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Spiro(Pyrrolidinyl-2,3'-Benzodiazepines) Related to MK-329

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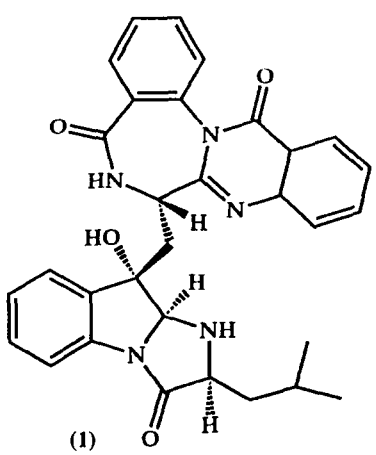
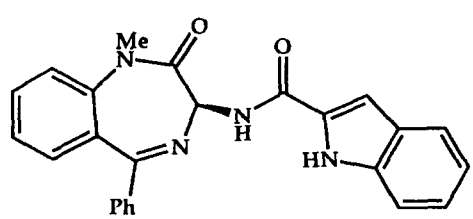
Abstract: Imines of 1-methyl-3-amino-1,3-dihydro-5-phenyl-(2H)-1,4-benzodiazepine-2-one undergo thermal (toluene, 110°C) or LiBr-DBU catalysed (MeCN, room temperature) regio- and stereo-specific cycloaddition to a range of achiral and chiral dipolarophiles giving racemic and homochiral spiro (pyrrolidinyl-2,3'-benzodiazepine) cycloadducts respectively in excellent yield. The reactions proceed via intermediate NH azomethine ylides and litho azomethine ylides respectively. Copyright © 1996 Elsevier Science Ltd

The isolation from *Aspergillus alliaceus* of asperlicin **1** a potent non-peptide cholecystokinin (CCK) antagonist selective for peripheral tissues[1] initiated studies which led to the discovery of a benzodiazapine series of non-peptide CCK receptor antagonists such as the selective CCK_A antagonist MK-329 **2**[2] and the selective CCK_B antagonists L-365,260 **3**[3] and YM022 **4**[4].

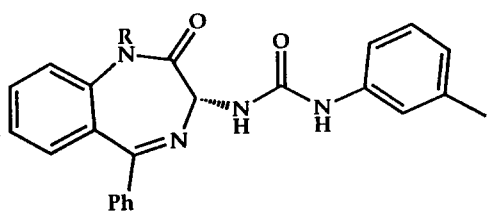


(1)

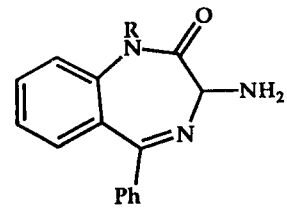


(2) MK-329

A substantial amount of novel chemistry,[5,6] mainly targeted at the gastrin/CCK_B receptor, has been developed from the parent 3-amino-1,3-dihydro-5-phenyl-(2H)-1,4-benzodiazepin-2-one **5**[7] as part of CCK antagonist drug development programmes. Recent reports have disclosed studies of dual histamine H_2 - gastrin receptor antagonists which also incorporate **5**.[8] Our thermal[9] and metal catalysed[10] imine→azomethine

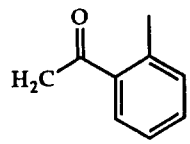


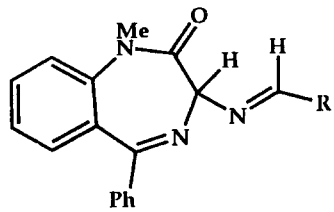
(3) R = Me L-365,260

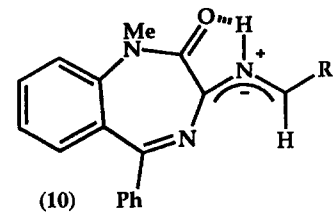


(5) R = H

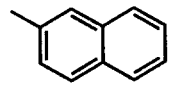
(6) R = Me L-655,848

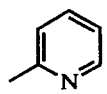
(4) R =  YM022

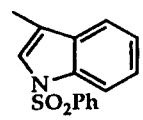


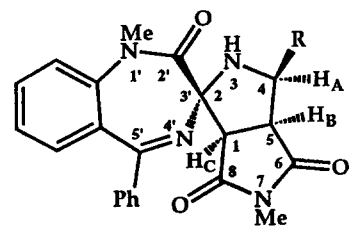


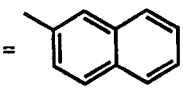
(10)

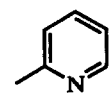
7. R = 

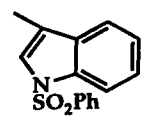
8. R = 

9. R = 



11. R =  82%

12. R =  84%

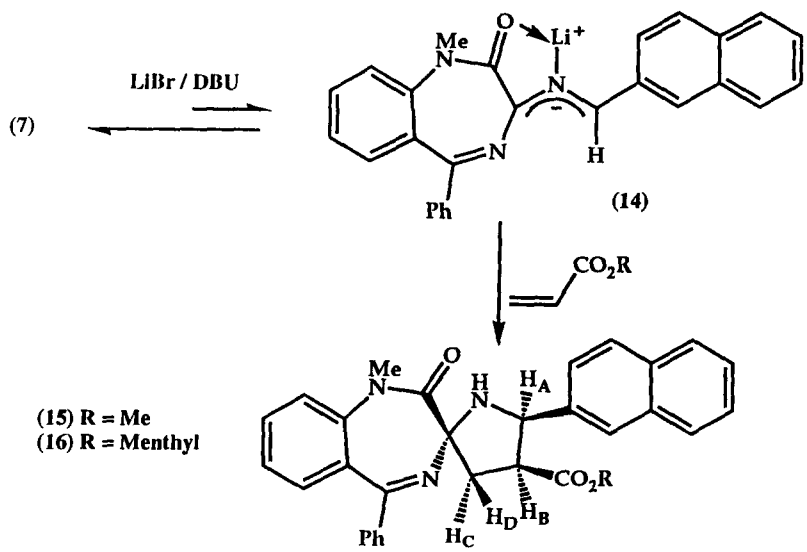
13. R =  89%

Scheme 1

ylide→cycloaddition cascade chemistry has provided a series of unusual conformationally restricted cephalosporin analogues[11] and potentially offers a facile route to conformationally restricted analogues of **2-4**. To explore this possibility a series of imines **7-9** was prepared from **6** which was liberated from its *p*-toluene sulphonic acid salt by treatment with ammonium hydroxide and extraction into dichloromethane.

When the imines **7-9** were boiled under reflux in toluene in the presence of *N*-methylmaleimide cycloaddition occurred stereospecifically to afford the cycloadducts **11-13** in 82-89% yield. During these cycloadditions a purple colour developed and then largely discharged. This colour is ascribed to the resonance stabilised 1,3-dipole **10**. The cis- stereochemistry of H_A, H_B and H_C was readily established from n.O.e. data and conforms to that expected,[9,10] whilst the C2-stereochemistry is assigned on the basis of previous studies[9,10] and an X-ray crystal structure of an analogue *(vide infra)*. The formation of single stereoisomers in these kinetically controlled cycloadditions indicates stereospecific formation of a single dipole **10** (Scheme 1) via 1,2-prototropy.

A series of room temperature, lithium bromide catalysed, cascade cycloaddition reactions of **7-9** was carried out with achiral and chiral dipolarophiles. Thus imine **7** reacted regio- and stereo-specifically with methyl acrylate under the influence of lithium bromide and DBU in acetonitrile over 3.5h to give a single cycloadduct **15** in 78% yield (Scheme 2).

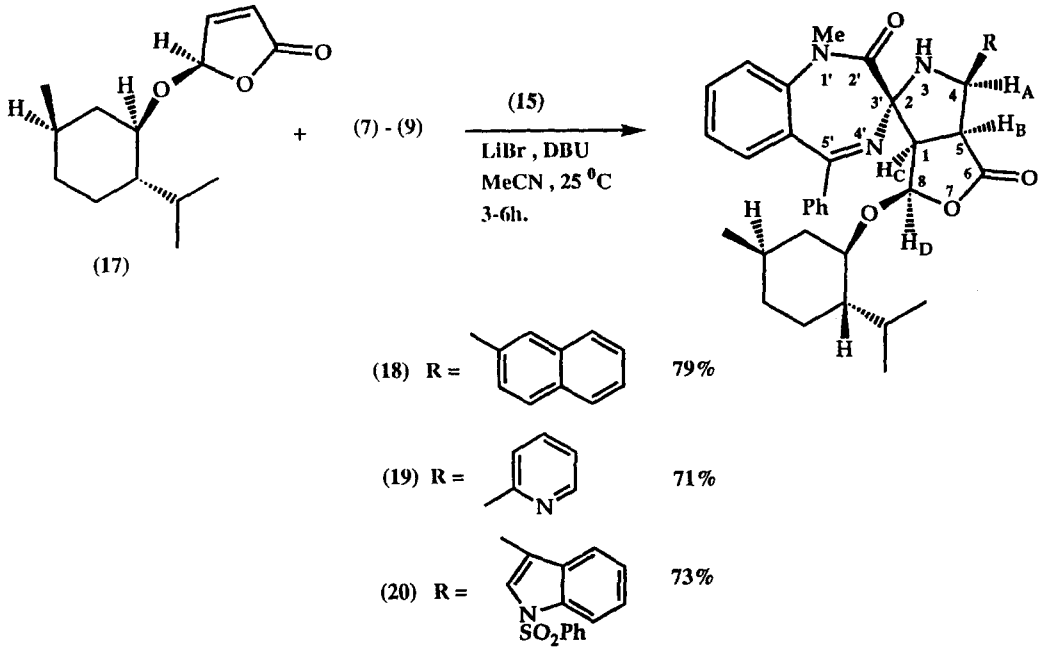


Scheme 2

When **7** was reacted with menthyl acrylate [from (+)-menthol] under the same conditions reaction occurred over 4h to yield a single homochiral cycloadduct **16**, $[\alpha]_D$+60°, in 58% yield. By analogy with our previous studies these cycloadditions are believed to proceed via the litho azomethine ylide **14** (Scheme 2).[10] In these reactions a purple colour develops immediately the imine is contacted with LiBr-DBU and this colour discharges as the reaction proceeds. This colour is believed to arise from the lithio dipole **14**. The

stereochemistry of **15** and **16** was assigned on the basis of n.O.e. data and the X-ray crystal structure of an analogue (vide infra).

A second series of cycloadducts was prepared from imines **7-9** and the chiral dipolarophile (R)-5(1R)-menthyloxy-2-(5H)-furanone **17**.



Reaction of **7-9** with **17** occurred over 3-6h at room temperature in acetonitrile using lithium bromide - DBU as the catalyst. Cycloadducts **18-20** were obtained in 71-79% yield. The stereochemistry of **18-20** was established by a single crystal X-ray structure of **18** (Fig. 1, see experimental) and by n.O.e. data for **19** and **20.** As expected the litho azomethine ylide adds to the face of the dipolarophile **17** trans to the *O*-menthyl group.[12]

Experimental Section

Melting points were determined on a Koffler hot-stage apparatus and are uncorrected. Mass spectral data were obtained from a V.G. Autospec instrument operating at 70 eV. Nuclear magnetic resonance spectra were recorded on QE300 and Bruker AM400 instruments operating at 300 and 400 MHz respectively. Unless otherwise specified deuteriochloroform was used as solvent. Microanalyses were obtained using a Carlo Erba MOD 11016 instrument. Optical rotations were determined on an Optical Activity Ltd., AA1000 polarimeter. Petroleum ether refers to the fraction with b.p. 60-80°C. (R)-5(1R)-Menthyloxy-2(5H)-furanone was purchased from Aldrich and used as received.

General Procedure for Imine Formation A mixture of aldehyde (1eq), amine (1.05eq) and activated 4Å molecular sieves in dry dichloromethane was stirred either at room temperature for **7** and **8** or 40°C for **9** for 3h [**7** and **8**] or 7h (**9**). After filtration to remove the molecular sieves the solvent was evaporated under

reduced pressure (bath temperature not higher than 30°C) and the residue was crystallised from an appropriate solvent.

N-(2'-Naphthylmethylidene)-1-methyl-3-amino-1,3-dihydro-5-phenyl-(2H)-1,4-benzodiazepine-2-one(7). The **product** (86%) crystallised from ether-petroleum ether as colourless prisms, m.p. 179-181°C (Found: C, 78.6; H, 5.25; N, 9.9. $C_{27}H_{21}N_3O$. $0.5H_2O$ requires C, 78.6; H, 5.55; N, 10.18%); m/z (%) 404(M+1, 100), 266(40), 249(49), 221(53) and 141(9); δ 9.39(s, 1H, CH=N), 8.4-7.19(m, 16H, ArH), 5.48(s, 1H, CHN) and 3.45(s, 3H, NMe).

N-(2'-Pyridylmethylidene)-1-methyl-3-amino-1,3-dihydro-5-phenyl-(2H)-1,4-benzodiazepine-2-one(8). The **product** (82%) precipitated from ether-petroleum ether as a pale yellow amorphous solid, m.p. 97-99°C (Found: C, 72.45; H, 4.95; N, 15.4. $C_{22}H_{18}N_4O$. $0.5H_2O$ requires C, 72.7; H, 4.95; N, 15.4%); m/z(%) 354(M^+,3), 265(36), 235(89), 222(65), 194(74), 122(68), 79(99) and 52(100); δ 9.35(s, 1H, CH=N), 8.7 and 8.31 (2xd, 2x1H, pyridine-H), 7.82-7.21(m, 11H, ArH), 5.5(s, 1H, CHN) and 3.49(s, 3H, NMe).

N-[3'-(N-phenylsulphonyl)-indolylmethylidene]-1-methyl-3-amino-1,3-dihydro-5-phenyl-(2H)-1,4-benzodiazepine-2-one(9). The **product** (79%) crystallised from ether-ethanol as colourless prisms, m.p. 212-214°C (Found: C, 69.8; H, 4.4; N, 10.4, S, 6.1. $C_{31}H_{24}N_4O_3S$ requires C, 69.9; H, 4.55; N, 10.5, S, 6.0%); m/z(%) (FAB) 593(M+1, 100), 393(8) 286(8), 266(38), 249(80), 221(6), 237(21), 193(11) and 77(15); δ 9.39(s, 1H, CH=N), 8.81(d, 1H, ArH), 8.03(s, 1H, indole-H), 8.02-7.21(m, 17H, ArH), 5.51(s, 1H, CHN) and 3.48(s, 3H, NMe).

General Procedure for Thermal Cycloaddition. A solution of imine (1mmol) and *N*-methylmaleimide (1mmol) in dry degassed toluene (30ml) was boiled under reflux under a nitrogen atmosphere for 9-16h. The solvent was then evaporated under reduced pressure and the residue crystallised from an appropriate solvent.

Spiro[2,3'-(1'methyl-1',3'-dihydro-2'-oxo-5'-phenyl-(2'H)-1',4'-benzodiazepinyl]-4-(2'-naphthyl)-3,7-diaza-6,8-dioxobicyclo[3.3.0]octane(11). After a reaction time of 9h and work up the **product** (82%) crystallised from dichloromethane as colourless prisms, m.p. 196-198°C (Found: C, 72.0; H, 5.1; N, 10.4. $C_{32}H_{26}N_4O_3$. $1.0\ H_2O$ requires C, 72.15; H, 5.25; N, 10.5%); m/z(%) (FAB): 514(M^+, 51), 513(100), 497(22), 237(93), 221(14) and 165(13); δ 8.01-7.2(m, 16H, ArH), 5.3(d, 1H, J 8.8Hz, H_A), 3.62(s, 3H, NMe), 3.44(br, 1H, NH), 2.25(dd, 1H, J 8.8 and 7.5Hz, H_B), 2.74(s, 3H, NMe) and 2.57(d, 1H, J 7.3 Hz., H_C). The stereochemistry was assigned from n.O.e. data (see below for a typical data set).

Spiro[2,3'-(1'-methyl-1',3'-dihydro-2'-oxo-5'-phenyl-(2'H)-1',4'-benzodiazepinyl)]-4-(2'-pyridyl)-3,7-diaza-6,8-dioxobicyclo[3.3.0]octane(12). After a reaction time of 12h the **product** (84%) crystallised from ether-ethanol as colourless prisms, m.p. 204-206°C (Found: C ,68.8; H, 4.95; N, 14.5; $C_{27}H_{23}N_5O_3$. $0.25H_2O$ requires C, 68.9; H, 5.3; N, 14.9%); m/z(%) 466(M+1, 11), 465(36), 447(100), 432(70), 375(30), 361(82), 237(98), 195(70), 165(51), 132(24), 78(31) and 51(13); δ 8.63(d, 1H, pyridine-H), 7.73-7.20(m, 12H, ArH), 5.2. (dd, 1H, J 8.6 and 3.6Hz., H_A), 3.59(s, 3H, NMe), 3.51(br, 1H, NH), 3.36(t, 1H, J 8.4, Hz, H_B), 2.76(s, 3H, NMe) and 2.59(d, 1H, J 7.4Hz, H_C). N.O.e. data:

Signal			Enhancement(%)		
irradiated	H_A	H_B	H_C	NH	ArH
H_A		15.2		3.4	4.4
H_B	14.3		16.2		
H_C		13.7			
NH	10.8				6.5

Spiro[2,3'-(1'-methyl-1',3'-dihydro-2'-oxo-5'-phenyl-(2'H)-1',4'-benzodiazepinyl]-4-(N'-phenylsulphonyl)-indolyl]-3,7-diaza-6,8-dioxobicyclo[3.3.0]octane(13). After a reaction time of 16h the **product** (89%) precipitated from ether-ethanol as a pale pink amorphous solid, m.p. 218-220°C (Found: C, 65.25; H, 4.25; N, 10.5. $C_{36}H_{29}N_5O_5S$. 1.0 H_2O requires C, 65.35; H, 4.7; N, 10.6%); m/z(%) 644(M+1, 39), 626(10), 532(12), 502(13), 387(18), 237(100), 222(10), 194(11) and 77(8); δ 8.0-7.18(m, 19H, ArH), 5.31(dd, 1H, J 8.6 and 2.2 Hz, H_A), 3.60(s, 3H, NMe), 3.30(br, 1H, NH), 3.23(t, 1H, J 8.0 Hz, H_B), 2.68(s, 3H, NMe), 2.57(d, 1H, J 6.1 Hz, H_C).

General Procedure for the Lithium Bromide Catalysed Cycloaddition Reactions. A mixture of the imine (1eq), DBU(1.1eq), dipolarophile (1eq) and LiBr (1.5eq) in freshly distilled acetonitrile was stirred at room temperature under an atmosphere of N_2 until reaction was complete. The reaction was then quenched by addition of saturated aqueous ammonium chloride solution and the mixture extracted with methylene chloride (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and the solvent evaporated. The residue was crystallised from an appropriate solvent.

Spiro[2,3'-(1'-methyl-1',3'-dihydro-2'-oxo-5'-phenyl-(2'H)-1',4'-benzodiazepinyl]-4-carbomethoxy-5-(2'-naphthyl)pyrrolidine(15). After a reaction time of 3.5h and work up the **product** (78%) precipitated from dichloromethane-ethanol as a colourless amorphous solid, m.p. 108-110°C (Found: C, 75.2; H, 5.4; N, 8.3. $C_{31}H_{27}N_3O_3$. 0.25 H_2O requires C, 75.35; H, 5.45; N, 8.5%); HRMS: 489.2047. $C_{31}H_{27}N_3O_3$ requires 489.2052. m/z(%) 489(M^+, 6), 476(56), 413(51), 394(65), 336(23), 261(25), 235(35), 222(43), 194(100), 165(39), 152(50), 127(43) and 91(34); δ 7.94-7.15(m, 16H, ArH), 5.13(t, 1H, J 7.0Hz, H_A), 4.41(br d, 1H, J 6.9 Hz, NH), 3.61(s, 3H, NMe), 3.28(m, 1H, H_B), 3.05(s, 3H, CO_2Me), 2.21 and 2.18(dd, 1H, J 5.3 and 13.8Hz, H_D) and 1.56 and 1.52(dd, 1H, J 7.7 and 13.8Hz, H_C). N.O.e. data:

Signal			Enhancement(%)			
irradiated	H_C	H_D	H_B	H_A	NH	ArH
H_C		19.2	8.3	1.6		
H_D	23.4		3.0			
H_B				10.4		
H_A			13.4			7.6
NH				5.8		10.4

Spiro[2,3'-(1'-methyl-1',3'-dihydro-2'-oxo-5'-phenyl-(2'H)-1',4'-benzodiazepinyl)]-4-(1'S, 2'R, 5'S-menthyloxycarbonyl-5-(2'-naphthyl)pyrrolidine(16). After a reaction time of 4h the **product** (58%) was obtained a colourless amorphous solid on precipitation from ether-ethanol, m.p. 96-98°C, $[\alpha]_D$+60 (0.5g/100ml $CHCl_3$). HRMS: 613.3304. $C_{40}H_{43}N_3O_3$ requires 613.3297. m/z(%) (FAB) 614(M+1, 66), 596(28), 458(6), 363(6), 237(100), 221(15), 194(20), 153(36), 83(27) and 69(10); δ 8.38-7.09(m, 16H, ArH), 5.08(d, 1H, J 7.6Hz, H_A), 4.46(d, 1H, J 9.1Hz, NH), 4.14(m, 1H, menthyl-CHO), 3.57(s, 3H, NMe), 3.25(m, 1H, H_B), 2.17(dd, 1H, J 13.9 and 4.0 Hz, H_D), 1.55(m, 4H, H_C and menthyl-H), 1.36(m, 3H, menthyl-H), 0.49(m, 2H, menthyl-H), 0.60(d, 3H, J 6.9 Hz, CHMe), 0.37 and 0.21(2xd, 6H, J 6.6Hz, CH<u>Me</u>$_2$) and -0.35(m, 1H, menthyl-H). N.O.e. data:

Signal		Enhancement(%)		
irradiated	H_A	H_B	H_C	ArH
H_A		10.9		5.2
H_B	11.2		2.9	
H_D		2.6	15.7	

Cycloadduct(18). Reaction time 4h. The **product** (79%) crystallised from dichloromethane-hexane-ether as colourless needles, m.p. 224-226°C, $[\alpha]_D$-300(0.5g/100ml, $CHCl_3$). (Found: C, 76.7; H, 6.85; N, 6.6. $C_{41}H_{43}N_3O_4$ requires C, 76.7; H, 6.75; N, 6.55%); m/z(%) (FAB) 642(M+1,5), 641(12), 623(86), 440(20), 424(80), 412(100), 237(38), 221(24), 206(41), 194(31), 165(30), 83(29), 69(21), 55(35) and 43(22); δ 8.09(s, 1H, ArH), 7.88-7.16(m, 15H, ArH), 5.53(d, 1H, J 3.9Hz, H_D), 5.25(dd, 1H, J 2.8 and 9.0Hz, H_A). 3.56(s, 3H, NMe), 3.37(m, 2H, menthyl-CHO and NH), 3.25(t, 1H, J 8.7Hz, H_B), 2.21(m, 2H, H_C and menthyl-H), 1.71(m, 3H, menthyl-H), 1.58 and 1.38(2xm, 2x2H, menthyl-H), 1.03(d, 3H, J 6.5Hz, Me), 0.95(m, 1H, menthyl-H), and 0.55 and 0.74(2xd, 6H, J 7.0Hz, CH<u>Me</u>$_2$). The X-ray crystal structure of this compound is shown in figure 1 and further X-ray data are given below.

Cycloadduct(19). Reaction time 5h. The **product** (71%) crystallised from dichloromethane-hexane-ethanol as colourless prisms, m.p. 154-156°C, $[\alpha]_D$ -212(0.3g/100ml, $CHCl_3$). HRMS: 592.3030. $C_{36}H_{40}N_4O_4$ requires 592.3050. m/z(%) (FAB) 593(M+ 1, 100), 575(14), 437(10), 393(5), 264(10), 237(41), 211(11), 83(24) and 69(31); δ 8.61(d, 1H, pyridine-H), 7.71-7.20(m, 12H, ArH), 5.43(d, 1H, J 3.4Hz, H_D), 5.24(dd, 1H, J 8.8 and 3.5Hz, H_A), 3.54(s, 3H, NMe), 3.53(br, 1H, NH), 3.65(m, 2H, menthyl-CHO and H_B), 2.22(d, 1H, J 6.5Hz, H_C). 2.14(m, 1H, menthyl-H), 1.71-1.56(m, 3H, menthyl-H), 1.35-1.17(m, 2H, menthyl-H), 0.84(m, 3H, menthyl-H), 1.01(d, 3H, J 6.4Hz, CH<u>Me</u>), and 0.55 and 0.74(2xd, 6H, J 6.9Hz, CH<u>Me</u>$_2$).

Cycloadduct(20). Reaction time 6h. The **product** (73%) crystallised from ethanol as colourless prisms, m.p. 172-174°C, $[\alpha]_D$ -225(0.5g/100ml, $CHCl_3$). (Found: C, 69.6; H, 6.05; N, 7.0. $C_{45}H_{46}N_4O_6S$ requires C, 70.1; H, 6.0; N, 7.25%); m/z(%) (FAB) 771(M+1, 26), 753(34), 611(18), 532(8), 399(9), 264(27), 237(100), 211(28), 194(18) and 83(22); δ 7.93-7.22(m, 19H, ArH), 5.43(d, 1H, J 3.3Hz, H_D), 5.28(d, 1H, J 6.2Hz, H_A), 3.56(s, 3H, NMe), 3.42(br, 1H, NH), 3.29(m, 2H, menthyl-CHO and H_B), 2.19(m, 2H, H_C and menthyl-H), 1.66(m, 5H, menthyl-H), 1.04(d, 3H, J 6.3Hz, CH<u>Me</u>), 0.83(m, 3H, menthyl-H), and 0.55 and 0.74(2xd, 6H, J 6.9Hz, CH<u>Me</u>$_2$).

N O.e. data:

Signal				Enhancement(%)		
irradiated	H_A	H_B	H_C	H_D	Menthyl-CHO	Indole-H
H_A		16.0				10.8
H_B	16.2		7.2			
H_C		3.3		2.2		
H_D					8.2	
Menthyl-CHO				9.9		
NH	11.2					7.8

Single crystal X-ray diffraction analysis of ***18***- All crystallographic measurements were carried out at 200K on a Stoe STADI4 diffractometer using graphite monochromated Copper K_α X-radiation (λ = 1.54184 Å). Two equivalent sets of data were collected in the range $4.0° < 2\theta < 130.0°$ using ω-θ scans. No significant variation was observed in the intensities of three standard reflections measured every hour during data collection. The data-set was corrected for Lorentz and polarisation effects but not for absorption. The structure was solved by direct methods using SHELXS-86[13] and was refined by full-matrix least-squares (based on F^2) using SHELXL-93[14] which uses all data in refinement. The weighting scheme was $w = [\sigma^2(F_o^2) + (0.0509P)^2 + 0.2988P]^{-1}$ where $P=(F_o^2 + 2F_c^2)/3$. Non-hydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms were constrained to predicted positions. The absolute configuration of **18** was initially based on the known configuration of the (-)-menthyl group but was later confirmed by refinement of a 'Flack' enantiopole parameter[15] to 0.1(2). The residuals wR_2 and R_1, given below, are defined as $wR_2=(\Sigma[w(F_O-F_C^2)^2] / \Sigma[wF_O^4])^{1/2}$ and $R_1=\Sigma||F_o|-|F_c|| / \Sigma|F_o|$. The latter, given for comparison with refinements based on F, uses reflections with $F_o > 4.0\ \sigma(F_o)$.

Crystal data - $C_{41}H_{43}N_3O_4$, 0.45 x 0.30 x 0.15 mm, M = 464.51, orthorhombic, space group $P2_12_12_1$, a = 10.8738(4), b = 16.4459(5), c = 19.7271(3) Å, U = 3527.8(2) Å^3, Z = 4, D_x = 1.208 Mg m^{-3}, μ = 0.618 mm^{-1}, $F(000)$ = 1368.

Data collection - Scan speeds 1.5 - 8.0° min^{-1}, ω scan widths 1.05° + α-doublet splitting, $4.0 < 2\theta < 130.0°$, 6097 Data collected 5413 of which were unique, R_{int}=0.0192, R_{sig} = 0.0385. There were 4569 reflections with $F_o > 4.0\ \sigma(F_o)$.

Structure refinement - Number of parameters = 437, goodness of fit s = 1.021, wR_2 = 0.0954, R_1 = 0.0375, maximum Δ/σ = 0.048.

Non-hydrogen atomic co-ordinates are listed in Table 1. Selected bond lengths and angles are listed in Table 2. Supplementary data have been deposited at the Cambridge Crystallographic Data Centre which include hydrogen co-ordinates and all thermal parameters together with complete bond lengths and angles and are available on request.

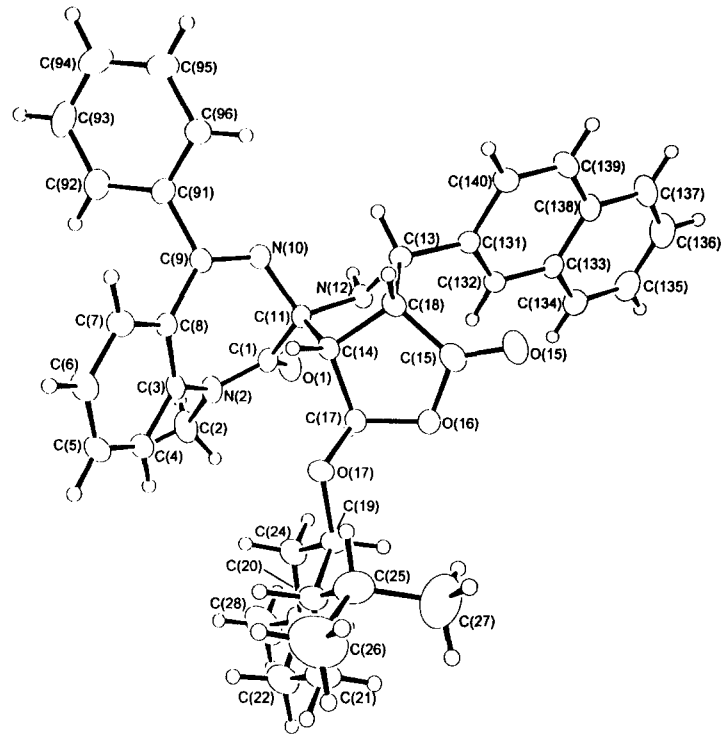


Figure 1. Molecular structure of compound **18**. Ellipsoids are shown at the 40% probability level and, in the interests of clarity, hydrogen atoms are drawn as circles with a small arbitary radius.

Table 1. Non-hydrogen atom co-ordinates (x 10^4) and equivalent isotropic thermal parameters ($Å^2$ x 10^3) for **18** with estimated standard deviations (e.s.d.'s) in parentheses.

Atom	x	y	z	U_{eq}*
C(1)	10063(2)	8785.3(14)	7525.9(12)	30.6(5)
O(1)	9346(2)	8364.9(11)	7198.9(8)	43.2(4)
N(2)	10431(2)	9526.2(12)	7289.5(9)	34.2(5)
C(2)	9872(3)	9787(2)	6637.6(13)	48.4(7)
C(3)	11275(2)	10060.5(13)	7615.9(11)	30.5(5)
C(4)	11035(2)	10895.9(14)	7599.5(13)	37.8(6)
C(5)	11840(2)	11451.6(14)	7876.6(14)	41.1(6)
C(6)	12929(2)	11185.4(14)	8171.9(13)	40.3(6)
C(7)	13184(2)	10363.5(14)	8191.3(13)	34.8(5)
C(8)	12367(2)	9788.3(13)	7924.6(11)	29.0(5)
N(10)	11930(2)	8326.4(11)	8106.3(9)	28.1(4)
C(9)	12688(2)	8911.9(13)	7987.9(11)	27.9(5)
C(91)	14026(2)	8686.9(13)	7949.7(11)	29.8(5)
C(92)	14777(2)	8957.2(15)	7424.5(13)	41.2(6)

C(93)	16011(3)	8709(2)	7396.5(15)	49.2(7)
C(94)	16483(3)	8218(2)	7903.0(15)	48.3(7)
C(95)	15749(2)	7965.7(15)	8429.0(14)	44.3(7)
C(96)	14516(2)	8183.5(14)	8451.2(12)	34.8(6)
C(11)	10611(2)	8477.7(13)	8202.6(11)	26.2(5)
N(12)	9984(2)	7719.2(11)	8370.2(10)	28.2(4)
C(13)	10419(2)	7485.0(12)	9051.5(10)	26.5(5)
C(131)	9706(2)	6771.2(13)	9332.1(10)	26.5(5)
C(132)	8532(2)	6597.1(13)	9119.3(11)	29.2(5)
C(133)	7885(2)	5896.8(13)	9355.9(11)	29.7(5)
C(134)	6695(2)	5687.7(15)	9115.0(13)	38.8(6)
C(135)	6114(3)	5003(2)	9343.8(14)	47.0(7)
C(136)	6706(3)	4483(2)	9807.2(15)	51.4(7)
C(137)	7861(3)	4660(2)	10042.1(13)	45.1(7)
C(138)	8482(2)	5377.0(14)	9830.4(11)	34.1(6)
C(139)	9684(2)	5578.5(14)	10052.4(12)	36.4(6)
C(140)	10282(2)	6247.3(13)	9809.4(11)	32.4(5)
C(14)	10329(2)	8968.0(12)	8863.8(10)	24.9(5)
C(18)	10318(2)	8319.6(12)	9432.8(11)	28.2(5)
C(15)	9113(3)	8442.5(14)	9798.8(12)	37.4(6)
O(15)	8758(2)	8126.2(11)	10312.7(9)	56.2(6)
O(16)	8398(2)	8988.6(10)	9462.1(9)	41.2(4)
C(17)	9026(2)	9322.5(13)	8868.8(11)	28.6(5)
O(17)	9074.5(14)	10159.8(9)	8925.8(8)	31.5(4)
C(19)	7911(2)	10574.7(14)	8801.4(13)	34.5(6)
C(20)	7990(2)	11416.3(14)	9128.4(14)	41.7(6)
C(21)	6791(3)	11879(2)	8966(2)	60.0(9)
C(22)	6538(3)	11927(2)	8201(2)	61.9(9)
C(23)	6485(3)	11096(2)	7871(2)	53.2(8)
C(24)	7667(2)	10631(2)	8040.0(13)	40.9(6)
C(25)	8327(3)	11388(2)	9893(2)	54.5(8)
C(26)	8677(5)	12232(2)	10162(2)	100.8(15)
C(27)	7347(4)	10996(3)	10337(2)	85.7(12)
C(28)	6286(3)	11141(2)	7104(2)	79.8(12)

*U_{eq} = $^1/_3$ x trace of the orthogonalised U_{ij} matrix

Table 2. Selected interatomic distances (Å) and angles between interatomic vectors (°) for **18** with e.s.d.s in parentheses with e.s.d.s in parentheses.

C(1)-O(1)	1.225(3)	C(1)-N(2)	1.365(3)
C(1)-C(11)	1.547(3)	N(2)-C(3)	1.424(3)
N(2)-C(2)	1.486(3)	C(3)-C(4)	1.399(3)
C(3)-C(8)	1.408(3)	C(4)-C(5)	1.378(4)
C(5)-C(6)	1.390(4)	C(6)-C(7)	1.381(3)
C(7)-C(8)	1.400(3)	C(8)-C(9)	1.488(3)
N(10)-C(9)	1.289(3)	N(10)-C(11)	1.469(3)
C(9)-C(91)	1.502(3)	C(11)-N(12)	1.460(3)
C(11)-C(14)	1.564(3)	N(12)-C(13)	1.476(3)
C(13)-C(131)	1.512(3)	C(13)-C(18)	1.569(3)

C(139)-C(140)	1.364(3)	C(14)-C(17)	1.532(3)
C(14)-C(18)	1.548(3)	C(18)-C(15)	1.510(3)
C(15)-O(15)	1.203(3)	C(15)-O(16)	1.361(3)
O(16)-C(17)	1.462(3)	C(17)-O(17)	1.383(3)
O(17)-C(19)	1.458(3)	C(19)-C(24)	1.528(3)
C(19)-C(20)	1.529(3)	C(20)-C(21)	1.543(4)
C(20)-C(25)	1.553(4)	C(21)-C(22)	1.537(5)
C(22)-C(23)	1.514(4)	C(23)-C(28)	1.531(4)
C(23)-C(24)	1.532(4)	C(25)-C(27)	1.522(5)
C(25)-C(26)	1.535(4)		
O(1)-C(1)-N(2)	120.7(2)	O(1)-C(1)-C(11)	121.0(2)
N(2)-C(1)-C(11)	118.3(2)	C(1)-N(2)-C(3)	125.8(2)
C(1)-N(2)-C(2)	115.7(2)	C(3)-N(2)-C(2)	118.5(2)
C(4)-C(3)-C(8)	118.6(2)	C(4)-C(3)-N(2)	118.4(2)
C(8)-C(3)-N(2)	122.9(2)	C(5)-C(4)-C(3)	121.6(2)
C(4)-C(5)-C(6)	119.9(2)	C(7)-C(6)-C(5)	119.4(2)
C(6)-C(7)-C(8)	121.5(2)	C(7)-C(8)-C(3)	118.9(2)
C(7)-C(8)-C(9)	118.3(2)	C(3)-C(8)-C(9)	122.8(2)
C(9)-N(10)-C(11)	121.4(2)	N(10)-C(9)-C(8)	126.1(2)
N(10)-C(9)-C(91)	116.4(2)	C(8)-C(9)-C(91)	117.5(2)
N(12)-C(11)-N(10)	109.9(2)	N(12)-C(11)-C(1)	107.2(2)
N(10)-C(11)-C(1)	108.7(2)	N(12)-C(11)-C(14)	99.2(2)
N(10)-C(11)-C(14)	112.8(2)	C(1)-C(11)-C(14)	118.4(2)
C(11)-N(12)-C(13)	106.2(2)	N(12)-C(13)-C(131)	111.8(2)
N(12)-C(13)-C(18)	100.7(2)	C(131)-C(13)-C(18)	117.9(2)
C(17)-C(14)-C(18)	104.5(2)	C(17)-C(14)-C(11)	112.5(2)
C(18)-C(14)-C(11)	104.5(2)	C(15)-C(18)-C(14)	105.1(2)
C(15)-C(18)-C(13)	114.0(2)	C(14)-C(18)-C(13)	104.7(2)
O(15)-C(15)-O(16)	120.9(2)	O(15)-C(15)-C(18)	128.6(2)
O(16)-C(15)-C(18)	110.5(2)	C(15)-O(16)-C(17)	111.9(2)
O(17)-C(17)-O(16)	109.1(2)	O(17)-C(17)-C(14)	110.1(2)
O(16)-C(17)-C(14)	107.1(2)	C(17)-O(17)-C(19)	114.8(2)
O(17)-C(19)-C(24)	110.1(2)	O(17)-C(19)-C(20)	107.7(2)
C(24)-C(19)-C(20)	111.7(2)	C(19)-C(20)-C(21)	108.2(2)
C(19)-C(20)-C(25)	113.3(2)	C(21)-C(20)-C(25)	114.6(2)
C(22)-C(21)-C(20)	112.4(3)	C(23)-C(22)-C(21)	112.5(2)
C(22)-C(23)-C(28)	112.7(3)	C(22)-C(23)-C(24)	109.0(2)
C(28)-C(23)-C(24)	111.0(3)	C(19)-C(24)-C(23)	112.9(2)
C(27)-C(25)-C(26)	111.0(3)	C(27)-C(25)-C(20)	114.0(3)
C(26)-C(25)-C(20)	111,6(3)		

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