) (Found: C, 63.6; H, 4.1; N, 3.0.  $C_{23}H_{17}N_1O_8$  requires C, 63.5; H, 3.9; N, 3.2%;  $\delta_H$ (300 MHz;  $CDCl_3$ ) 3.44 (1 H, d,  $J$  13.0,  $NCH_2$ ), 3.99 (3 H, s,  $CO_2Me$ ), 4.09 (1 H, dd,  $J$  9.8, 6.8, H-3a), 4.35 (1 H, d,  $J$  13.0,  $NCH_2$ ), 4.54 (1 H, d,  $J$  6.8), 4.72 (1 H, d,  $J$  9.8, H-10a), 5.96 (2 H, s,  $OCH_2O$ ), 6.52 (1 H, d,  $J$  9.3,  $ArH$ ), 6.70–6.74 (2 H, m,  $ArH$ ), 7.14 (1 H, d,  $J$  7.0,  $ArH$ ), 7.53 (1 H, m,  $ArH$ ), 7.66 (1 H, m,  $ArH$ ), 8.05 (1 H, d,  $J$  7.8,  $ArH$ );  $m/z$  435 ( $M + 1$ , 1%), 204 (28), 172 (25), 135 (75), 99 (100).

#### Preparation of methyl 12-(1,3-benzodioxol-5-ylmethyl)-11-cyano-8-oxo-12-azatricyclo[7.2.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene-9-carboxylate 8 (endo CN) and 9 (exo CN) and methyl 12-(1,3-benzodioxol-5-ylmethyl)-10-cyano-8-oxo-12-azatricyclo[7.2.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene-9-carboxylate 10 (endo CN)

To **4** (0.256 g, 0.685 mmol) was added acrylonitrile (2.0  $cm^3$ ) and triethylamine (0.10  $cm^3$ , 0.71 mmol). The yellow suspension was transferred to an oil bath at 70 °C. After 1 h the pale yellow solution was evaporated *in vacuo*. Chromatography, eluting with 20% ethyl acetate in hexane, afforded three products. The least polar isomer **8** (0.072 g, 29%) was isolated as a colourless oil  $\delta_H$ (400 MHz;  $CDCl_3$ ) 2.37 [1 H, dd,  $J$  14.6, 7.6, C(10)H (*endo*)], 3.22 [1 H, dd,  $J$  14.6, 14.4, C(10)H (*exo*)], 3.28 (1 H, d,  $J$  12.9,  $NCH_2$ ), 3.44 [1 H, m, C(11)H], 3.85 (3 H, s,  $CO_2Me$ ), 4.28 [1 H, d,  $J$  5.4, C(12)H], 4.38 (1 H, d,  $J$  12.9,  $NCH_2$ ), 5.90 (2 H, s,  $OCH_2O$ ), 6.46 (1 H, dd,  $J$  7.8, 1.2,  $ArH$ ), 6.65 (1 H, d,  $J$  8.1,  $ArH$ ), 6.69 (1 H, d,  $J$  1.5,  $ArH$ ), 7.23 (1 H, d,  $J$  6.8,  $ArH$ ), 7.51 (1 H, t,  $J$  7.6,  $ArH$ ), 7.67 (1 H, t,  $J$  7.6,  $ArH$ ), 8.07 (1 H, d,  $J$  7.8,  $ArH$ );  $\delta_C$ (100 MHz,  $CDCl_3$ ) 192.0, 168.4, 147.9, 147.0, 138.3, 135.3, 131.5, 129.8, 129.5, 128.6, 127.5, 121.6, 118.4, 108.9, 108.0, 101.0, 75.3, 63.2, 52.7, 50.7, 34.5, 30.5. The hydrochloride salt was prepared by treatment with ethereal HCl; mp 165–166 °C (Found: C, 61.8; H, 4.5; N, 6.5.  $C_{22}H_{18}N_2O_5 \cdot HCl$  requires C, 61.9; H, 4.5; N, 6.6%;  $m/z$  390 ( $M$ , 3%), 338 (3), 255 (23), 204 (7), 172 (7), 135 (100).

The next to elute was compound **9** (0.005 g, 2%), also an oil;  $\delta_H$ (400 MHz,  $CDCl_3$ ) 2.57 [1 H, dd,  $J$  14.9, 9.4, C(10)H (*endo*)], 2.87 [1 H, dd,  $J$  9.4, 2.9, C(11)H], 3.14 [1 H, dd,  $J$  14.9, 2.9, C(10)H (*exo*)], 3.29 (1 H, d,  $J$  13.4,  $NCH_2$ ), 3.86 (3 H, s,  $CO_2Me$ ), 4.38 [1 H, s, C(12)H], 4.53 (1 H, d,  $J$  13.4,  $NCH_2$ ), 5.90 (2 H, s,  $OCH_2O$ ), 6.57 (1 H, dd,  $J$  7.9, 1.3,  $ArH$ ), 6.67 (1 H,

d,  $J$  7.9, ArH), 6.77 (1 H, d,  $J$  1.3, ArH), 7.13 (1 H, d,  $J$  7.6, ArH), 7.45 (1 H, t,  $J$  6.6, ArH), 7.59 (1 H, t,  $J$  6.1, ArH), 8.01 (1 H, d,  $J$  6.4, ArH);  $m/z$  390 (M, 4%), 338 (4), 255 (15), 204 (10), 172 (9), 135 (100).

The final fraction was the more polar isomer **10** (0.135 g, 54%) as a white solid, mp 208–209 °C (Found: C, 67.5; H, 4.8; N, 7.1.  $C_{22}H_{18}N_2O_5$  requires C 67.7; H 4.7; N 7.2%);  $\delta_H$ (300 MHz; DMSO) 1.85 [1 H, dd,  $J$  13.0, 4.1, C(11)-H (*endo*)], 2.98 [1 H, m, C(11)-H (*exo*)], 3.33 (1 H, d,  $J$  13.5, NCH<sub>2</sub>), 3.80 (3 H, s, CO<sub>2</sub>Me), 3.86 (1 H, d,  $J$  13.5, NCH<sub>2</sub>), 4.31 [1 H, d,  $J$  6.2, C(12)H], 4.37 [1 H, dd,  $J$  11.5, 4.1, C(10)-H], 5.97 (2 H, s, OCH<sub>2</sub>O), 6.63 (1 H, dd,  $J$  7.9, 1.5, ArH), 6.75 (1 h, d,  $J$  1.5, ArH), 6.80 (1 H, d,  $J$  7.9, ArH), 7.36 (1 H, d,  $J$  7.5, ArH), 7.50 (1 H, t,  $J$  6.8, ArH), 7.68 (1 H, t,  $J$  6.27, ArH), 7.93 (1 H, d,  $J$  7.7, ArH);  $\delta_C$ (100 MHz, DMSO) 190.6, 167.8, 147.8, 146.9, 146.6, 136.2, 132.0, 129.0, 128.6, 127.3, 126.9, 122.0, 120.0, 109.0, 108.5, 101.4, 82.4, 62.2, 53.5, 52.0, 34.6, 30.7;  $m/z$  391 (M + 1, 3%), 338 (7), 255 (7), 204 (12), 172 (8), 135 (100).

## References

- 1 D. C. Spellmeyer, *Annu. Rep. Med. Chem.*, 1994, **29**, 65.
- 2 A. R. Katritzky and N. Dennis, *Stud. Org. Chem.*, 1979, **3**, 290–308;

- A. Padwa, *1,3-Dipolar Cycloaddition Chemistry*, Wiley, 1984, vol. 2, p. 543.
- 3 I. G. Hinton and F. G. Mann, *J. Chem. Soc.*, 1959, 599.
- 4 P. E. Hanna, V. R. Grund and M. W. Anders, *J. Med. Chem.*, 1974, **17**, 1020.
- 5 A. M. Bunker, J. J. Edmunds, K. A. Berryman, S. Haleen, M. A. Flynn, D. M. Walker, K. M. Welch, E. E. Reynolds and A. M. Doherty, Book of Abstracts, 210th ACS National Meeting, Chicago, August 20–24, 1995, ACS, Washington D.C., Issue pt. 2, MEDI-037.
- 6 J. F. Beattie and N. J. Hales, *J. Chem. Soc., Perkin Trans. 1*, 1992, 751.
- 7 O. Tsuge and S. Kanemasa, *Adv. Heterocycl. Chem.*, 1989, **45**, 231; N. Dennis, A. R. Katritzky and S. K. Parton, *Chem. Pharm. Bull.*, 1975, **23**, 2899; N. Dennis, A. R. Katritzky and Y. Takeuchi, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2054.
- 8 SPARTAN, ver. 3.0, Wavefunction Inc., Irvine, California.
- 9 J. W. Lown and K. Matsumoto, *J. Org. Chem.*, 1971, **36**, 1405.
- 10 J. C. DiCesare, J. P. Burgess, S. W. Mascarella and F. I. Carroll, *J. Heterocycl. Chem.*, 1994, **31**, 187.

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