Electron-rich 2-Pyridones, III[1]:

Stereochemistry and Reactivity of Phenylsulfonyl- substituted 2-Azabicyclo[2.2.2]octan-6-ones

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[4+2]cycloaddition of electron-rich 5-benzyloxy-2-pyridone (**1**) with phenylvinyl sulfone furnished, after functional group transformation, **2** in a syn/anti ratio of 3/7. Deprotonation with LDA provided the thermodynamic stable **2a**. The α-sulfonyl carbanion can be alkylated to **4**. During reductive desulfonylation complete epimerisation to **5** occured. Synthesis of **5b** was also accomplished by conjugate addition of ethylphenylsulfonyl carbanion to **11**.

Elektronenreiche 2-Pyridone, 3. Mitt.: Stereochemie und Reaktivität von Phenylsulfonyl-substituierten 2- Azabicyclo[2.2.2]octan-6-onen

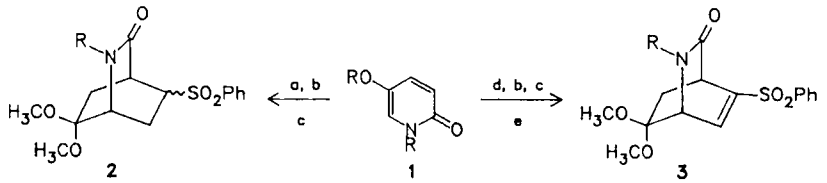
Das durch [4+2] Cycloaddition von Phenylvinylsulfon an 1-Benzyl-5-benzyloxy-2-pyridon (**1**) erhaltene syn/anti Addukt wird nach Ketalisierung zum thermodynamisch stabilen **2a** umgewandelt. Deprotonierung und Alkylierung liefert **4**. Reduktive Abspaltung der Phenylsulfongruppe läuft unter Epimerisierung zu **5** ab. Die Struktur von **5b** wird durch die Reaktionssequenz **9** → **12** → **5b** bewiesen.

Early investigations in the field of Diels-Alder cycloaddition of 2-pyridones[2] have shown that they react sluggishly and behave as "neutral" dienes. Also N-alkyl-3-methoxy-2-pyridones have more aromaticity than conjugated diene character[3]. Putting steric strain into this system, *Diels-Alder* reactivity can be facilitated[4]. Contrary to these observations, we found that 1-benzyl-5-benzyloxy-2-pyridone (**1**) reacts readily with a variety of acceptor substituted olefines[1,5]. Even with acceptor substituted acetylenes (e.g. **8**) high yields of cycloaddition products were achieved[6].

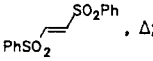
In connection with an ongoing synthetic program on the construction of the iboga alkaloid skeleton with the vinyl sulfone **3** as a key intermediate[1], we investigated the deprotonation of **2** with various bases to the α-phenylsulfonyl carbanion[7] and alkylation with the electrophiles RX to **4**. Together with the following reductive desulfonation of **4** to **5**, we gained further insight into the nature of stereoselective synthesis of 2-azabicyclo[2.2.2]octane-one derivatives[1].

Results and Discussion

We found two facile entries to the isoquinuclidine system **2**. First [4+2] cycloaddition of **1** and phenyl vinyl sulfone in boiling toluene gave cycloaddition products, in a syn/anti ratio of 3/7 [5]. Transformation of the resulting benzylenolether to the dimethylketal could be accomplished in high yield. The diastereometric mixture of **2a** and **2b** can be separated by flash chromatography. Secondly, **3**, prepared also from **1** via *Diels-Alder* reaction [1], could be hydrogenated in methanol with Pd/C to give only one diastereomer



a: $PhSO_3-CH=CH_2$, Δ, toluene; b: $H_3O^{\oplus}$/AcOH; c: $HC(OCH_3)_3$, MeOH, $H^{\oplus}$;

d:  , Δ; toluene; e: KOH, THF;

Scheme 1

Herrn Prof. Dr. *F. Eiden* mit besten Wünschen zum 65. Geburtstag gewidmet.

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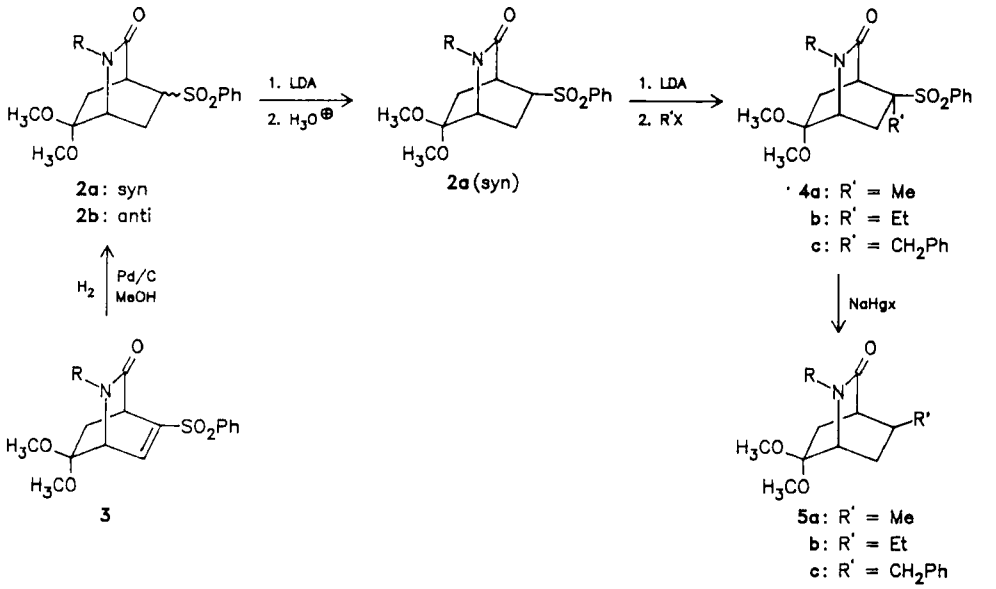


Scheme 2

namely **2b** (anti). This high diastereofacial hydrogenation from the syn side was in consistence with our observations that attack of nucleophiles at the β-position of the vinylsulfone moiety in **3** occurred also exclusively from the syn side[1].

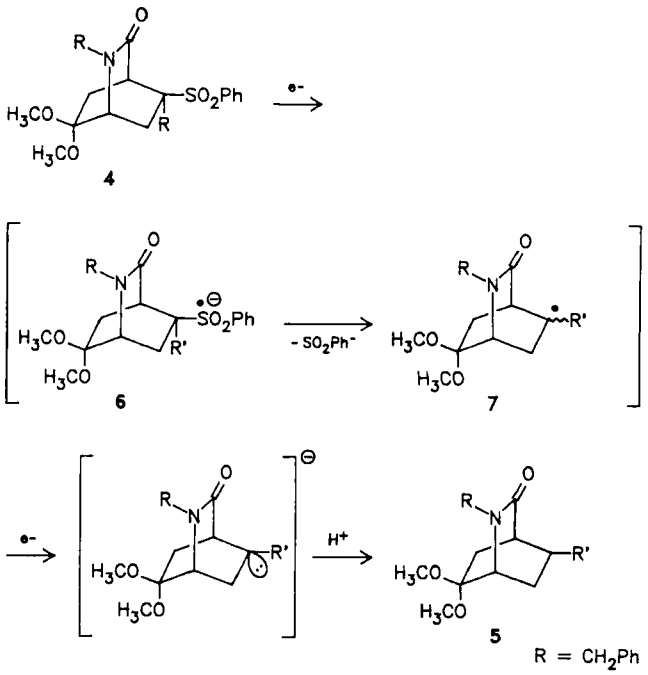
Deprotonation of **2b** with lithium diisopropylamide furnished the thermodynamic more stable compound **2a**, whose structure was unambigously characterised by X-ray crystallographic analysis. The α-sulphonyl carbanion of **2a** could be alkylated to **4a, b, c** in high yields.

Reductive desulfonation with sodium amalgam in methanol gave **5a, b, c** under complete epimerisation. Following a single-electron transfer mechanism for this reduction [8], the isomerization can be rationalized via **7**. The syn position of the alkyl substituent reflects the equilibrium position like the phenyl sulfonyl group in **2a**.

Synthesis of **5b** *via vinylsulfone derivative* **9**

We initially envisioned that the desired vinyl sulfone **3** might be prepared via [4+2] cycloaddition of **8** [10] to **1**. Interestingly, however, this cycloaddition gave the regioisomeric compound **9**, its regioisomer **3** could not be isolated. In contrast methyl propiolate was added with the expected regiochemistry[6]. The benzyl enolether of **9** could be hydrolyzed to ketone **10** which was protected as the dimethyl ketal **11**. With **11** in hand we were pleased to find that conjugate addition of ethylphenyl sulfonyl carbanion afforded **12** by syn addition to the vinyl sulfone moiety. X-ray analysis of **12** unambigously revealed the stereochemical outcome of the reaction.

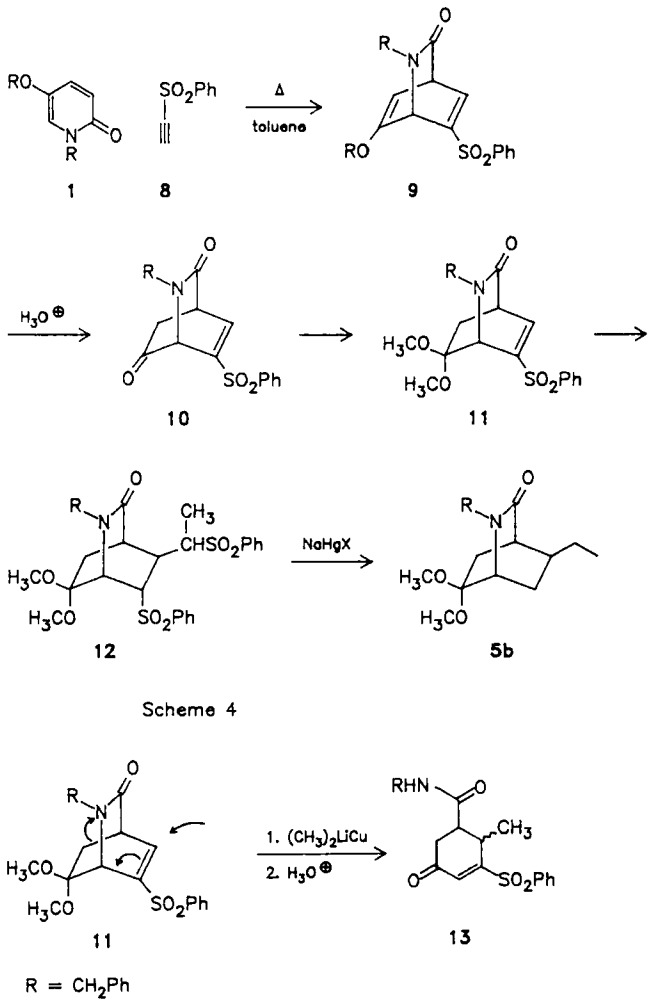
Hard nucleophiles like $^-OCH_3$, $^-OCH_2CH_3$ gave also syn addition products. Reductive desulfonation of **12** with sodium amalgam furnished a compound identical in all analytical data with **5b**. *Grignard-* and organo cuprate reagents added to **11** under ringopening reaction affording the cyclohexane derivatives in high yields (scheme 5). No ring cleavage could be detected when the regioisomeric vinyl sulfone



Scheme 3

3 was treated with organo cuprate reagents. The same reaction conditions afforded high yields of syn-addition products [9]. Obviously, two conditions may contribute to the facile ring-opening of **11**: first, the resulting amide anion is fairly stabilized and second, the coordination of Li^+ to the amide functionality helps to cleave the carbon nitrogen bond.

Crystals of compound **12** suitable for X-ray analysis were grown from EtOH as transparent colourless plates (specimen size 0.5 x 0.2 x 0.1 mm). Crystal data: monoclinic space group $P2_1/c$ with 4 molecules in the unit cell; a = 11.490(3) Å, b = 21.173(6) Å, c = 11.943(2) Å, β =



X-ray Structure Analysis of **12**

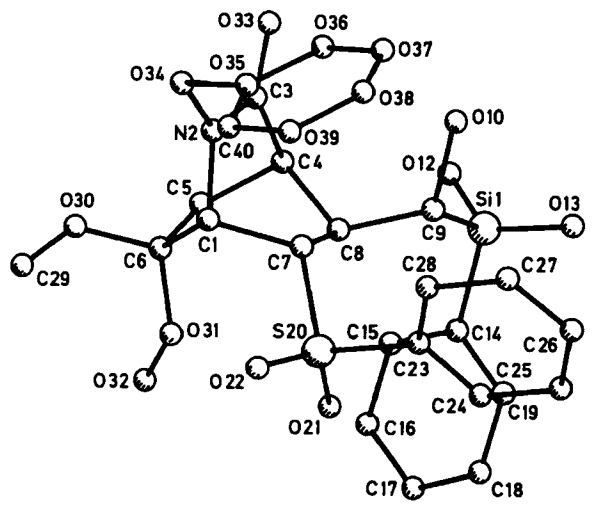


Fig. 1: Stereoscopic view of **12** showing the atom numbering system

atoms	bond length (Å)	atoms	bond angles °
C1-N2	1.459 (0.008)		
C1-C6	1.564 (0.009)	C1,N2,C6	107.7 (0.5)
C1-C7	1.562 (0.008)	C1,N2,C7	104.6 (0.4)
		C1,C6,C7	111.3 (0.5)
N2-C3	1.344 (0.009)	N2,C1,C3	115.7 (0.5)
C3-C4	1.530 (0.009)	C3,N2,C4	112.2 (0.5)
C4-C5	1.531 (0.009)	C4,C3,C5	106.1 (0.5)
C4-C8	1.572 (0.009)	C4,C3,C8	112.2 (0.5)
		C4,C5,C8	106.4 (0.5)
C5-C6	1.555 (0.010)	C5,C4,C6	108.2 (0.5)
		C6,C5,C1	109.2 (0.5)
C6-O30	1.412 (0.006)	C6,C1,O30	113.0 (0.5)
		C6,C5,O30	105.8 (0.5)
C6-O31	1.413 (0.006)	C6,C1,O31	102.6 (0.5)
		C6,C5,O31	114.5 (0.5)
		C6,O30,O31	111.9 (0.4)
C7-C8	1.560 (0.009)	C7,C1,C8	108.5 (0.5)
C7-S20	1.827 (0.006)	C7,C1,S20	114.4 (0.4)
		C7,C8,S20	113.0 (0.4)
C8-C9	1.561 (0.009)	C8,C4,C9	115.4 (0.5)
		C8,C7,C9	110.4 (0.5)
C9-C10	1.550 (0.010)	C9,C8,C10	116.4 (0.6)
C9-S11	1.819 (0.007)	C9,C8,C11	110.5 (0.4)
		C9,C10,S11	107.7 (0.5)

97.14(2)°; $d_{meas.}$ = 1.32 gcm^{-3}, $d_{calc.}$ = 1.36 gcm^{-3}. A total of 3884 unique reflections was measured of which 3252 were considered observed with I>30(I). Data were collected on a Nicolet R3m diffractometer up to 2 ϑ = 114° with nickel filtered CuKα radiation in Ω scan method and a scan speed of 3°/min. 25 centered reflections served as input for a least-squares determination of the unit cell parameters. An empirical absorption was necessary (μ = 20.3 cm^{-1}) and applied to the measured intensities. The structure was solved by direct methods using SHELXTL (*). A first attempt with best phase set showed the two sulfur atoms with a few reasonable peaks for a molecule fragment. Subsequent Sim weighed E-maps and difference *Fourier* syntheses revealed the complete structure as shown in fig. 1. Refinement cycles with anisotropic thermal parameters converged at R = 8.5%. It was not searched for hydrogens.

Experimental Part

General methods

Ether and tetrahydrofurane were distilled from sodium wire immediately prior to use. - Melting points are uncorrected. - IR spectra: Perkin-Elmer Model 48. - ^{1}H-NMR-spectra: WP 200 Bruker Model, deuteriochloroform as the solvent. - Thin-layer chromatography: Merck Silicagel 60 GF_{254}

(*) G.M. Sheldrick, SHELXTL (Release 4.1), A Program for Crystal Structure Determination, Cambridge - Göttingen 1983
Atomic coordinates, bond distances and angles are deposited at the Cambridge Crystallographic Data Centre.

TLC plates, 0.25 mm. Compound visualisation: iodine vapor. - Elemental analyses: Microanalytical Laboratory at the Chemistry Department of the University of Würzburg and from I. Beetz Laboratory, Kronach.

(±)-(5-syn)-2-Benzyl-7,7-dimethoxy-5-phenylsulfonyl-2-azabicyclo-[2.2.2]-octane-3-one (**2a**)

To diisopropylamine (0.16 ml, 1.1 mmol) in anhydrous THF (5 ml) was added n-BuLi (0.7 ml, 1.05 mmol of 1.59 molar solution in hexane) under N_2 at -78°C. The mixture was stirred for 30 min at -20°C. Then a solution **2a, 2b** (0.42 g, 1.0 mmol) in THF (20 ml) was added in one portion. The mixture was stirred for 30 min. at room temp., then quenched with saturated NH_4Cl solution (50 ml) and extracted with CH_2Cl_2 (4x). The combined org. extracts were washed with water, dried (Na_2SO_4) and evaporated to give a yellow oil. Trituration with ethanol/ether gave a colourless powder. - mp. 157°C (EtOH). Yield 0.31 g (74%). - Analytical and spectral data see lit.[5].

(±)-2-Benzyl-7,7-dimethoxy-5-anti-methyl-5-syn-phenylsolfonyl-2-azabicyclo[2.2.2] octane-3-one (**4a**)

To diisopropylamine (0.23 ml), 1.6 mmol in anhydrous THF (8 ml) was added n-BuLi (1 ml, 1.58 mmol) at -78°C. The mixture was stirred 30 min at -10°C and then cooled to -78°C again. Then a solution of **2a** (0.42 g, 1.0 mmol) in THF (20 ml) was added. After 10 min the solution was warmed up to room temp., stirred for 30 min and cooled down again to -78°C. Then methyl iodide (0.3 ml, 30 mmol) was added. After 10 min the mixture was brought to room temp., stirred for 90 min, quenched with saturated NH_4Cl solution (50 ml) and extracted with CH_2Cl_2 (4x). The combined org. extracts were washed with water, dried (Na_2SO_4) and evaporated to give a yellow oil. Trituration with ether (-20°C) gave a colourless powder, which was crystallized from EtOH. - mp. 122°C, Yield 0.28 g (65 %) colourless cubes. - $C_{23}H_{27}NO_5S$ (429.5) Calcd. C 64.3 H 6.34 N 3.3 Found C 64.6 H 6.39 N 3.2. - IR (KBr.): 1683 (C=O); 1455; 1428; 1302; 1155 cm^{-1}. - ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.41 (3H; s; CH_3), 1.77 (1H; dd, $J_{1,6a}$ = 2.2 Hz, $J_{6a,6e}$ = 14.5 Hz; H_a-6), 1.93 (2H; m; $H_{a,e}$-8), 2.49 (1H; m; H-4), 2.55 (1H, dd, $J_{1,6e}$ = 3.6 Hz, $J_{5a,5e}$ = 14.5 Hz; H_e-6), 3.10 (3H; s; OCH_3), 3.12 (3H, s; OCH_3), 3.58 (1H; dd, $J_{1,6a}$ = 2.2 Hz, $J_{1,6e}$ = 3.5 Hz; H-1), 3.97/5.39 (2H; J_{AB} = 14.9 Hz; NCH_2), 7.30-8.13 (10H; m; $H_{arom.}$). - ^{13}C-NMR ($CDCl_3$): δ (ppm) = 21.11 (CH_3), 30.55 (C-6), 32.61 (C-8), 45.02 (C-4), 48.17 (NCH_2), 48.65 (OCH_3), 49.07 (OCH_3), 55.38 (C-5), 63.35 (C-1), 102.54 (C-7), 127.60, 128.63, 128.94, 129.03, 130.96, 133.96, 134.47, 136.38 ($C_{arom.}$), 171.72 (C-3).

(±)-2-Benzyl-7,7-dimethoxy-5-anti-ethyl-5-syn-phenylsulfonyl-2-azabicyclo-[2.2.2]octane-3-one (**4b**)

4b was prepared as described for **4a**. Instead of methyliodide ethyliodide (0.3 ml, 2.8 mmol) was added. Colourless cubes, mp. 159°C (MeOH). Yield 0.34 g (77%). $C_{24}H_{29}NO_5S$ (443.6) Calcd. C 65.0 H 6.59 N 3.2 Found C 64.6 H 6.59 H 3.0. - IR (KBr): 1680 (C=O); 1450; 1425; 1295, 1150, 1095 cm^{-1}. - ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.80 (3H; t, J = 7.5 Hz; $CH_2\underline{CH_3}$), 1.66-2.07 (5H; m; H_a-6, $H_{a,e}$-8, $\underline{CH_2}CH_3$), 2.50 (1H; dd, $J_{1,6e}$ = 3.7 Hz, $J_{6a,6e}$ = 14.6 Hz; H_e-6), 2.91 (1H; m; H-4), 3.10 (6H; s; 2xOCH_3), 3.55 (1H; dd, $J_{1,6a}$ = 2.2 Hz, $J_{1,6e}$ = 3.5 Hz; H-1), 4.00/5.37 (2H; J_{AB} = 14.8 Hz, NCH_3), 7.30-8.12 (10H; m; $H_{arom.}$). - ^{13}C-NMR ($CDCl_3$): δ (ppm) = 8.72 ($CH_2\underline{CH_3}$), 27.03 ($\underline{CH_2}CH_3$), 31.18 (C-6), 32.75 (C-8), 42.74 (C-4), 48.13 (NCH_2), 48.66 (OCH_3), 49.02 (OCH_3), 55.00 (C-5), 67.32 (C-1), 102.55 (C-7), 127.54, 128.54, 129.03, 129.17, 130.49, 133.85, 136.61, 136.69 ($C_{arom.}$), 171.57 (C-3).

(±)-2,5-anti-Dibenzyl-7,7-dimethoxy-5-syn-phenylsulfonyl-2-azabicyclo-[2.2.2]octane-3-one (**4c**)

Prepared like **4a**. Instead of methyl iodide benzyl bromide (0.26 ml, 3 mmol) was added. The yellow oil was purified by flash chromatography ($CHCl_3$/Etac 9+1). Trituration with ether gave a colourless powder which was crystallized from ethanol. - mp. 165°C (EtOH). Yield 0.4 (79%). $C_{29}H_{31}NO_5S$ (505.6) Calcd. C 68.9 H 6.38 N 2.8 Found C 69.2 H 6.24 N 2.7. - IR (KBr): 1670 (C=O); 1300; 1140; 1125; 1045 cm^{-1}. - ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.79 (2H; m; H-6,8), 2.92/3.34 (2H; J_{AB} = 15.3 Hz; CH_2Ph), 3.03 (3H; s; OCH_3), 3.10 (3H; m; H-4,6,8), 3.23 (3H; s; OCH_3), 3.59 (1H; m; H-1), 3.96/4.95 (2H; J_{AB} = 14.6 Hz; NCH_2), 7.04-7.61 (15H; m; $H_{arom.}$). - ^{13}C-NMR ($CDCl_3$): δ (ppm) = 28.03 (C-6), 30.39 (C-8), 43.79 (C-4), 46.49 ($\underline{CH_2}Ph$), 48.29 (NCH_2), 48.89 (OCH_3), 49.34 (OCH_3), 55.19 (C-5), 67.81 (C-1), 102.78 (C-7), 127.15, 127.88, 128.21, 128.78, 128.88, 129.64, 131.46, 133.46, 135.06, 136.00, 136.79 ($C_{arom.}$), 170.85 (C-3).

(±-(5-anti)-2-Benzyl-7,7-dimethoxy-5-phenylsulfonyl-2-azabicyclo-[2.2.2]octane-3-one (**2b**)

To a solution of **3** (0.2 g, 0.48 mmol) in methanol (100 ml) was added 20 mg Pd/C (10% Pd). After evacuation the suspension was saturated with H_2 and shaken for 3 h at 3 bar. After filtration, the solution was evaporated and the residue triturated with ether. Crystallization from ethanol afforded colourless needles, mp. 176-177°C. Yield 0.19 g (95%). Spectral data see Lit.[5].

(±)-(5-syn)-2-Benzyl-7,7-dimethoxy-5-methyl-2-azabicyclo[2.2.2]octane-3-one (**5a**)

To a solution of **4a** (0.2 g, 0.47 mmol) in anhydrous methanol (40 ml) was added 0.4 g NaH_2PO_4. Under rapid stirring 1.6 g sodium amalgam were added in 3 portions during 3 h. Stirring was continued over night. The reaction was monitored by TLC. When the starting material was consumed, mercury was filtered off and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 and washed with saturated NH_4Cl solution and water. The org. extract was dried (Na_2SO_4) evaporated and the oily residue was brought to crystallisation with petrolether at -20°C. Yield 0.11 g (82%) colourless powder, mp. 92-93°C. $C_{17}H_{23}NO_3$ (298.4) Calcd. C 70.6 H 8.01 N 4.8 Found C 70.3 H 8.04 N 5.2. - IR (KBr): 2955; 1655 (C=O); 1462; 1450; 1120; 1045 cm^{-1}. - ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.82 (1H; dd, $J_{1,6e}$ = 3.5 Hz, $J_{6e,5}$ = 8.2 Hz, H_e-6), 1.01 (3H; d, J = 6.5 Hz; CH_3), 1.71 (1H; dd, $J_{4,8a}$ = 2.7 Hz, $J_{8a,8e}$ = 13.7 Hz; H_a-8), 2.05 (3H; m; H-5, H_a-6, H_e-8), 2.48 (1H; m; H-4), 3.11 (3H; s; OCH_3), 3.13 (3H, s; OCH_3), 3.45 (1H; m; H-1), 3.84/5.30 (2H; J_{AB} = 14.7 Hz; NCH_2), 7.28-7.33 (5H; m; $H_{arom.}$).

(±)-(5-syn)-2-Benzyl-7,7-dimethoxy-5-ethyl-2-azabicyclo[2.2.2]octane-3-one (**5b**)

Preparation see **5a**. **4b** (0.44 g, 1 mmol) furnished 0.28 g (92%) **5b** as colourless cubes. - mp. 52-54°C. $C_{18}H_{25}NO_3$ (303.4) Calcd. C 71.3 H 8.31 N 4.6 Found C 71.4 H 8.36 N 4.7. - IR (KBr): 1660 (C=O), 1440, 1298, 1285, 1125, 1110 cm^{-1}. - ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.86 (4H; t, J = 7.3 Hz; $CH_2\underline{CH_3}$ and m; H-6), 1.15-1.50 (2H; m; $\underline{CH_2}CH_3$), 1.65-2.10 (4H; m; H-5,6,$H_{a,e}$-8). 2.60 (1H; m; H-4), 3.11 (3H; s; OCH_3), 3.14 (3H; m; OCH_3), 3.47 (1H; m; H-1), 3.85/5.27 (2H; J_{AB} = 14.7 Hz; NCH_2), 7.24-7.38 (5H; m; $H_{arom.}$). - ^{13}C-NMR ($CDCl_3$): δ (ppm) = 11.67 ($CH_2\underline{CH_3}$), 29.61 ($\underline{CH_2}CH_3$), 30.03 (C-5), 36.30 (C-6), 37.41 (C-8), 44.02 (C-4), 48.05 ($N\underline{CH_2}$), 48.70 (OCH_3), 49.05 (OCH_3), 56.60 (C-1), 103.50 (C-7), 127.42, 128.46, 137.67 ($C_{arom.}$), 173.28 (C-3).

(±)-(5-syn)-2,5-Dibenzyl-7,7-dimethoxy-2-azabicyclo[2.2.2]octane-3-one (**5c**)

Preparation see **5a**. **4c** (0.49 g, 0.97 mmol) furnished 0.29 g (82%) **5c** as colourless needles. - mp. 92°C (EtOH/petrolether). $C_{23}H_{27}NO_3$ (365.5) Calcd. C 75.6 H 7.45 N 3.8. Found C 75.7 H 7.55 N 3.9. - IR (KBr): 1655 (C=O); 1461; 1450; 1428; 1122; 1045 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.93 (1H; ddd, $J_{1,6e}$ = 3.6 Hz, $J_{5,6e}$ = 5.0 Hz, $J_{6a,6e}$ = 13.5 Hz; H_e-6), 1.65

(1H; dd, $J_{4,8a}$ = 2.6 Hz, $J_{8a,8e}$ = 13.8 Hz; H_a-8), 1.89 (1H; ddd, $J_{1,6a}$ = 2.1 Hz, $J_{5,6a}$ = 9.8 Hz, $J_{6a,6e}$ = 13.5 Hz; H_a-6), 2.04 (1H; dd, $J_{4,8e}$ = 3.4 Hz, $J_{8a,8e}$ = 13.8 Hz; H_e-8), 2.15 (1H; m; H-5), 2.45/2.29 (2H; dd, $J_{5,CH}$ = 7.8 Hz, J_{AB} = 13.6 Hz; C_5-C<u>H</u>$_2$Ph), 2.61 (1H; m; H-4), 3.10 (3H; s; OCH_3), 3.12 (3H; s; OCH_3), 3.49 (1H; dd, $_{1,6a}$ = 2.1 Hz, $J_{1,6e}$ = 3.5 Hz; H-1), 3.84/5.36 (2H; d, J_{AB} = 14.6 Hz, NCH_2), 7.13-7.37 (10H; m; $H_{arom.}$).

(±)-2-Benzyl-7-benzyloxy-6-phenylsulfonyl-2-azabicyclo[2.2.2]octa-5,7-diene-3-one (**9**)

A mixture of **1** (1.74 g, 6 mmol) and **8**[10] (1.5 g, 9 mmol) in toluene (100 ml) was refluxed for 4 d under N_2 in the dark. After evaporation the brown residue was brought to crystallization by treatment with ethylacetat at -20°C. The brown solid was washed thoroughly with ethyl acetate. Filtrate and washings were concentrated to afford another crop of **9**. Crude **9** was "filtered" over neutral Al_2O_3 ($CHCl_3$/MeOH 9+1). The solvent was evaporated and the colourless solid crystallized from ethyl acetate. - mp 158°C. Yield 1.1 g (40%). $C_{27}H_{23}NO_4S$ (457.5) Calcd. C 70.8 H 5.07 N 3.1 Found C 69.5 H 5.07 N 3.1. - IR (KBr): 1670 (C=O); 1638 (C=C-O-Bz); 1602 (C=C-SO_2Ph); 1315; 1305; 1150 cm^{-1}. - ^{1}H-NMR ($CDCl_3$); δ (ppm) = 3.45/4.65 (2H; J_{AB} = 15.1 Hz; NCH_2), 4.33 (1H; m; H-4), 4.51 (2H; s; OCH_2), 4.66 (1H; m; H-1), 5.33 (1H, dd, $J_{1,8}$ = 2.3 Hz, $J_{4,8}$ = 6.4 Hz, H-8), 6.98-7.86 (15H; m; $H_{arom.}$), 7.70 (1H; dd, $J_{1,5}$ = 2.2 Hz, $J_{4,5}$ = 6.1 Hz, H-5).

(±)-2-Benzyl-6-phenylsulfonyl-2-azabicyclo[2.2.2]oct-5-ene-3,7-dione (**10**)

9 (1.25 g, 2.7 mmol) was stirred at 40°C for 10 min in a mixture of acetic acid (30 ml) and 2N HCl (10 ml). After further stirring for 1 h at room temp., water was added (250 ml) and the mixture was extracted with CH_2Cl_2 (4x30 ml). The combined org. extracts were washed with sat. $NaHCO_3$ solution (2x) and water (2x), dried (Na_2SO_4) and concentrated. The oily residue crystallized on standing. Recrystallization from ethyl acetate afforded colourless needles. - mp. 203°C. Yield 0.93 g (93%). $C_{20}H_{17}NO_4S$ (367.4) Calcd. C 65.4 H 4.66 N 3.8 Found C 65.6 H 4.61 N 3.7. - IR (KBr): 1745 (C=O); 1672 (C=O). 1608 (C=O); 1449; 1442; 1320; 1308; 1155 cm^{-1}. - ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.14 (1H; dd, $J_{4,8e}$ = 2.8 Hz, $J_{8a,8e}$ = 18.0 Hz, H_e-8), 2.46 (1H; dd, $J_{4,8a}$ = 2.5 Hz, $J_{8a,8e}$ = 18.0 Hz; H_a-8), 3.91 (1H; m; $J_{4,8}$ = 2.7 Hz, $J_{4,5}$ = 6.6 Hz, H-4), 4.08/4.55 (2H; J_{AB} = 14.8 Hz; NCH_2), 4.45 (1H; d, $J_{1,5}$ = 2.3 Hz, H-1), 6.99-7.79 (10H; m; $H_{arom.}$), 7.49 (1H; dd, $J_{1,5}$ = 2.3 Hz, $J_{4,5}$ = 6.6 Hz; H-5). - ^{13}C-NMR ($CDCl_3$): δ (ppm) = 30.06 (C-8), 44.47 (C-4), 49.26 (NCH_2), 64.20 (C-1), 127.98, 128.32, 128.99, 129.70, 134.76, 138.36 ($C_{arom.}$), 134.38 (C-5), 143.16 (C-6), 168.79 (C-3), 196.97 (C-7).

(±)-2-Benzyl-7,7-dimethoxy-6-phenylsulfonyl-2-azabicyclo[2.2.2]oct-5-ene-3-one (**11**)

A mixture of **10** (1.84 g, 5 mmol), toluoenesulfonic acid 1.0 g, and trimethyl orthoformate (40 ml) in methanol (80 ml) was refluxed for 36 h. The solution was concentrated, the residue dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$ solution (2x) then with water (2x). Drying and evaporation of the solvent afforded a colourless oil which crystallized upon treatment with ether/EtOH. Recrystallization from Etac afforded colourless needles. - mp. 125°C. Yield 1.7 g (82%). $C_{22}H_{23}NO_5S$ (413.5). Calcd. C 63.9 H 5.61 N 3.4 Found C 63.5 H 5.43 N 3.2. - IR (KBr): 1670 (C=O); 1610 (C=C); 1445; 1320; 1310; 1150 cm^{-1}. - ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.69 (1H; dd, $J_{4,8a}$ = 3.0 Hz, $J_{8a,8e}$ = 13.1 Hz; H_a-8), 2.01 (1H, dd, $J_{4,8e}$ = 2.8 Hz, $J_{8a,8e}$ = 13.1 Hz, H_e-8), 2.98 (3H; s, OCH_3), 2.99 (3H; s, OCH_3), 3.63 (1H; m, $J_{4,5}$ = 6.4 Hz, H-4), 4.16/4.54 (2H, J_{AB} = 15.0 Hz; NCH_2), 4.52 (1H, d, $J_{1,5}$ = 2.3 Hz; H-1), 7.07-7.71 (10H; m; $H_{arom.}$), 7.21 (1H, dd, $J_{1,5}$ = 2.3 Hz, $J_{4,5}$ = 6.4 Hz; H-5). - ^{13}C-NMR ($CDCl_3$): δ (ppm) = 32.20 (t, C-8), 45.03 (d, C-4), 49.19, 49.35, 49.65 (m, N<u>C</u>H$_2$, 2x O<u>C</u>H$_3$), 58.05 (d, C-1), 106.56 (s; C-7), 127.66, 128.03, 128.44, 128.61, 129.03, 133.52, 135.86, 139.54 (m, $C_{arom.}$), 141.61 (d, C-5), 146.95 (s; C-6), 170.96 (s, C-3).

(±)-(5-syn,6-anti)-2-Benzyl-7,7-dimethoxy-5-[1-(phenylsulfonyl)-ethyl]-6-phenylsulfonyl-2-azabicyclo[2.2.2]octan-3-one (**12**)

To a solution of diisopropylamine (0.44 ml, 2.75 mmol) in anhydrous THF (15 ml) was added n-BuLi (1.74 ml, 2.75 mmol) at -78°C. The mixture was stirred for 30 min at -10°C and then cooled to -78°C. Then a solution of ethylphenylsulfone (0.51 g, 2.75 mmol) in THF (20 ml) was added. To this mixture a cooled (-28°C) solution of **11** (1.035 g, 25 mmol) in THF (50 ml) was added. After 30 min of stirring the mixture was warmed up to room temp. and stirred for 18 h, quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2 (4x). The combined org. extracts were washed with water (2x), dried and concentrated. Trituration with EtOAc afforded a crystalline residue. Recrystallization from EtOH gave colourless cubes. - mp. 184°C. Yield 0.95 g (65%). Evaporation of the mother liquor and trituration with ether afforded 0.34 g of ring-opened product.

12: $C_{30}H_{33}NO_7S_2$ (583.7) Calcd. C 61.7 H 5.70 N 2.4. Found C 61.6 H 5.82 N 2.4. - IR (KBr): 1670 (C=O); 1442; 1320; 1305; 1142; 1080; 1052 cm^{-1}. - ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.02 (3H; d, J = 7.2 Hz, CHR<u>C</u>H$_3$), 1.79 (1H; dd, $J_{4,8e}$ = 3.4 Hz, $J_{8a,8e}$ = 14.1 Hz; H_e-8), 2.08 (1H; dd, $J_{4,8a}$ = 2.7 Hz, $J_{8a,8e}$ = 14.1 Hz; H_a-8), 2.81 (1H; dd, $J_{1,6}$ = 2.1 Hz, $J_{5,6}$ = 9.7 Hz, H-6), 2.98 (3H; s; OCH_3), 3.02 (1H; m; C<u>H</u>RCH$_3$), 3.05 (3H; s; OCH_3), 3.26 (2H; m, $J_{5,6}$ = 9.7 Hz; H-4,5), 3.78/5.25 (2H; J_{AB} = 14.3 Hz; NCH_2), 4.06 (1H; d, $J_{1,6}$ = 2.1 Hz; H-1), 7.29-7.87 (15H; m; $H_{arom.}$). - ^{13}C-NMR ($CDCl_3$): δ (ppm) = 8.56 (q, CHR<u>C</u>H$_3$), 35.31 (d, C-5), 36.00 (t, C-8), 39.96 (d, C-4), 48.31 (t, NCH_2), 48.56/48.71 (m; 2x OCH_3), 55.31 (d, <u>C</u>HRCH$_3$), 60.10 (d, C-6), 66.15 (d, C-1), 101.74 (s; C-7), 128.27, 128.46, 128.72, 128.96, 129.08, 129.18, 129.25, 133.52, 134.05, 135.13, 137.34, 139.98 (m, $C_{arom.}$), 171.93 (s; C-3).

Preparation of **5b** from **12** see **5a**. The sodium amalgam reduction of **12** gave a compound identical in all analytical data with **5b**.

(±)-N-Benzyl-(6-methyl)-3-oxo-5-phenylsulfonyl-cyclohex-4-enyl)-carbonamid (**13**)

Cu_2Br_2-dimethyl sulfide complex (0.514 g, 2.5 mmol) was suspensed in ether (30 ml) at -20°C. Under vigorous stirring CH_3Li (3.1 ml, 5 mmol, 1.6 molar) was added and the mixture was cooled to -50°C. **11** (0.2 g, 0.5 mmol) was added and stirred for 1 h. The yellow suspension was warmed up slowly (2 h) to 0°C, quenched with NH_4Cl solution and extracted with CH_2Cl_2 (4x). The combined org. extracts were washed with water (2x), dried (Na_2SO_4) and evaporated. The colourless oil crystallized after trituration with ether. This matieral was dissolved in acetic acid (15 ml) and 2N-HCl (5 ml) at 40°C. After 15 min the solution was cooled to r.t. and stirred for 1 h. After addition of water (150 ml) the org. material was extracted with CH_2Cl_2 (3x). The combined org. extracts were washed with water, dried and evaporated. The oily residue crystallized after trituration with ether. Colourless crystals. Yield 110 mg (91%), mp. 142°C. $C_{21}H_{21}NO_4S$ (383.11912). High resolution MS: 383.11740 (m) = 383 (M^+, 34.0%), 250 (18.5), 242 (25.0), 106 (100). - IR (KBr): 3290 (NH); 1689 (C=O); 1645 (C=O); 1622 (C=C); 1558; 1449; 1425; 1312; 1152 cm^{-1}. - ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.42 (3H; d, J = 7.0 Hz; C<u>H</u>$_3$), 2.66 (2H; m; H-6), 2.78 (1H; m; H-4), 3.05 (1H; ddd, J = 2.5, 7.0, 13.9 Hz; H-4), 3.95 (1H; dd, J_{NH-CH} = 5.1 Hz, J_{AB} = 14.6 Hz; NH-C<u>H</u>$_2$), 4.23 (1H; dd, J_{NH-CH} = 5.8 Hz, J_{AB} = 14.6 Hz; NH-C<u>H</u>$_2$), 5.96 (1H; m; N<u>H</u>), 6.55 (1H; s, H-2), 7.01-7.86 (10H; m; $H_{arom.}$). - ^{13}C-NMR ($CDCl_3$) δ (ppm) = 19.84 (q, <u>C</u>H$_3$), 32.70 (d, C-4), 35.33 (t, C-6), 43.71 (t, <u>C</u>H$_2$Ph), 47.40 (d, C-5), 127.67, 127.73, 128.74, 129.47, 130.67, 137.04, 137.49 (m, $C_{arom.}$), 134.37 (d, C-2), 158.89 (s, C-3), 171.33 (s, O=<u>C</u>-NHR), 195.15 (s, C-1).

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