[4+2] CYCLOADDUCTS OF 5-BENZYLOXY-2-PYRIDONE WITH ELECTRON DEFICIENT DIENOPHILES. REGIO- AND STEREOCHEMISTRY [1].

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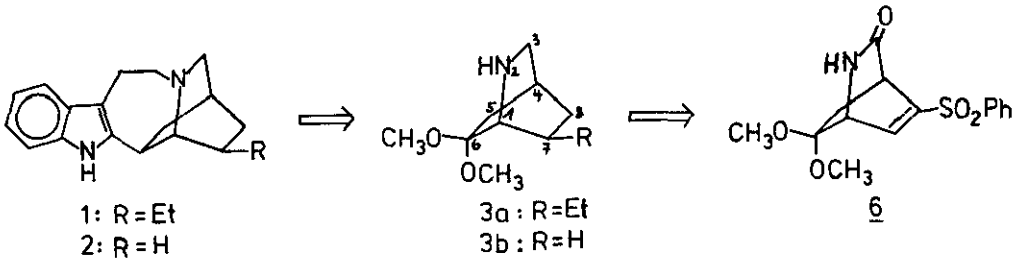
Abstract - The electron-rich 2-pyridone 4 is converted into the 2-azabicyclo[2.2.2]octane derivatives 8-12 via [4+2] cycloaddition. 10b is transformed to vinyl sulfone 6, an intermediate in a potential route to ibogamine 1. The regio- and stereochemistry of the cycloaddition reaction is reported.

Recently we reported a synthetic approach to the 2-azabicyclo[2.2.2]octan-6-one skeleton[2] 3b, an intermediate in the synthesis of desethylibogamine 2.



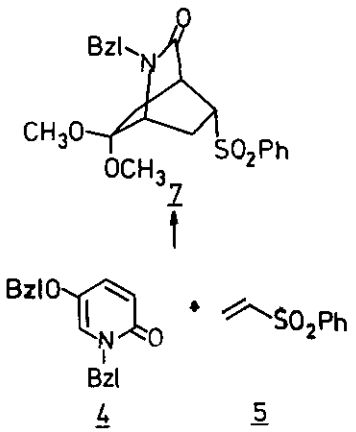
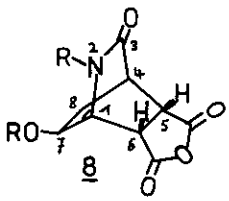
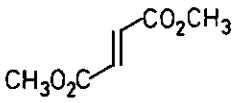
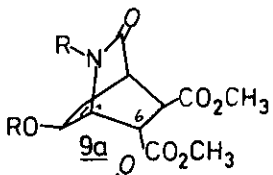
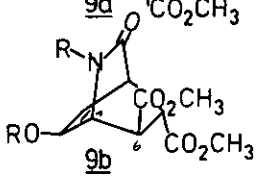
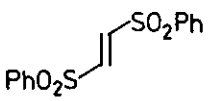
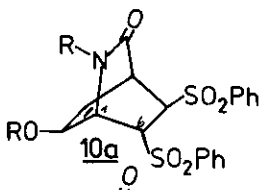
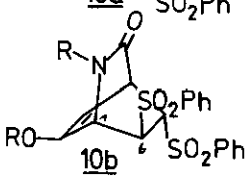
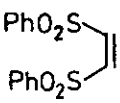
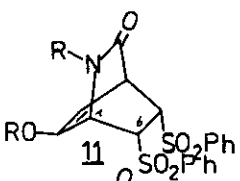
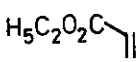
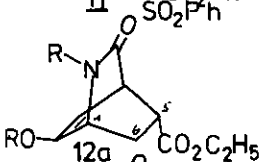
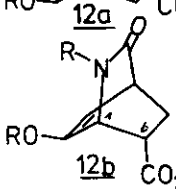


Table 1 Cycloaddition of 4 with different dienophiles

Dienophile	Product (R= CH_2Ph)	$H_1 - H_6$ (coupling const.(Hz))	Yield(%)
	 8	4.2	97
	 9a	3.5	58*
	 9b	1.9	4.6*
	 10a	3.1	8.3*
	 10b	1.8	87*
	 11	2.4	6.7*
	 12a	$1,6_{syn}$ 2.6 $1,6_{anti}$ 1	73*a
	 12b	3.4	3.6*a

*separated by flash chromatography

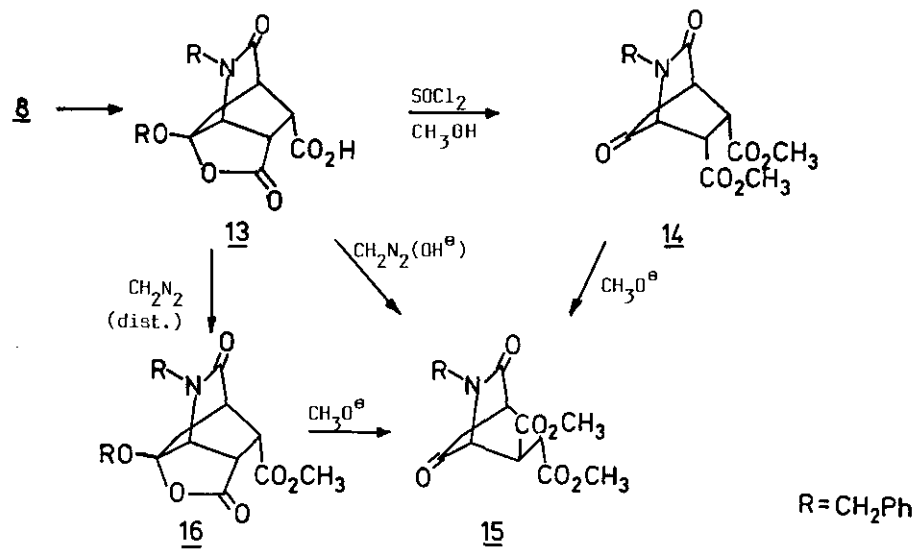
[a]heated in toluene in a sealed tube(150°C)

A variety of elegant strategies were successfully developed in the last years for the synthesis of ibogamine skeleton with 1,2-dihydropyridines. All of them use the Diels-Alder approach[3]. In view of pharmacological tests of compounds with the "iboga structure" we need intermediates with high synthetic flexibility.

With compound 7[2] we can introduce various substituents via the α-sulfonylcarbanion. Futhermore the vinyl sulfone[4] intermediate 6 serves as a substrate for 1,4-conjugate addition of nucleophiles and metallorganic reagents.

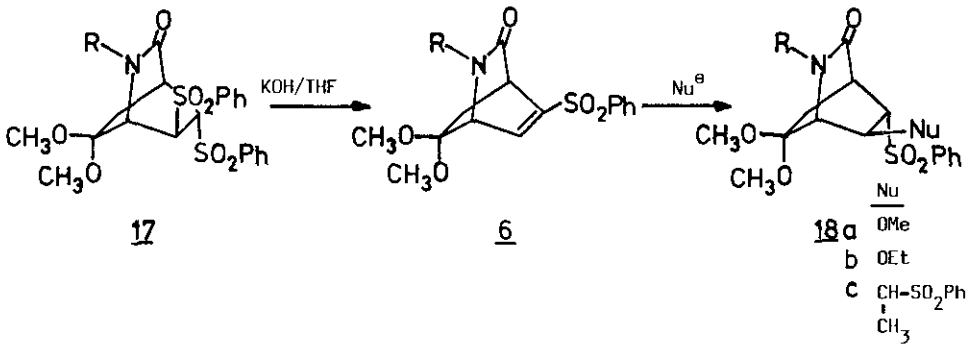
Here we want to show the regio- and stereochemistry of the cycloaddition reaction of 4 with electron-deficient olefins and some chemical transformations of the products. In contrary to 2-pyridone and alkyl substitued derivatives[5] 5-benzyl-oxy-2-pyridone reacts as an electron-rich diene in the Diels-Alder reaction[2]. This results in high yields of cycloaddition products. Even in the case of sterically demanding dienophiles one regioisomer is the main cycloaddition product. The benzyl enol ether function in the products can smoothly transformed to dimethyl ketals like e.g. 17. This ketal serves for C-C bond connection with the indole moiety in a later stage of the ibogamine synthesis[3]. The stereochemistry of the cycloaddition products can unambigously deduced from the 200 MHz ^{1}H-nmr spectra. Characteristicly the coupling constant of the bridgehead hydrogen H_1 to $H_{6,syn}$ is in the range 2.6 to 4.2 Hz, H_1 to $H_{6,\ anti}$ 1.0 to 1.9 Hz[7]. (Table 1)

Treatment of 8, first with dil. sodium hydroxide solution, then acidification, furnishes the tricyclic lactone 13 in quantitative yield[8].



The esterification of 13 with thionyl chloride in MeOH (-10 °C) produces the cis configurated ketone 14. Whereas treatment of 13 with diazomethane and traces of base gives the trans product 15[5c]. This product is identical with the hydrolysis product of 9b. With distilled ethereal diazomethane solution 13 is methylated quantitatively to 16.

Hydrolysis of the benzyl enol ether mojety in the cycloaddition products with acetic acid and 2N hydrochloric acid furnishes the ketones with retention of stereochemistry. This ketones can be transformed to the ketals with tosic acid and trimethyl orthoformate in nearly quantitative yield e.g. 10b → 17. The ketal of 9a is quantitavely transformed with $NaOCH_3$ in methanol to the thermodynamic more stable ketal of 9b. On the other hand we were very pleased to find that treatment of 17 with KOH/THF furnishes 6, the key intermediate in our retro synthetic plan.



Compound 6 adds a variety of hard and soft nucleophiles diastereospecific to 18. We assume that syn attack of the nucleophiles is the preferred way over anti, since there is a large 1,3 diaxial interaction between one of the methoxy substituents and the entering nucleophile. Reductive desulfonylation of 18c and transformation to 3a and 1 are currently underway.

EXPERIMENTAL

Infrared spectra were determined with a Perkin-Elmer Model 480. ^{1}H-Nmr spectra were run on a WP 200 Bruker model. Flash chromatography was done with silica gel Merck 60 (230-400 mesh). Thin-layer chromatography was performed on Merck silicagel 60 GF_{254} TLC plates of thickness 0.25 mm. Compound visualisation was effected with Iodine vapor. Elemental analyses were performed by the Micro-analytical Laboratory at the Chemistry Department of the University of Würzburg.

(±)-(5,6-anti)-2-Benzyl-7-benzyloxy-2-azabicyclo[2.2.2]oct-7-en-3-one-5,6-dicarbonic Acid Anhydride (8)

To a solution of 4 (5 mmol, 1.45 g) in toluene (50 ml) maleic anhydride (15 mmol, 1.47 g) was added. The mixture was refluxed for 6 h. After cooling to room temperature ether (20 ml) was added with stirring and the clear brownish solution was kept at -20 °C. The crude cycloaddition product was isolated by suction and washed with cold ether. Crystallisation from toluene gave 8 as colourless crystals (1.75g, 90%), mp 194 °C. Ir(KBr): 1870, 1780, 1685, 1642 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): (ppm) 3.44 (1H, dd, J=8.6, 4.2 Hz, H-5); 3.55 (1H, dd, J=8.6, 3.2 Hz, H-6); 3.89 (1H, dd, J=6.7, 3.2 Hz, H-4); 4.43 (1H, dd, J=4.2, 2.7 Hz, H-1); 4.42 (1H, d, J=14.7 Hz, N-CH_2); 4.55 (1H, d, J=14.7 Hz, N-CH_2); 4.66 (2H, s, OCH_2); 5.07 (1H, dd, J=6.7, 2.7 Hz, H-8); 7.14-7.36 (10H, m, $H_{arom.}$). Anal. Calcd for $C_{23}H_{19}NO_5$ (389.4): C,70.94; H, 4.92; N, 3.60. Found: C, 70.91; H, 5.10; N, 3.76.

(±)-(5-anti,6-syn)-Dimethyl-2-benzyl-7-benzyloxy-2-azabicyclo[2.2.2]oct-7-en-3-one-5,6-dicarboxylate(9a)
(±)-(5-syn,6-anti)-Dimethyl-2-benzyl-7-benzyloxy-2-azabicyclo[2.2.2]oct-7-en-3-one-5,6-dicarboxylate(9b)

A solution of 4 (5 mmol, 1.45 g) and dimethyl fumarate (8 mmol, 1.03 g) in toluene (50 ml) was refluxed for 6 days. The solvent was evaporated. Flash chromatography gave on elution with chloroform ethyl acetate (9+1) 9a (1.2 g, 58%) and 9b (0.096 g, 4.6%) as colourless solids upon titration with ether at -20 °C. 9a; mp 77 °C. Ir (KBr): 1745, 1730, 1675, 1648 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): (ppm) 3.32 (1H, dd, J=4.6, 2.8 Hz, H-6); 3.53 (1H, dd, J=4.6, 3.5 Hz, H-5); 3.60 (3H, s, OCH_3); 3.72 (1H, dd, J=7.1, 2.8 Hz, H-4); 3.75 (3H, s, OCH_3); 4.28 (1H, t, J=3.5 Hz, H, H-1); 4.48 (1H, d, J=15 Hz, NCH_2); 4.59 1H, d, J=15 Hz, NCH_2); 4.61 (1H, d, J=11Hz, OCH_2); 4.66 (1H, d, J=11 Hz, OCH_2); 5.14 (1H, dd, J=7.1, 2.8 Hz, H-8); 7.15-7.34 (10H, m, $H_{arom.}$). Anal. Calcd for $C_{25}H_{25}NO_6$ (435.5): C, 68.95; H, 5.79; N, 3.22. Found: C, 68.86; H 5.63; N, 3.16. 9b, mp. 157 °C. Ir(KBr): 1740, 1725, 1670, 1640 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): (ppm) 3.38 (1H, dd, J=5.0, 1.9 Hz, H-5); 3.51 (1H, dd, J=5.0, 2.4 Hz, H-6); 3.59 (3H, s, OCH_3); 3.71 (3H, s, OCH_3); 3.79 (1H, dd, J=6.6, 2.4 Hz, H-4); 4.07 (1H, d, J=14.8 Hz, NCH_2); 4.41 (1H, t, J=1.9 Hz, H-1); 4.61 (2H, s, OCH_3); 4.87 (1H, d, J=14.8 Hz, NCH_2); 4.92 (1H, dd, J= 6.6, 2.5 Hz, H-8); 7.11-7.36 (10H, m, $H_{arom.}$).

(±)-(5-syn,6-anti-2-Benzyl-7-benzyloxy-5,6-phenylsulfonyl-2-azabicyclo[2.2.2] oct-7-en-3-one (10a)

(±)-(5-anti,6-syn)-2-Benzyl-7-benzyloxy-5,6-phenylsulfonyl-2-azabicyclo 2.2.2 oct-7-en-3-one- (10b)

4 (10 mmol, 3.0 g) and E-1,2-bis(phenylsulfonyl)ethene (12 mmol, 3.6 g) were refluxed in toluene (80 ml) for 8 days. The solvent was evaporated to give a crystalline residue. Flash chromatography ($CHCl_3$/EtOAc 9+1) (see 9) gave 10b (5.4 g, 90%) and 10a (0.5 g, 8.3%). 10a, mp 199 °C. Ir(KBr): 1690, 1650, 1450 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): (ppm) 3.42 (1H, dd, J=7.3, 2.4 Hz, H-4); 3.84 (1H, dd, J=5.1, 2.4 Hz, H-5); 3.91 (1H, dd, J=5.1, 3.1 Hz, H-6); 4.05 (1H, t, J=2.1 Hz, H-1); 4.09 (1H, d, J=14.7 Hz, NCH_2); 4.70 1H, d, J=11.0 Hz, OCH_2); 4.80 (1H, d, J=11.0 Hz, OCH_2); 4.83 (1H, d, J=14.7 Hz, NCH_2); 5.09 (1H, dd, J=7.3, 2.7 Hz, H-8); 7.21-8.05 (20H, m, $H_{arom.}$). Anal. Calcd for $C_{33}H_{29}NO_6S_2$ (599.7): C, 66.09; H, 4.87; N, 2.33. Found: C, 65.81; H, 4.96; N, 2.31. 10b, mp 178 °C. Ir(KBr): 1700, 1655, 1453 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): (ppm) 3.63 (1H, dd, J=6.6, 2.3 Hz, H-4); 4.13 (1H, dd, J=5.1, 1.8 Hz, H-6); 4.26 (1H, dd, J=5.1, 2.3 Hz, H-5); 4.14 (1H, d, J=15.1 Hz, NCH_2); 4.52 (1H, d, J=11.4 Hz, (OCH_2); 4.68 (1H, d, J=11.4 Hz, OCH_2) 4.73 (1H, t, J=2.0 Hz, H-1); 5.08 (1H, dd, J=6.6, 2.4 Hz, H-8)); 5.30 (1H, d, J=15.1 Hz, NCH_2); 7.05- 7.95 (20H, m, H_{arom}). Anal. Calcd for $C_{33}H_{29}N_6S_2$ (599.7): C, 66.09; H, 4.87; N, 2.33. Found: C, 65.85; H, 4.91; N, 2.52

(±)-(5-anti,6-anti)-2-Benzyl-7-benzyloxy-5,6-phenylsulfonyl-2-azabicyclo[2.2.2] oct-7-en-3-one (11)

4 (3 mmol, 0.87 g) and Z-1,2-bis (phenylsulfonyl)ethene (3.5 mmol, 1.08 g) were refluxed in toluene (20 ml) for 13 days. The solvent was evaporated and the residue flash chromatographed (see 9). 1 g (55.6%) of 10b, 120 mg (6.7%) of 11 and 340 mg of E-1,2-bis(phenylsulfonyl)ethene was isolated. 11, mp 266 °C. Ir(KBr): 1695, 1650, 1425 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): (ppm) 3.67 (1H, dd, J=9.5, 2.4, Hz, H-6); 3.68 (1H, d, J=14.2 Hz, NCH_2); 3.74 (1H, dd, J=6.9, 1.6 Hz, H-4); 3.99 (1H, dd, J=9.5, 1.6 Hz, H-5); 4.09 (1H, t, J=2.5 Hz, H-1); 4.74 (1H, d, J=14.2 Hz, NCH_2); 4.83 (1H, d, J=10.8 Hz, OCH_2); 5.03 (1H, d, J=10.8 Hz, OCH_2); 5.36 (1H, dd, J=6.9, 2.5 Hz, H-8); 6.85-8.03 (20H, m, $H_{arom.}$).

(±)-(5-anti)-Ethyl-2-benzyl-7-benzyloxy-3-oxo-2-azabicyclo[2.2.2]oct-7-en-5-carboxylate (12a)

(±)-(6-anti)-Ethyl-2-benzyl-7-benzyloxy-3-oxo-2-azabicyclo[2.2.2]oct-7-en-6-carboxylate (12b)

A solution of 4 (3 mmol, 0.87 g) in freshly distilled ethyl acrylate (10 ml) and toluene (10 ml) was heated in a sealed tube (150 °C) for 48 h. The solvent was evaporated and the remaining oil was flash chromatographed (see 9) to give 12a (850 mg, 73%) and 12b (42 mg, 3,6%). 12a, mp 83 °C. Ir (KBr). 1725, 1655, 1600 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): (ppm) 1.23 (3H, t, J=7.1 Hz); 1.97-2.04 (2H, m, H-6); 2.00 (1H, ddd, J=8.9, 5.3, 2.4 Hz, H-5); 3.79 (1H, dd, J=6.7, 2.4 Hz, H-4); 3.96 (1H, dd, J=5.2, 2.6, H-1); 4.11 (2H, q, J=7.1 Hz); 4.49 (2H, s, NCH_2); 4.65 (2H, s, OCH_2); 4.93 (1H, dd, J=6.7, 2.6 Hz, H-8); 7.18-7.37 (10H, m, $H_{arom.}$). Anal. Calcd for: $C_{24}H_{25}NO_4$ (391.5): C, 73.64; H, 6.44; N, 3.58. Found: C, 73.42; H, 6.60; N, 3.60. 12b, colourless oil. ^{1}H-Nmr ($CDCl_3$): (ppm) 1.14 (3H, t, J= 7.2 Hz); 2.07 (2H, dd, J=7.0, 2.7 Hz, H-5); 2.90 (1H, dt , J=7.0, 3.5 Hz, H-6); 3.41 (1H, dt ,

J=6.9, 2.7 Hz, H-4); 4.04 (2H, q, J=7.2 Hz); 4.27 (1H, dd, J=3.4, 2.7 Hz, H-1); 4.44 (1H, d, J= 15.0 Hz, NCH_2); 4.57 (1H, d, J=15.0 Hz, NCH_2); 4.61 (1H, d, J=9.7 Hz, OCH_2); 4.66 (1H, d, J=9.7 Hz, OCH_2); 5.11 (1H, dd, J=6.9, 2.7 Hz, H-8); 7.17-7.39 (10H, m, $H_{arom.}$).

(±)-(5-anti,6-anti)-Dimethyl-2-benzyl-3,7-dioxo-2-azabicyclo[2.2.2]octan-5,6-carboxylate (14)

To a cooled (-10 °C) suspension of 13 (5 mmol, 2 g) in MeOH (30 ml) was added dropwise with stirring thionyl chloride (3 ml). After 20 min the solution was warmed to room temp. and stirred another 2 h. MeOH was evaporated and the oily residue brought to crystallization with ether (-20 °C). The colourless powder was isolated by suction and recrystallized with EtOH. mp 145-146 °C. Ir(KBr): 1740, 1720, 1680 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): (ppm) 2.58 (1H, dd, J=19.2, 3.1 Hz, H-8); 3.04 (1H, dd, J=19.2, 1.9 Hz, H-8); 3.28 (2H, s, H-5,6); 3.33 (1H, s, H-4); 3.61 (3H, s, OCH_3); 3.66 (3H, s, OCH_3); 3.82 (1H, s, H-1); 4.27 (1H, d, J=14.6 Hz, NCH_2), 4.86 (1H, d, J=14.6 Hz, NCH_2); 7.20-7.36 (5H, m, $H_{arom.}$). Anal. Calcd for $C_{18}H_{19}NO_6$ (345.3): C, 62.60; H, 5.55; N, 4.05. Found: C, 61.94; H, 5.63; N, 4.09.

(±)-(5-anti)-Methyl-8-benzyl-1-benzyloxy-3,7-dioxo-2-aza-8-azatricyclo[4.3.1.0^{4,9}]decan-5-carboxylate (16)

A solution of 8 (5 mmol, 1.94 g) in dioxane (30 ml) was treated with water (10 ml) at 60 °C for 1 h. Evaporation of the volatiles furnished a colourless powder which was dried under vacuum. This material was dissolved in dioxane/methanol (30 ml/10 ml) and treated with distilled ethereal diazomethane solution until nitrogen evolution stoped. After evaporation of the solvents, the colourless material was recrystallized from ethanol. mp 171-172 °C (1.95 g, 92%). Ir(KBr): 1790, 1735, 1685 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): (ppm) 2.28 (1H, d, J=14.8 Hz, H-10); 2.84-3.10 (4H, m, H-4,5,6,10); 3.73 (3H, s, OCH_3); 3.97 (1H, d, J=14.7 Hz, NCH_2); 4.13 (1H, d, J=5.2 Hz, H-9); 4.45 (1H, d, J=11.3 Hz, OCH_2); 4.67 (1H, d, J=11.3 Hz, OCH_2); 4.89 (1H, d, J=14.7 Hz, NCH_2); 7.13-7.38 (10H, m, $H_{arom.}$). Anal. Calcd for $C_{24}H_{23}NO_6$ (421.4): C, 68.40; H, 5.50; N, 3.32. Found: C, 68.46; H, 5.48, N, 3.90.

(±)-(5-anti,6-syn)-2-benzyl-7-dimethoxy-5,6-phenylsulfonyl-2-azabicyclo[2.2.2]octan-3-one (17)

A suspension of 10b (3 mmol, 1.8 g) in acetic acid (60 ml) and 2N-HCl (20 ml) was stirred for 15 min at 60 °C and then for 1 h at room temp. After diluting with H_2O (100 ml) the mixture was extracted with CH_2Cl_2 (3x50 ml). The combined organic extracts were washed first with water, then with sat. $NaHCO_3$ solution, dried over sodium sulfate and concentrated. The colourless residue was dissolved in MeOH (150 ml). To this solution tosic acid (1 g) and trimethyl orthoformate (30 ml) was added. The mixture was refluxed for 2 days, the solvent was evaporated and the residue was dissolved in CH_2Cl_2 100 ml). The solution was washed with water, sat. $NaHCO_3$ solution and dried over sodium sulfate. After filtration and evaporation of the solvent the residue was triturated with ether and the product recrystallized from ethanol. (1.6 g, 100%), mp 188 °C. Ir(KBr): 1665, 1445 cm^{-1}. ^{1}H-Nmr ($CDCl_3$), ppm 1.65 (1H, ddd, J=13.1, 2.6, 1.3 Hz, H-8); 2.89-3.03 (2H, m, H-4,8,); 2.38 (3H, s, OCH_3);

3.15 (3H, s, OCH_3); 4.04 (1H, ddd, J=6.1, 2.3, 1.4 Hz, H-5); 4.14 (1H,d, J=15.1 Hz, NCH_2); 4.55 (1H, d, J=1.6 Hz, H-1); 4.62 (1H, dd, J=6.1, 1.6 Hz, H-6); 5.32 (1H, d, J=15.1 Hz, NCH_2); 7.28-7.98 15H, m, $H_{arom.}$). Anal. Calcd for $C_{28}H_{29}NO_7S_2$ (555.3): C, 60.56; H, 5.22; N, 2.52. Found: C, 60.64; H, 5.40; N, 2.31.

(±)-2-Benzyl-7-dimethoxy-5-phenylsulfonyl-2-azabicyclo[2.2.2]oct-5-en-3-one (6)

To a solution of 17 (2,5 mmol, 1.4 g) in THF (70 ml) was added 0.5 N KOH (7 ml). The mixture was stirred at room temp. until TLC showed conversion to essentially one product. The reaction mixture was poured into sat.NH_4Cl solution (70 ml) and extracted with CH_2Cl_2 (3x50 ml). The combined organic extracts were washed with water, dried (Na_2SO_4), and evaporated, to leave a colourless oil. Trituration with ether/ethanol furnished crystalline 6 (1.03 g, 99%), mp 176 °C. Ir(KBr): 1673, 1612, 1448 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): (ppm) 1.55 (1H, dd, J=13.0, 3.1 Hz, H-8); 1.94 (1H, dd, J=13.0, 2.7 Hz, H-8); 3.08 (3H, s, OCH_3); 3.16 (3H, s, OCH_3); 3.69 (1H, dd, J=5.4, 2.7 Hz, H-4); 4.20 (1H, d, J=6.0 Hz, H-1); 3.82 (1H, d, J=15.2 Hz, NCH_2); 5.11 (1H, d, J=15.2 Hz, NCH_2); 6.89-7.89 (10H, m, $H_{arom.}$); 7.13 (1H, dd, J=6.0, 2.4 Hz, H-6). Anal. Calcd for $C_{22}H_{23}NO_5S$ (413.5): C, 63.91; H, 5.61; N, 3.39. Found: C, 64.07; H, 5.42; N, 3.26.

(±)-(5-anti,6-syn)-2-Benzyl-7-dimethoxy-6-methoxy-5-phenylsulfonyl-2-azabicyclo[2.2.2]octan-3-one (18a)

Sodium (1.5 mmol, 35 mg) was dissolved in methanol (30 ml). To this solution was added 6 (1.2 mmol, 500 mg). The mixture was stirred for 1 h at room temp. The solvent was evaporated and the residue was partitioned between CH_2Cl_2 (50 ml) and sat.NH_4Cl solution (100 ml). The organic phase was washed with water, dried (Na_2SO_4), and evaporated, to leave a colourless oil. Crystallization with ether gave 18a (418 mg, 94%), mp 198 °C. Ir(KBr): 1660, 1445, 1300 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): (ppm) 1.72 (1H, ddd, J=14.4, 3.4, 1.5 Hz, H-8); 2.74 (3H, s, OCH_3); 2.83 (1H, dd, J=14.4, 2.4 Hz, H-8); 2.98 3H, s, OCH_3); 3.01 (1H, m, H-4); 3.20 (1H, dt, J=4.8, 1.8 Hz, H-5); 3.26 (3H, s, OCH_3); 3.77 (1H, d, J= 1.9 Hz, H-1); 4.15 (1H, d, J=14.7 Hz, NCH_2); 4.24 (1H, dd, J=4.8, 1.9 Hz, H-6); 4.89 (1H, d, J=14.7 Hz, NCH_2); 7.24-7.92 (10H, m, $H_{arom.}$). Anal. Calcd for $C_{23}H_{27}NO_6S$ (445.5): C, 62.00; H, 6.11; N, 3.14. Found: C, 62.19; H, 6.19; N, 3.15.

(±)-(5-anti,6-syn)-2-Benzyl-7-dimethoxy-6-(9-methyl-9-phenylsulfonylmethyl)-8-phenylsulfonyl-2-azabicyclo[2.2.2]octan-3-one (18c)

To a solution of diisopropylamine (2.75 mmol, 0.44 ml) in anhydrous THF (5 ml) was added n-Buli (2.7 mmol, 1.9 ml of 1.59 molar solution in hexane) at -78 °C. The mixture was stirred for 30 min at -10°C and then cooled to -78 °C. Then a solution of ethylphenylsulfone (2.75 mmol, 515 mg) in THF (20 ml) was added in one portion. To the yellow solution 6 (2.5 mmol, 1.03 g) in THF (40 ml) was added. The mixture was stirred at -78 °C for 30 min, then warmed up to room temp. and stirred overnight. The yellow solution was quenched with sat. NH_4Cl solution (50 ml) and extracted with CH_2Cl_2 (3x50 ml).

The combined organic extracts were washed with water, dried (Na_2SO_4) and evaporated to give a yellow oil. Trituration with ethyl acetate gave a colourless powder. Which could be recrystallized from EtOH to give 18c (1.3 g, 86%), mp 168 °C. Ir(KBr): 1695, 1445, 1422 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): (ppm) 0.93 (3H, d, J=7.4 Hz, CH_3); 1.77 (1H, ddd, J = 14.3, 2.7, 1.2, Hz, H-8)); 2.47 (1H, m); 2.71-2.84 (2H, m, H-4, H-8); 3.09 (3H, s, OCH_3); 3.22 (1H, m, H-5); 3.41 (3H, s, OCH_3); 3.47 (1H, m, H-6); 4.02 (1H, d, J=14.6 Hz, NCH_2); 4.47 (1H, d, J=1.5 Hz, H-1); 5.13 (1H, d, J=14.6 Hz, NCH_2); 7.32-7.56 (15H, m, $H_{arom.}$). Anal. Calcd for $C_{30}H_{33}NO_7S_2$ (583.7): C, 61.73, H, 5.70; N, 2.40. Found: C, 61.56; H, 5.83, N, 2.41.

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