Synthesis of Some 2,5-Substituted 7-Oxabicyclo[2.2.1]heptanes: Stereochemistry of Diels–Alder Adducts of a 3-Alkylfuran

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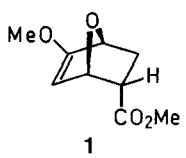
From the Diels–Alder reaction of 3-benzylfuran with acrylonitrile were isolated three of the four possible isomeric adducts, 5(or 6)-benzyl-7-oxabicyclo[2.2.1]hept-5-ene-2-*endo*(or *exo*)-carbonitriles **6–8**, with the 5-benzyl-2-*endo*-carbonitrile **7** predominating. The two 5-benzyl isomers, **7** and **8**, were further elaborated to compounds 2-*endo*-aminomethyl-5-*endo*-benzyl-7-oxabicyclo[2.2.1]heptane hydrochloride (**11**) and 5-*endo*-benzyl-7-oxabicyclo[2.2.1]heptane-2-*exo*-carboxamidine hydrochloride (**12**).

In connection with designing potential antagonists of the interaction of Human Immunodeficiency Virus (HIV) surface protein gp120 with the cellular receptor CD4 we wished to synthesise small molecule mimetics of the binding region of CD4. For the binding interaction with gp120, two particularly significant residues on the surface of CD4 are the benzyl side-chain of phenylalanine 43 and the guanidine moiety of arginine 59,[1] and in the X-ray structure of a soluble form of CD4 these are closely located.[2,3] A suitable rigid framework of appropriate geometry to append a benzyl group and a basic functionality was considered to be the bicyclo[2.2.1]heptane system. Because of its accessibility by Diels–Alder methodology, the 7-oxabicyclo[2.2.1]heptane skeleton was chosen, with target structures such as **11** and **12**.

The Diels–Alder reaction of furans has been extensively studied and frequently exploited in natural product syntheses.[4] However, the stereochemistry of addition of monoactivated dienophiles to 3-substituted furans has been largely neglected. 3-Methoxyfuran adds to acrylic derivatives to give a high predominance of the 2,5-substituted endo adduct such as **1**,[5] and phenyl vinylsulfonate adds to 2,4-dimethylfuran to give largely (2.6:1) the *endo* isomer **2**.[6] However, the stereochemistry of addition to simple 3-alkylfurans does not appear to be documented. Lewis acid catalysis of furan Diels–Alder reactions has been described both for inter- and intramolecular reactions.[7,8]



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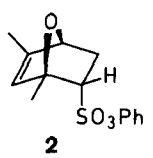

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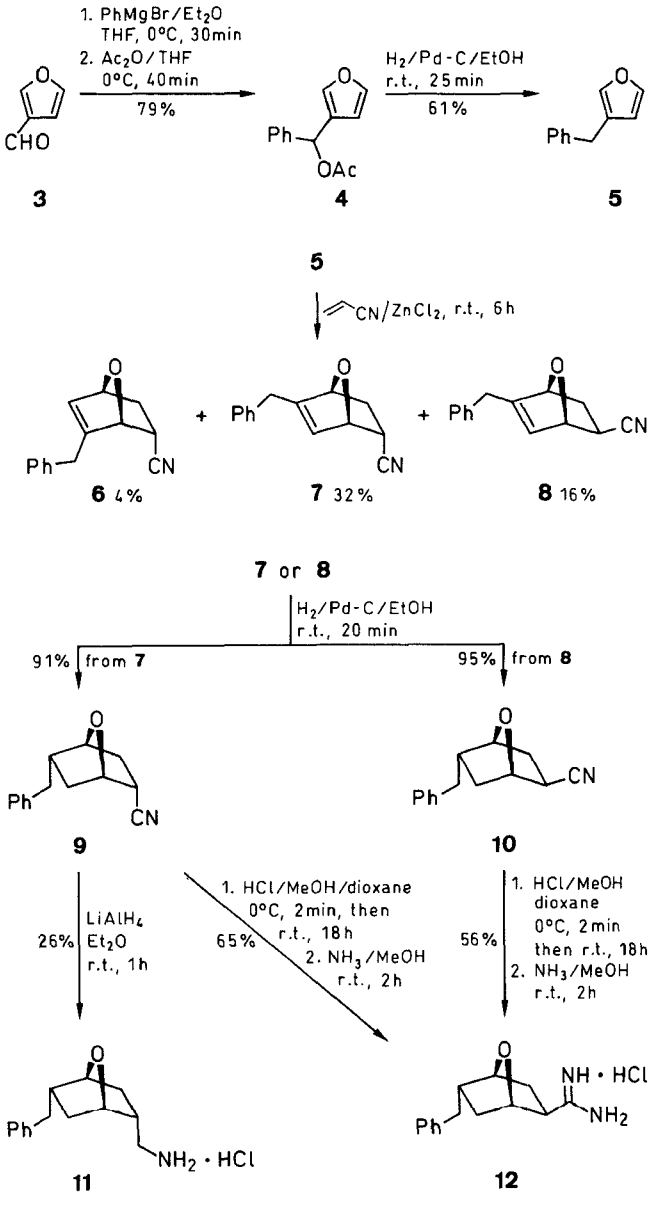
3-Benzylfuran (**5**)[9] was conveniently prepared by reaction of phenylmagnesium bromide with 3-furaldehyde (**3**), quenching the reaction with acetic anhydride, and hydrogenolysis (with care to avoid over-reduction) of the intermediate acetate **4**. The uncatalysed Diels–Alder reaction of **5** with acrylonitrile was extremely slow and the use of Lewis acids was investigated. Aluminum choride in dichloromethane caused rapid decomposition but zinc bromide and zinc chloride were both effective catalysts, resulting in almost complete conversion of the furan to cycloadducts within 6 hours at room temperature. Using zinc chloride in dichloromethane, diethyl ether, toluene or neat acrylonitrile as solvent, one *endo*/*exo* adduct pair predominated to the extent of about 85%. Within this pair the *endo*/*exo* ratio (by ^{1}H NMR) was 1.08 in dichloromethane, 1.13 in diethyl ether, and 1.53 in neat acrylonitrile. The preparative reaction was carried out



Scheme

Table. Proton NOE Data for Compounds **6**, **7** and **8**

Irradiated Proton	Observed NOE's 6	7	8
1-H	2-H, 6-CH_A, 6-CH_B	2-H, 6-H	2-H, 6-H
2-H	1-H, 3-*exo*-H	1-H, 3-*endo*-H,[a] 3-*exo*-H	1-H, 3-*endo*-H, 6-H
3-*endo*-H	2-H,[a] 3-*exo*-H, 4-H, 5-H	3-*exo*-H, 4-H, 5-CH_2	2-H, 3-*exo*-H, 4-H, 5-CH_2
3-*exo*-H	2-H, 3-*endo*-H, 4-H	2-H, 3-*endo*-H, 4-H	3-*endo*-H, 4-H
4-H	3-*endo*-H, 3-*exo*-H, 5-H	3-*endo*-H, 3-*exo*-H, 5-CH_2, C_6H_5	2-H,[a] 3-*endo*-H, 3-*exo*-H, 5-CH_2, C_6H_5
5-H	3-*endo*-H, 4-H, 6-CH_A, C_6H_5		
6-H		1-H, 5-CH_2, C_6H_5	1-H, 2-H, 5-CH_2, C_6H_5
5-CH_2		3-*endo*-H, 4-H, 6-H, C_6H_5	2-H, 3-*endo*-H, 4-H, 6-H, C_6H_5
6-CH_A	1-H, 5-H, 6-CH_B, C_6H_5		
6-CH_B	1-H, 6-CH_A, C_6H_5		

[a] Small NOE's.

with zinc chloride in neat acrylonitrile and after extensive column chromatography, three isomers were obtained, **6**, **7**, and **8**, in yields of 4, 32 and 16%, respectively.

The structures of **6**–**8** were assigned on the basis of their ^1H NMR spectra, the *endo*/*exo* stereochemistry being apparent from the vicinal coupling constants of the bridgehead protons.[10–13] In the case of **6** and **7**, the values of $^3J_{1-H,2-H}$ (4.4 Hz and 4.2 Hz, respectively) dictated that 2-H must be *exo* and hence **6** and **7** are *endo* isomers. Conversely the assignment of **8** as an *exo* isomer followed from the immeasurably small coupling constant for 2-H with the adjacent bridgehead proton 1-H. The stereochemistry of this isomer was confirmed by nuclear Overhauser effects (NOE's), particularly the mutual NOE observed between protons 2-H and 6-H (Table). More importantly, the NOE's involving the various bridgehead protons of each isomer confirmed the regiochemical assignment of **6** as a 2,6-isomer and of **7** and **8** as 2,5-isomers. Selected NOE's important in the stereochemical and regiochemical assignment of these isomers are depicted in the Figure.

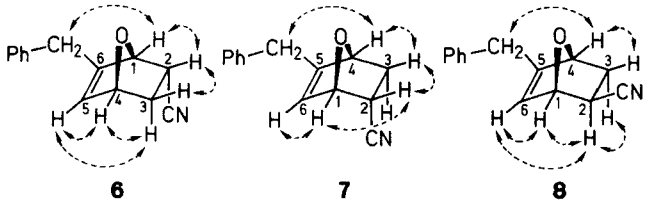


Figure. Selected NOE's for **6**, **7** and **8**.

Catalytic hydrogenation of **7** and **8** afforded exclusively the 5-*endo*-benzyl isomers **9** and **10** which were isolated in yields of 91% and 95% respectively. Whereas the adducts **6**–**8** were oils unstable at room temperature, the reduced compounds **9** and **10** were stable crystalline solids. Treatment of **10** with methanolic hydrogen chloride in dioxan followed by methanolic ammonia afforded the amidine hydrochloride **12** in 56% yield. Similar treatment of **9** afforded the identical *exo*-amidine in 64% yield, presumably by equilibration to the more thermodynamically stable isomer via the enediamine tautomer of the neutral amidine. An *endo* basic function was obtained by reducing **9** with lithium aluminum hydride to afford the amine **11** as its hydrochloride in 26% yield.

Melting points were determined using a Reichert Kofler apparatus and are uncorrected. NMR spectra were recorded on a Jeol GX270 or a Bruker AMX400 NMR spectrometer using $CDCl_3$ as solvent and TMS as internal reference unless otherwise indicated. NOE difference spectroscopy was performed on the Bruker AMX400 NMR spectrometer using standard software. IR spectra were recorded with a Bio-Rad FTS-7 spectrometer. Mass spectra were recorded on a Jeol JMS-SX102 spectrometer and microanalyses were performed on a Carlo Erba model 1106 analyser. Column chromatography was carried out on Merck 7736 silica gel. All compounds were homogeneous by TLC on silica gel $60F_{254}$ coated aluminum sheets.

3-(α-Acetoxybenzyl)furan (4):
To an ice-cooled solution of 3-furaldehyde (3.90 mL, 45 mmol) in THF (3 mL) was added dropwise 3 M PhMgBr in Et_2O (15 mL) and the solution stirred for 30 min. To this solution was added a solution of Ac_2O (7.56 mL, 80 mmol) in THF (15 mL) and stirring with cooling was continued for a further 40 min. The solution was partitioned between hexane (60 mL) and H_2O (100 mL), the organic layer was dried ($MgSO_4$), the solvent was evaporated and the residue was purified by column chromatography on silica gel eluting with 3% EtOAc in hexane to afford **4** as an oil (7.67 g, 79%).

IR (KBr): ν = 1604, 1500, 1494, 1453 cm^{-1}.

^1H NMR: δ = 2.12 (s, 3H, CH_3), 6.32 (dd, J = 0.6, 1.9 Hz, 1H, 4-H), 6.82 (s, 1H, α-H), 7.25–7.42 (m, 7H, 2-H, 5-H, C_6H_5).

3-Benzylfuran (5):
To a solution of the acetate **4** (7.35 g, 34 mmol) in EtOH (100 mL) was added 10% Pd–C (0.4 g) and the mixture was stirred under H_2 for 25 min (uptake of 1.2 equiv H_2). The solution was filtered, the solvent was evaporated and the residue was purified by column chromatography on silica gel eluting with 3% EtOAc in hexane to afford **5**[9] (3.27 g, 61%).

IR (KBr): ν = 1604, 1500, 1494, 1453 cm^{-1}.

^1H NMR: δ = 3.77 (s, 2H, CH_2), 6.32 (dd, J = 0.6, 1.4 Hz, 1H, 4-H), 7.17–7.36 (m, 7H, 2-H, 5-H, C_6H_5).

$C_{11}H_{10}O$	calc.	C 83.51	H 6.37
(158.2)	found	83.21	6.39

Diels–Alder Reaction of 3-Benzylfuran (5) with Acrylonitrile:
To a solution of the furan **5** (3.36 g, 21.2 mmol) in acrylonitrile (25 mL) was added $ZnCl_2$ (4.09 g, 30 mmol) and the mixture was stirred at r.t. for 6 h. The mixture was partitioned between Et_2O (80 mL) and H_2O (50 mL) and the aqueous layer was further extracted with Et_2O (50 mL). The organic layers were combined, dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography on silica gel eluting with $CHCl_3/CH_2Cl_2$ (1:1) and repeating with 4% MeOH in $CHCl_3$ to afford the adducts **6**–**8** as oils which slowly decomposed at r.t.

6-Benzyl-7-oxabicyclo[2.2.1]hept-5-ene-2-endo-carbonitrile (**6**):
The first adduct to elute was **6** (0.19 g, 4%).

IR (film): ν = 3025, 3002, 2958, 2238, 1623, 1601, 1494, 1453, 1428 cm^{-1}.

^{1}H NMR: δ = 1.65 (dd, J = 3.6, 11.4 Hz, 1 H, 3-*endo*-H), 2.32 (ddd, J = 4.4, 9.5, 11.2 Hz, 1 H, 3-*exo*-H), 2.96 (dt, J_d = 9.4, J_t = 4.1 Hz, 1 H, 2-H), 3.62 (dd, J = 2.0, 17.2 Hz, 1 H, 6-CH_B), 3.76 (d, J = 17.2 Hz, 1 H, 6-CH_A), 4.94 (d, J = 4.4 Hz, 1 H, 1-H), 5.03 (d, J = 4.2 Hz, 1 H, 4-H), 5.91 (q, J = 1.8 Hz, 1 H, 5-H), 7.26 (m, 5 H, C_6H_5).

HRMS (CI, NH_3): m/z, $C_{14}H_{13}NO + NH_4$, calc.: 229.1341; found: 229.1345 (MNH_4^+).

5-Benzyl-7-oxabicyclo[2.2.1]hept-5-ene-2-endo-carbonitrile (**7**):

The second adduct to elute was **7** (1.45 g, 32%).

IR (film): ν = 3025, 3002, 2957, 2239, 1626, 1602, 1495, 1453, 1427 cm^{-1}.

^{1}H NMR: δ = 1.34 (dd, J = 3.8, 11.6 Hz, 1 H, 3-*endo*-H), 2.18 (ddd, J = 4.6, 9.5, 11.5 Hz, 1 H, 3-*exo*-H), 2.93 (dt, J_d = 9.5, J_t = 4.1 Hz, 1 H, 2-H), 3.57 (s, 2 H, $PhCH_2$), 4.85 (d, J = 4.5 Hz, 1 H, 4-H), 5.13 (d, J = 4.2 Hz, 1 H, 1-H), 6.04 (q, J = 1.6 Hz, 1 H, 6-H), 7.32 (m, 5 H, C_6H_5).

HRMS (CI, NH_3): m/z, $C_{14}H_{13}NO + NH_4$, calc.: 229.1341; found: 229.1346 (MNH_4^+).

5-Benzyl-7-oxabicyclo[2.2.1]*hept-5-ene-2-exo-carbonitrile* (**8**):

The third adduct to elute was **8** (0.73 g, 16%).

IR (film): ν = 3024, 3001, 2957, 2236, 1626, 1600, 1494, 1452, 1426 cm^{-1}.

^{1}H NMR: δ = 1.57 (dd, J = 8.6, 11.7 Hz, 1 H, 3-*endo*-H), 2.04 (dt, J_d = 11.7, J_t = 4.2 Hz, 1 H, 3-*exo*-H), 2.42 (dd, J = 3.9, 8.5 Hz, 1 H, 2-H), 3.48 (s, 2 H, $PhCH_2$), 4.91 (d, J = 4.6 Hz, 1 H, 4-H), 5.15 (d, J = 0.6 Hz, 1 H, 1-H), 5.79 (q, J = 1.7 Hz, 1 H, 6-H), 7.30 (m, 5 H, C_6H_5).

HRMS (CI, NH_3): m/z, $C_{14}H_{13}NO + NH_4$, calc.: 229.1341; found: 229.1346 (MNH_4^+).

5-*endo*-Benzyl-7-oxabicyclo[2.2.1]heptane-2-*endo*-carbonitrile (9):

To a solution of the alkene **7** (1.27 g, 6.0 mmol) in EtOH (30 mL) was added 10% Pd–C (0.1 g) and the mixture was stirred under H_2 for 20 min. The solution was filtered, the solvent was evaporated and the residue was purified by column chromatography on silica gel eluting with 20% EtOAc in hexane to afford **9** as a white crystalline solid (1.16 g, 91%), mp 60–62 °C (from EtOAc/hexane).

IR (KBr): ν = 2994, 2939, 2238, 1605, 1498, 1456, 1439 cm^{-1}.

^{1}H NMR: δ = 1.74 (dd, J = 5.6, 13.1 Hz, 1 H, 3/6-*endo*-H), 1.95–2.15 (m, 2 H, 3-*exo*-H, 6-*exo*-H), 2.24 (dd, J = 4.7, 12.9 Hz, 1 H, 6/3-*endo*-H), 2.58 (m, 1 H, 5-H), 2.74 (dd, J = 7.7, 14.0 Hz, 1 H, $PhCH_2$), 2.87 (dd, J = 8.1, 13.9 Hz, 1 H, $PhCH_2$), 2.93 (m, 1 H, 2-H), 4.47 (t, J = 5.0 Hz, 1 H, 1/4-H), 4.71 (t, J = 5.2 Hz, 1 H, 4/1-H), 7.27 (m, 5 H, C_6H_5).

$C_{14}H_{15}NO$	calc.	C 78.84	H 7.09	N 6.57
(213.3)	found	78.87	7.07	6.67

5-*endo*-Benzyl-7-oxabicyclo[2.2.1]heptane-2-*exo*-carbonitrile (10):

To a solution of the alkene **8** (0.62 g, 2.9 mmol) in EtOH (15 mL) was added 10% Pd–C (0.05 g) and the mixture was stirred under H_2 for 20 min. The solution was filtered and the solvent evaporated to afford **10** as a white crystalline solid (0.59 g, 95%), mp 90–92 °C (from EtOAc/hexane).

IR (KBr): ν = 2986, 2955, 2240, 1603, 1497, 1452, 1443 cm^{-1}.

^{1}H NMR: δ = 1.04 (dd, J = 5.5, 12.6 Hz, 1 H, 6-*endo*-H), 2.03 (m, 2 H, 3-*exo*-H, 6-*exo*-H), 2.44 (dd, J = 9.1, 12.9 Hz, 1 H, 3-*endo*-H), 2.52–2.74 (m, 4 H, 2-H, 5-H, $PhCH_2$), 4.53 (t, J = 5.0 Hz, 1 H, 4-H), 4.77 (d, J = 5.8 Hz, 1 H, 1-H), 7.23 (m, 5 H, C_6H_5);

$C_{14}H_{15}NO$	calc.	C 78.84	H 7.09	N 6.57
(213.3)	found	79.13	6.86	6.72

5-*endo*-Benzyl-7-oxabicyclo[2.2.1]heptane-2-*exo*-carboxamidine Hydrochloride (12):

HCl was bubbled through an ice-cooled solution of the nitrile **10** (0.15 g, 0.7 mmol) in MeOH (0.5 mL) and dioxane (0.5 mL) for 2 min and the solution was allowed to stand at r.t. for 18 h. The solvent was evaporated and the residue was taken up in methanolic NH_3 and allowed to stand for a further 2 h. The solvent was evaporated and the residue was purified by reverse phase column chromatography on C_{18} silica gel eluting with H_2O followed by 10% aq MeOH to afford **12** as a white crystalline solid (0.11 g, 56%), mp 183–186 °C.

IR (KBr): ν = 3262, 3084, 1675, 1523, 1497, 1453 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.10 (dd, J = 5.5, 12.4 Hz, 1 H, 6-*endo*-H), 1.72 (dt, J_d = 13.5, J_t = 5.4 Hz, 1 H, 3-*exo*-H, 1.89 (dt, J_d = 5.7, J_t = 11.8 Hz, 1 H, 6-*exo*-H), 2.33 (m, 1 H, 5-H), 2.37 (dd, J = 9.1, 13.2 Hz, 1 H, 3-*endo*-H), 2.68 (d, J = 8.0 Hz, 2 H, $PhCH_2$), 2.97 (dd, J = 4.8, 8.9 Hz, 1 H, 2-H), 4.40 (t, J = 5.0 Hz, 1 H, 4-H), 4.59 (d, J = 5.8 Hz, 1 H, 1-H), 7.24 (m, 5 H, C_6H_5), 8.64 [br s, D_2O exchangeable, 4 H, $C(NH_2)_2^+$].

MS (CI, NH_3): m/z = 231 (MH^+ for free base).

$C_{14}H_{18}N_2O \cdot HCl \cdot 0.25H_2O$	calc.	C 61.99	H 7.26	N 10.33
(271.2)	found	61.81	7.27	10.60

Reaction of **9** under similar conditions afforded a 65% yield of material identical (NMR, IR, MS, TLC) to **12**.

2-*endo*-Aminomethyl-5-*endo*-benzyl-7-oxabicyclo[2.2.1]heptane Hydrochloride (11):

To an ice-cooled suspension of $LiAlH_4$ (0.14 g) in Et_2O (5 mL) was added dropwise a solution of the nitrile **9** (0.51 g, 2.4 mmol) in Et_2O (3 mL) and the mixture was stirred at r.t. for 1 h. To this solution were added with care H_2O (2 mL) followed by 10% aq NaOH and the mixture was then partitioned between Et_2O (30 mL) and H_2O (30 mL). The organic layer was washed with dilute HCl (20 mL) and the aqueous layer was basified and extracted with Et_2O (30 mL and 10 mL). The organic layers were dried ($MgSO_4$) and the solvent was evaporated. The residue was taken up in EtOAc and acidified with a solution of HCl in EtOAc. The resulting hygroscopic precipitate was dissolved in H_2O, evaporated to dryness and triturated with EtOAc to afford **11** as a white crystalline solid (0.16 g, 26%), mp 207–211 °C.

IR (KBr): ν = 3414, 3026, 2976, 2910, 1584, 1522, 1497, 1453 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.27 (dd, J = 5.5, 12.9 Hz, 1 H, 3/6-*endo*-H), 1.65 (m, 3 H, 3-*exo*-H, 6-*exo*-H, 6/3-*endo*-H), 2.29 (m, 2 H, 2-H, 5-H), 2.69 (AB of ABX, J_{AB} = 14.0, J_{AX} = 7.6, J_{BX} = 8.5 Hz, 2 H, $PhCH_2$), 2.97 (AB of ABX, J_{AB} = 12.9, J_{AX} = 7.8, J_{BX} = 8.0 Hz, 2 H, CH_2N), 4.20 (t, J = 5.0 Hz, 1 H, 1/4-H), 4.43 (t, J = 5.2 Hz, 1 H, 4/1-H), 7.25 (m, 5 H, C_6H_5), 7.99 (br s, D_2O exchangeable, 3 H, NH_3^+).

MS (CI, NH_3): m/z = 218 (MH^+ for free base).

$C_{14}H_{19}NO \cdot HCl$	calc.	C 66.26	H 7.94	N 5.52
(253.7)	found	66.25	7.73	5.62

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