HETEROCYCLES, Vol. 65, No. 6, 2005, pp. 1359 - 1371
Received, 9th February, 2005, Accepted, 8th April, 2005, Published online, 8th April, 2005

SYNTHESIS OF SPIRO-SUBSTITUTED BENZO[*c*]AZEPINONES

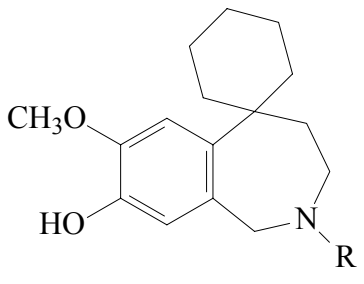
Álmos Gorka,[a] **László Hazai**,[b] **Csaba Szántay, Jr**.,[c] **Viktor Háda**,[c] **Lajos Szabó**,[a] **and Csaba Szántay**[a,b]*

[a]Department of Organic Chemistry, University of Technology and Economics
[b]Research Group for Alkaloid Chemistry of the Hungarian Academy of Sciences, H-1111 Budapest, Gellért tér 4. Hungary, E-mail: szantay@mail.bme.hu
[c]Spectroscopic Research Division, Gedeon Richter Ltd., H-1475 Budapest 10, P. O. Box 27, Hungary

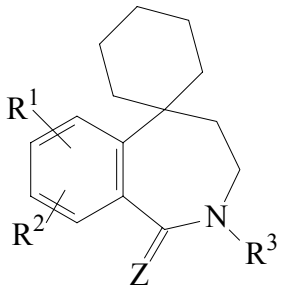
Abstract – Benzo[*c*]azepinones spiro-substituted by cyclohexanone, cyclohexenone and cyclohexadienone rings were synthesized from 2-tetralone *via* simple and convenient reaction steps.

INTRODUCTION

Recently we reported[1] the synthesis of several derivatives of benzo[*c*]azepines spiro-substituted with a cyclohexane ring (**1**) by Grewe cyclization. In the course of our work we found the first case of seven-membered ring formation using Grewe cyclization. In the literature only a few relatives of this type of compounds (**2**) were described[2,3] with analgetic[4] and cholinesterase inhibition activity[5].



1, R=H, Me, CHO

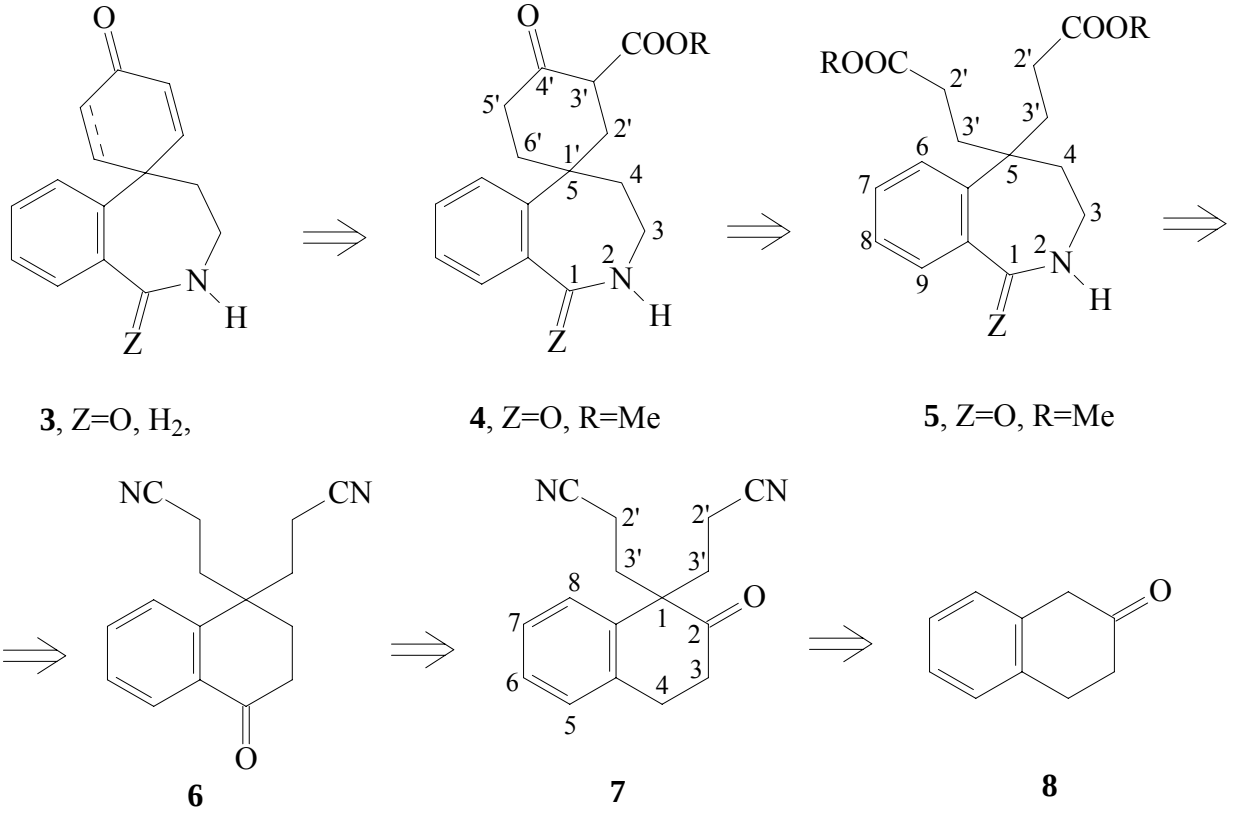


2, R^1, R^2=H, OH, OMe
R^3=H, alkyl
Z=H_2, O

In this paper a convenient synthetic route is presented for preparation of spiro[2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5,1'-cyclohexane] derivatives (**3**; Scheme 1) possessing

carbonyl and unsaturated carbonyl function in the cyclohexane ring, which could be good precursors for the synthesis of new derivatives with useful biological activity. Our retrosynthetic analysis is shown in Scheme 1.

For building up the spirocyclohexanone ring (**5**→**4**) the Dieckmann condensation of compound (**5**) would be used after the Beckmann rearrangement of the oxime of ketone (**6**). To convert the nitrile groups to ester substituents, Pinner reaction would be achieved. Compound (**6**) would be prepared from bis(cyanoethyl) derivative of 2-tetralone (**7**) with removal of the 2-oxo group by reduction and subsequent oxidation to position 4. 2-Tetralone cyanoethylated with acrylonitrile (**7**) is known in the literature[6] and 2-tetralone (**8**) is commercially available.



3, Z=O, H_2, **4**, Z=O, R=Me **5**, Z=O, R=Me

6 **7** **8**

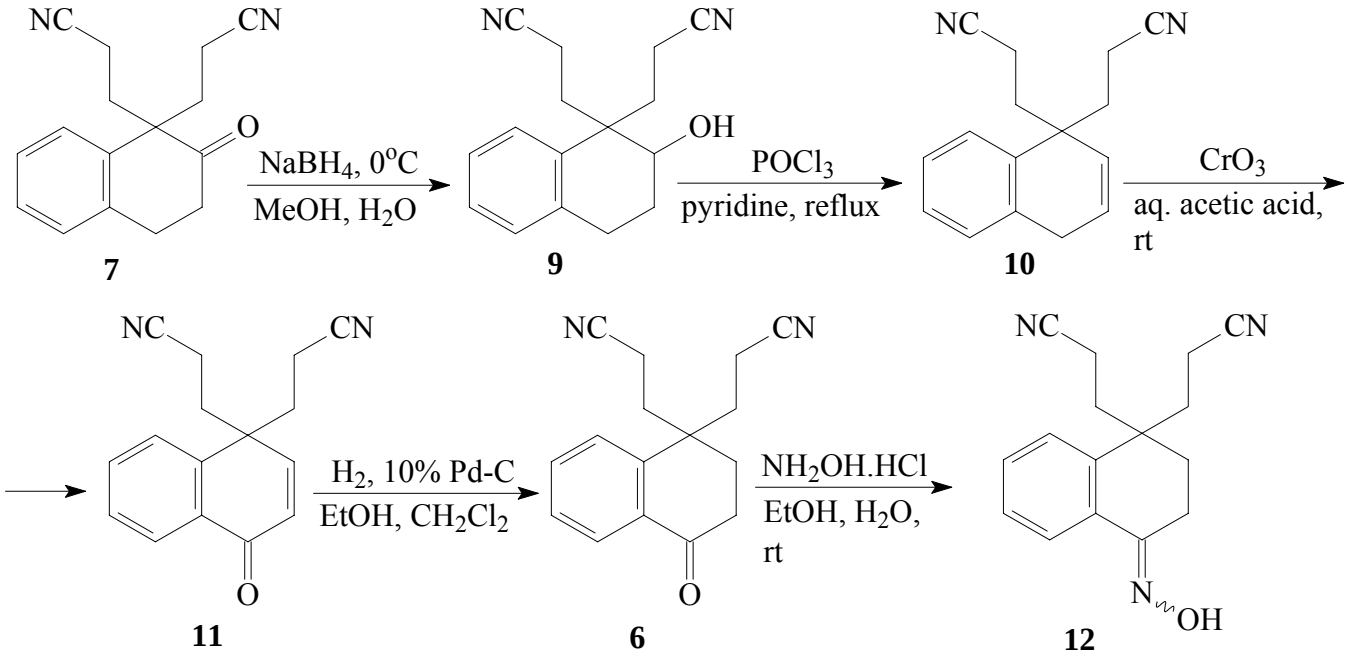
Scheme 1

The title compounds (**3**) would be obtained from azepinone (**4**) after dealkoxycarbonylation reaction and then the α,β-olefinic bond(s) would be formed by oxydation of the corresponding cyclohexanone.

RESULTS AND DISCUSSION

In the first step of our synthetic work bis(cyanoethyl)tetralone (**7**) was prepared in 88.4% yield from 2-tetralone (**8**) by treatment with acrylonitrile in *t*-BuOH and THF solution at room temperature. Contrary to the literature data[6] in the reaction between **8** and acrylonitrile, we used potassium *tert*-butoxide as a base instead of Triton-B. Considering that the removal of the keto group from compound (**7**) using the generally known reduction methods was unsuccessful, ketone (**7**) was reduced (98%) by sodium

borohydride to the corresponding alcohol (**9**). After dehydration reaction of compound (**9**)**,** performed with phosphorus oxychloride in refluxing pyridine, olefin (**10**) was quantitatively obtained (Scheme 2). Oxidation of the allylic methylene group in the unsaturated derivative (**10**) with chromium(VI) oxide resulted in ketone (**11**) in quantitative yield. This allylic oxidation could also be observed under the effect of the air oxygen, but this method did not proved to be suitable for preparation of ketone (**11**). Catalytic hydrogenation of **11** at room temperature and at atmospheric pressure in the presence of palladium on charcoal yielded (96%) the required saturated 1-tetralone derivative (**6**), which can be considered the appropriate intermediate for the ring expansion reaction to obtain the benzo[*c*]azepine heterocycle. Thus, oxime (**12**) was prepared in the usual way (91.7%); in reaction of ketone (**6**) with hydroxylamine hydrochloride in aqueous ethanol at room temperature.



7 **9** **10** **11** **6** **12**

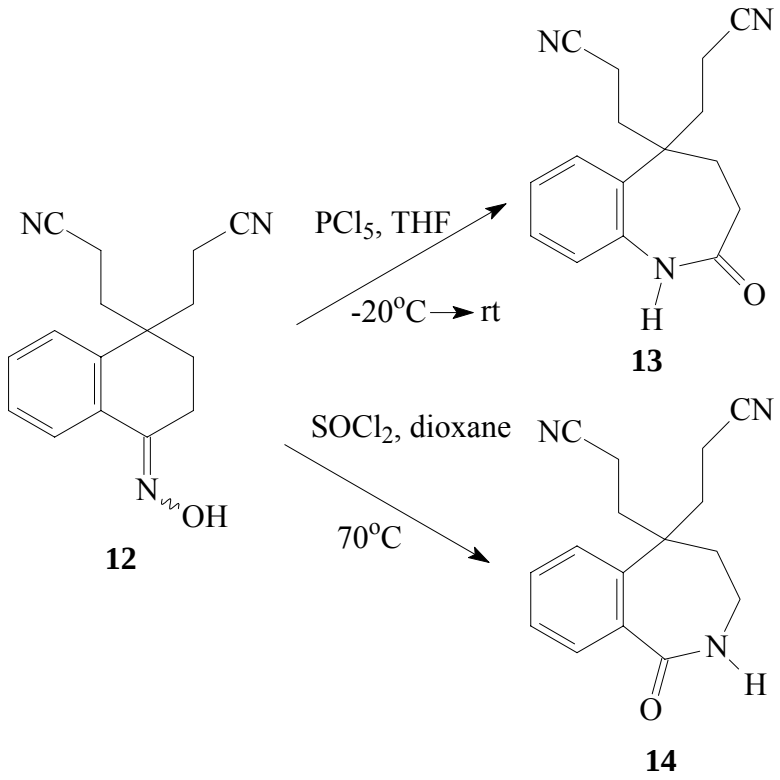
Scheme 2

The Beckmann rearrangement of oxime (**12**) in THF in the presence of phosphorus pentachloride did not afford the desired lactam (Scheme 3), only the 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepinone derivative (**13**) could be isolated from the reaction mixture in 25% yield.

Using thionyl chloride as reagent in dioxane solution at 70°C, however, in the reaction the expected benzo[*c*]azepinone (**14**) was obtained (54%).

The nitrile substituents of azepinone (**14**) were converted to ester groups (89%) by Pinner reaction in refluxing methanolic solution with gaseous hydrogen chloride (Scheme 4). The Dieckmann condensation of diester derivative (**5**) was successful in refluxing benzene using a catalytic amount of potassium *tert*-butoxide giving the corresponding spiro β-keto ester (**4**) in 79.6%. Hydrolysis of the ester group and

decarboxylation reaction resulted in the spiro ketone (**15**) only in 37.4% yield, therefore demethoxycarbonylation of ester (**4**) was investigated. The reaction was carried out in DMF in the presence of NaCl and water at 150°C and the expected ketone (**15**) was obtained in 86.4% yield.



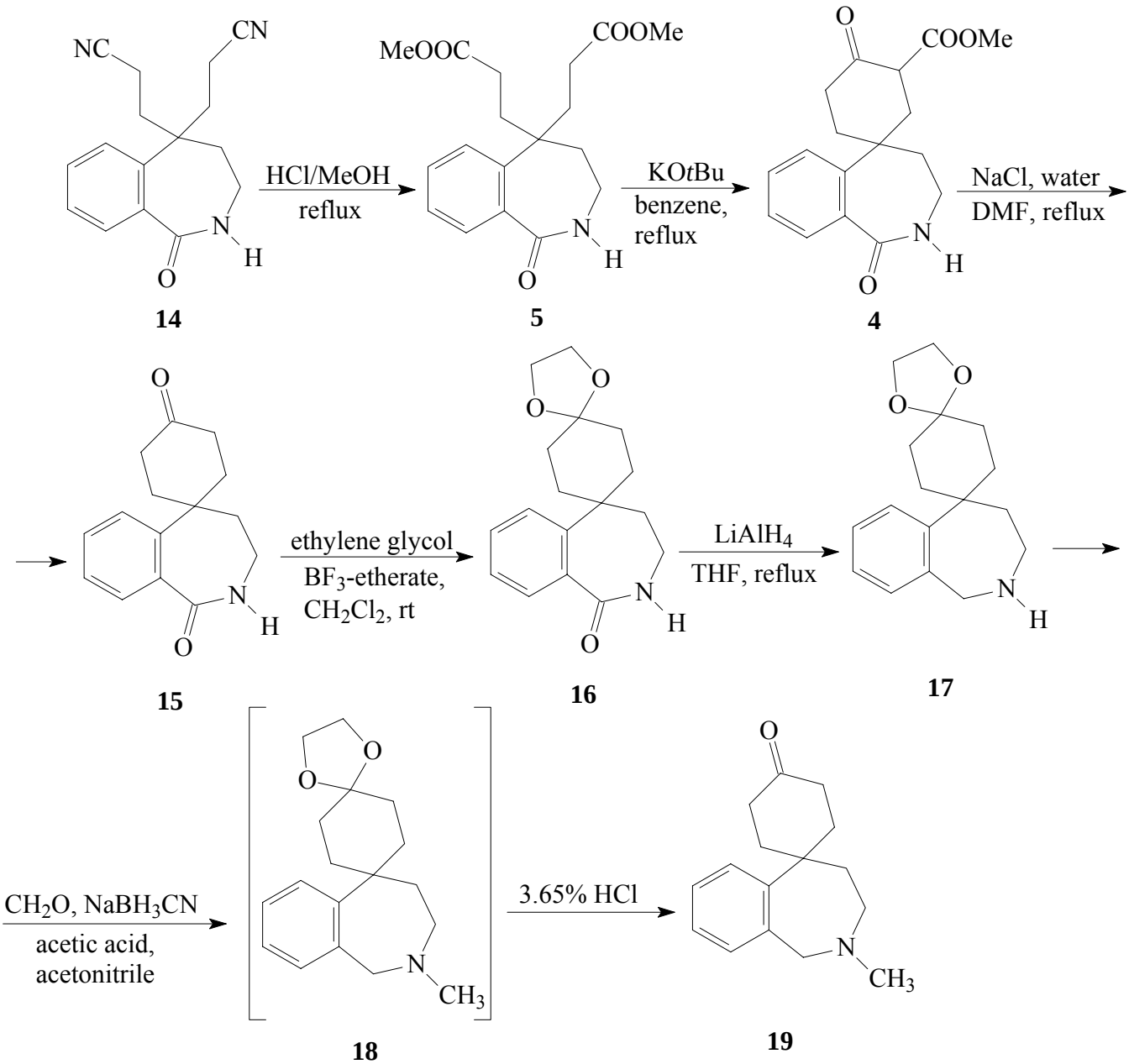
Scheme 3

For reducing the lactam carbonyl group in azepinone (**15**), the ketone carbonyl group was protected as cyclic ketal. Preparation of ketal (**16**) was achieved with ethylene glycol in dichloromethane in the presence of boron trifluoride diethyl etherate at room temperature (92%). After reduction of lactam (**16**) in refluxing THF with lithium aluminum hydride (66.7%), methylation of the nitrogen atom of the saturated azepine ring was carried out by an Eschweiler-Clark type procedure. The expected *N*-methylazepine spiro-substituted by a cyclohexanone ring (**19**) was obtained in 65.3% yield by a simple hydrochloric acid treatment of the *N*-methylketal (**18**), which was not isolated.

Oxidation of azepine (**19**) to introduce one and/or two carbon carbon double bonds to the α,β-position(s) of the cyclohexanone carbonyl group, however, was unsuccessful. The reaction was tried by using *o*-iodoxybenzoic acid[7] elaborated by Nicolaou *et al*.[8] and by reagents (MnO_2, DDQ, SeO_2, Pd/C, Raney Ni *etc*.) generally used, but only decomposition products could be isolated from the reaction mixtures. Moreover, bromination of ketone (**19**) also failed. Therefore oxidation with *o*-iodoxybenzoic acid was achieved using the more stable intermediate, lactam (**15**).

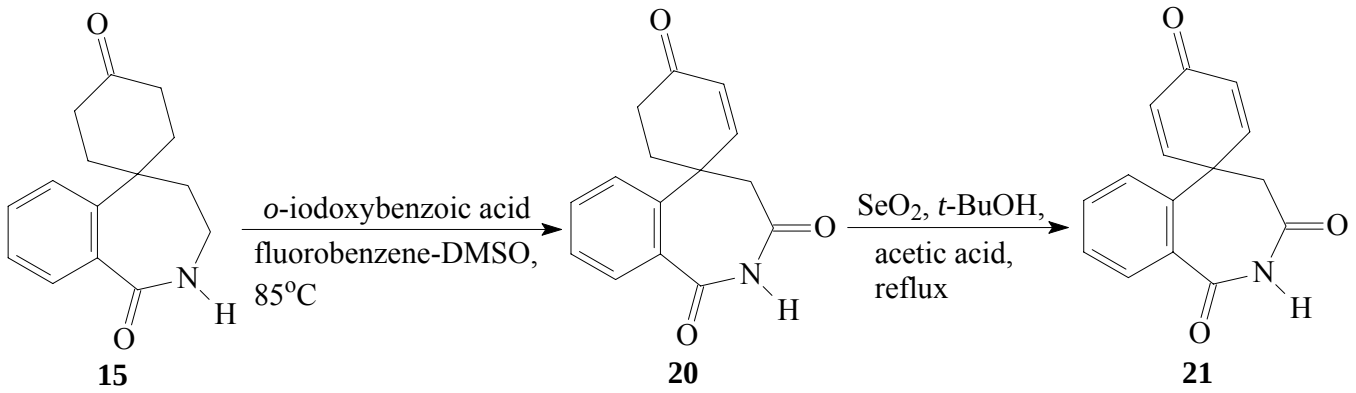
The reaction was carried out in fluorobenzene-DMSO solution at 85°C and resulted in the cyclohexenone

derivative (**20**) in 50.3% yield in which not only the carbon carbon double bond was formed, but the lactam group was transformed to the corresponding cyclic imide structure (Scheme 5). Azepinedione containing two C=C bonds in the spirocyclohexanone substituent (**21**) could be prepared by further oxidation of imide (**20**) with selenium dioxide (38%).



Scheme 4

In conclusion we established an efficient method for the synthesis of benzo[*c*]azepines and benzo[*c*]azepinones spiro-substituted with a saturated or unsaturated cyclohexanone ring containing one or two carbon carbon double bonds.



Scheme 5

EXPERIMENTAL

General

Melting points are uncorrected. IR spectra were recorded on Zeiss IR 75 and 80 instruments. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian INOVA 300 spectrometer. MS spectrometric measurements were performed on a VG-Trio-2 and a Finnigan MAT 95XP (EI, 70 eV) mass spectrometer. High-resolution MS measurements were carried out on a Finnigan MAT 95XP mass spectrometer; perfluorotributylamine was used as a reference compound. TLC was carried out using Kieselgel $60F_{254}$ (Merck) glass plates. 2-Tetralone (**8**) was purchased from Aldrich.

3',3'-(2-Oxo-3,4-dihydronaphthalene-1,1(2*H*)-diyl)dipropanenitrile (7)

To a stirred solution of 2 mL (2.212 g, 15.1 mmol) of 2-tetralone (**8**) in *tert*-butanol (15 mL) 1.8 mL (1.45 g, 27.3 mmol) of acrylonitrile in THF (3 mL) was added under Ar. Then potassium *tert*-butoxide (561 mg, 5 mmol) was added is small portions over approximately 0.5 h. The reaction mixture was stirred for 2 h and the crystals that had separated out were filtered off and washed with cold EtOH. Yield: 2.304 g (88.4%) of product (**7**), mp 93-95°C, lit.,[6] 105.5-16.5°C. The spectroscopic data of product (**7**) were identical with the ketone obtained using Triton-B as catalyst[6].

3',3'-(2-Hydroxy-3,4-dihydronaphthalene-1,1(2*H*)-diyl)dipropanenitrile (9)

6.557 g (26 mmol) of ketone (**7**) was dissolved in a mixture of MeOH (465 mL) and water (5.2 mL) and sodium borohydride (2.95 g, 78 mmol) was added in small portions over 1.5 h at 0°C with stirring. Then the reaction mixture was stirred at 0°C for 15 min and was acidified (pH 5) with acetic acid (*ca*. 30 mL). The solvent was evaporated under reduced pressure, the residue was taken up in dichloromethane (250 mL) and washed with 10% aqueous sodium carbonate and with water. The aqueous layer was washed with dichloromethane (2x250 mL) and the combined organic layers were dried (magnesium sulfate), filtered and evaporated to dryness under reduced pressure to yield 6.48 g (98%) of pure alcohol (**9**), mp 121-123°C (ethyl acetate). TLC (CH_2Cl_2-MeOH 50:1) R_f 0.2; IR (KBr) 3416, 2960, 2260, 1470, 1455, 1040, 790, 760, 745 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.88-2.44 (m, 10H, 2xH_2-2', 2xH_2-3', H_2-4),

2.80-3.00 (m, 2H, H_2-3), 3.97 (m, 1H, H-2), 7.09-7.26 (m, 4H, H-5,6,7,8). Anal. Calcd for $C_{16}H_{18}N_2O$: C 75.56, H 7.13, N 11.01. Found C 75.33, H 7.05, N 11.01.

3',3'-(Naphthalene-1,1(4*H*)-diyl)dipropanenitrile (10)

To a solution of 10.124 g (39.8 mmol) of alcohol (**9**) in pyridine (80 mL) 5.6 mL (9.212 g, 60 mmol) of phosphorus oxychloride was added with stirring. After refluxing for 3 h the reaction mixture was evaporated to dryness under reduced pressure, the residue was poured into ice and acidified with a mixture of water and concd hydrochloric acid 1:1 (*ca*. 150 mL) to pH 1. The acidic mixture was then washed with dichloromethane (3x200 mL), the combined organic layers after drying ($MgSO_4$) were evaporated to dryness. 9.4 g (100%) of oily product (**10**) was obtained which was directly oxidized without any purification. TLC (CH_2Cl_2-MeOH 50:1) R_f 0.67; IR (film) 3020, 2930, 2260, 1490, 1460, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.76-2.30 (m, 8H, 2xH_2-2', 2xH_2-3'), 3.40 (dd, *J*=3.6 Hz and 2.1 Hz, 2H, H_2-4), 5.35 (dt, *J*=10.2 Hz and 2.1 Hz, 1H, H-2), 6.23 (dt, *J*=10.2 Hz and 3.6 Hz, 1H, H-3), 7.12-7.32 (m, 4H, H-5,6,7,8).

3',3'-(4-Oxonaphthalene-1,1(4*H*)-diyl)dipropanenitrile (11)

Olefin derivative (**10**) (9.4 g, 39.8 mmol) freshly prepared was dissolved in acetic acid (360 mL) and 14.9 g (148.6 mmol) of CrO_3 was added dropwise in acetic acid (180 mL)-water (18) mL solution at 14-16°C over 1 h under stirring. The reaction mixture was stirred at rt for 1 h and isopropanol (410 mL) was added dropwise under external ice-water cooling. After stirring for 1 h at rt reaction mixture was evaporated to dryness in vacuum. The residue was suspended in water (250 mL) and made to alkaline (pH 8) with solid sodium hydrogencarbonate. Then the mixture was extracted with dichloromethane (3x200 mL), the combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was treated with diisopropyl ether (35 mL) yielded 9.8 g (98.5%) of unsaturated ketone (**11**), mp 118-120°C. TLC (CH_2Cl_2-MeOH 50:1) R_f 0.22; IR (KBr) 2930, 2250, 1670, 1610, 1460, 1310, 840, 770, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70-2.53 (m, 8H, 2xH_2-2', 2xH_2-3'), 6.71 and 6.73 (d, *J*=10.5 Hz, 2H, H-2,3), 7.44 (m, 1H, H-8), 7.54 (m, 1H, H-6), 7.72 (m, 1H, H-7), 8.24 (m, 1H, H-5). MS *m/z* (%): 250(6.6), 210(39.3), 196(100), 168(8.3), 157(6.9), 141(66.9), 128(59.3), 115(12.8), 102(13.8); HRMS: calcd 250.1101, found 250.1106 (delta: 2.2 ppm).

3',3'-(4-Oxo-3,4-dihydronaphthalene-1,1(2*H*)diyl)dipropanenitrile (6)

9.54 g (38.1 mmol) of unsaturated ketone (**11**) was hydrogenated in a mixture of dichloromethane (120 mL) and ethanol (120 mL) in the presence of 10% palladium on charcoal (1.3 g) at rt under atmospheric pressure. The catalyst was filtered off, the filtrate was evaporated to dryness to give 9.2 g (96%) of saturated product (**6**), mp 91-92°C (ethanol). TLC (benzene-MeOH 14:2) R_f 0.42; IR (KBr) 2950, 2255, 1690, 1600, 1460, 1195, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.00-2.18 and 2.22-2.35 (m, 10H, H_2-2, 2xH_2-2', 2xH_2-3'), 2.77 (t, *J*=7.2 Hz, 2H, H_2-3), 7.22 (m, 1H, H-8), 7.42 and 7.65 (m, 2H, H-6,7), 8.14 (m,

1H, H-5). Anal. Calcd for $C_{16}H_{16}N_2O$: C 76.16, H 6.39, N 11.101. Found C 75.79, H 6.18, N 11.04.

3',3'-(4-Hydroxyimino-3,4-dihydronaphthalene-1,1(2*H*)-diyl)dipropanenitrile (12)

To a solution of ketone (**6**) (2.58 g, 10.24 mmol) in ethanol (60 mL) and dichloromethane (35 mL) 1.42 g (20.47 mmol) of hydroxylamine hydrochloride dissolved in water (14 mL) was added. The reaction mixture was stirred for 1 week at rt and was evaporated to dryness in vacuum. The residue was shared between water (280 mL) and dichloromethane (280 mL) and the pH was adjusted to 8-9 by adding of solid sodium hydrogencarbonate. After separation the water phase was extracted with dichloromethane (3x280 mL), the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give 2.51 g (91.7%) of product (**12**), mp 169-170°C (ethyl acetate). TLC (CH_2Cl_2-MeOH 40:1) R_f 0.41; IR (KBr) 3380, 2950, 2270, 2250, 1495, 1470, 1430, 1320, 1070, 960, 780 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.72 (t, J=6.9 Hz, 2H, H_2-2), 1.80-2.40 (m, 8H, 2xH_2-2', 2xH_2-3'), 2.70 (t, J=6.9 Hz, 2H, H_2-3), 7.18-7.44 (m, 3H, H-6,7,8), 7.92 (m, 1H, H-9), 11.21 (s, 1H, OH). MS *m/z* (%): 267(24.8), 252(8.3), 213(22.6), 198(100), 195(67.5), 182(73.9), 174(29.3), 168(24.8), 157(89.2), 154(32.5), 141(95.5), 128(42.0), 120(30.6), 115(41.4); HRMS: calcd 267.1366, found 267.1368 (delta: 0.6 ppm). Anal. Calcd for $C_{16}H_{17}N_3O$: C 71.89, H 6.41, N 15.72. Found C 72.02, H 6.19, N 15.25.

3',3'-(2-Oxo-1,2,3,4-tetrahydrobenzo[*b*]azepin-5,5-diyl)dipropanenitrile (13)

To a solution of 190 mg (0.71 mmol) of oxime (**12**) in THF (5 mL) phosphorus pentachloride 171 mg (0.82 mmol) was added in small portions at -20°C with stirring. The reaction mixture was stirring at -20°C for 2 h and at rt for 21 h, then made alkaline (pH 10) with cooled saturated aqueous sodium hydrogencarbonate. After extracting with dichloromethane (3x40 mL) the combined organic layers were dried ($MgSO_4$), the solvent was evaporated and the residue was purified by preparative layer chromatography on silica gel (CH_2Cl_2-MeOH 20:1) yielded 48 mg (25%) of product (**13**), mp 149-151°C. TLC (CH_2Cl_2-MeOH 20:1) R_f 0.43; IR (KBr) 3330, 2950, 1680, 1405, 1210, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.06-2.50 (m, 12H, H_2-3,4, 2xH_2-2', 2xH_2-3'), 7.04 (m, 1H, H-9), 7.21-7.37 (m, 3H, H-6,7,8), 8.27 (br s, 1H, N(1)H [NOE: N(1)H→H-9]); MS *m/z* (%): 267(43.9), 238(1.6), 227(1.3), 213(100), 185(49.0), 171(12.7), 158(8.9), 144(31.8), 130(34.1), 115(8.3); HRMS: calcd 267.1366, found 267.1372 (delta: 2.0 ppm).

3',3'-(1-Oxo-1,2,3,4-tetrahydrobenzo[*c*]azepin-5,5-diyl)dipropanenitrile (14)

3.654 g (13.67 mmol) of oxime (**12**) was dissolved in dioxane (75 mL) and 5.35 mL (8.73 g, 73.3 mmol) of thionyl chloride was added dropwise in dioxane solution (40 mL). The reaction mixture was heated at 70°C for 2 h, was poured into a mixture of saturated aqueous sodium hydrogencarbonate (400 mL) and ice and was extracted with dichloromethane (3x350 mL). The organic layers were combined, after drying ($MgSO_4$) the solvent was evaporated under reduced pressure and the residue was treated with methanol. 1.26 g of product (**14**) was separated by filtration and another crop of **14** (710 mg) was isolated by

column chromatography (silica gel; dichloromethane-methanol 30:1) from the methanolic mother liquor. Yield: 1.97 g (54%), mp 174-176°C. TLC (CH_2Cl_2-MeOH 20:1) R_f 0.17; IR (KBr) 3400, 2950, 2260, 1665, 1470, 1360, 780, 730 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.85 (t, *J*=6.3 Hz, 2H, H_2-4), 2.00-2.48 (m, 8H, 2xH_2-2', 2xH_2-3'), 2.92 (q, *J*=6.3 Hz, 2H, H_2-3), 7.33 (m, 1H, H-6), 7.40 and 7.50 (m, 2H, H-7,8), 7.57 (m, 1H, H-9) 8.15 (t, 1H, *J*=6.3 Hz, N(2)H [NOE: N(2)H→H_2-3]). MS *m/z* (%): 268(64.8) [MH^+], 238(1.4), 227(4.1), 213(2.8), 198(27.6), 184(42.8), 157(7.9), 144(22.1), 128(15.2), 115(42.7), 30(100); HRMS: calcd 267.1366, found 267.1358 (delta: -2.9 ppm). There are some diagnostic differences in the mass spectra of compounds (**13**) and (**14**); in particular, the structure of **14** is verified by the base peak of *m/z* 30 [CH_2=NH_2^+].

Dimethyl 3',3'-(1-Oxo-1,2,3,4-tetrahydrobenzo[*c*]azepin-5,5-diyl)dipropanoate (5)

Into a suspension of 4.3 g (16 mmol) of dinitrile (**14**) in methanol (45 mL) dry hydrochloric acid was introduced for 1 h. Then the reaction mixture was refluxed for 3 h, was poured in a mixture of ice and saturated aqueous sodium carbonate solution (180 mL) and extracted with dichloromethane (3x120 mL). The combined organic layers were dried ($MgSO_4$), the solvent was evaporated to dryness under reduced pressure and the residue was treated with ether to give 4.75 g (89.1%) of diester (**5**), mp 104-105°C. TLC (CH_2Cl_2-MeOH 20:1) R_f 0.37; IR (KBr) 3210, 2960, 1740, 1670, 1470, 1440, 1370, 1210, 1180, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.97 (t, *J*=6.3 Hz, 2H, H_2-4), 2.01-2.41 (m, 8H, 2xH_2-2', 2xH_2-3'), 3.17 (q, *J*=6.3 Hz, 2H, H_2-3), 3.63 (3, 6H, 2xOCH_3), 6.79 (t, *J*=6.3 Hz, 1H, N(2)H), 7.34-7.51 (m, 3H, H-6,7,8), 7.80 (m, 1H, H-9). Anal. Calcd for $C_{18}H_{23}NO_5$: C 64.85, H 6.95, N 4.20. Found C 64.92, H 7.00, N 4.05.

Methyl {1,4'-dioxo-1,2,3,4-tetrahydrospiro[benzo[*c*]azepine-5,1'-cyclohexane]-3'-carboxylate} (4)

To a solution of 4.1 g (12.3 mmol) of diester (**5**) in benzene (162 mL) 3.12 g (27.83 mmol) of potassium *tert*-butoxide was added and the reaction mixture was refluxed for 30 min. After cooling to rt 2 mL of water was added with stirring, the mixture was evaporated to dryness, acidified by 2N hydrochloric acid and extracted with dichloromethane (3x120 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated to yield 3.0 g (79.6%) of β-oxo ester derivative (**4**) as a foam. TLC (CH_2Cl_2-MeOH 20:1) R_f 0.54; IR (KBr) 3240, 2930, 1659, 1620, 1450, 1290, 1235, 1210, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (in $CDCl_3$ the compound is predominantly present in its enolic tautomer form) δ 1.64-2.20 (m, 6H, H_2-4,5',6'), 2.44 (d, *J*=16.2 Hz, 1H, H_x-2'), 2.80 (d, *J*=16.2 Hz, 1H, H_y-2'), 3.17 (m, 2H, H_2-3), 3.83 (s, 3H, OCH_3), 6.62 (br t, 1H, N(2)H), 7.16 (m, 1H, H-6), 7.32-7.44 (m, 2H, H-7,8), 7.74 (m, 1H, H-9), 12.01 (s, 1H, enolic OH). MS *m/z* (%): 301(12.4), 283(6.6), 269(6.9), 258(18.6), 226(26.9), 213(28.3), 198(7.6), 185(12.4), 174(100), 145(26.2), 128(28.3), 115(35.2); HRMS: calcd 301.1309, found 301.1308 (delta: -0.2 ppm).

3,4-Dihydrospiro[benzo[*c*]azepin-5,1'-cyclohexane]-1(2*H*),4'-dione (15)

Method A. The solution of 96 mg (0.32 mmol) of oxo ester (**4**) in ethanol (2.6 mL) and 1N hydrochloric acid (2 mL) was refluxed for 13 h. The reaction mixture was evaporated to dryness under reduced pressure, the residue was shared between water (5 mL) and dichloromethane (10 mL) and made to alkaline with saturated aqueous sodium hydrogencarbonate (5 mL). After washing with dichloromethane the combined organic layers were dried ($MgSO_4$) and the solvent was evaporated in vacuum. The residue was purified by preparative layer chromatography on silica gel (CH_2Cl_2-MeOH 20:1) to give 29 mg (37.4%) of cyclohexanone derivative (**15**), mp 151-152°C. TLC (CH_2Cl_2-MeOH 20:1) R_f 0.25; IR (KBr) 3200, 2930, 1660, 1600, 1470, 1400, 800, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.06 (t, *J*=6.6 Hz, 2H, H_2-4), 2.07-2.53 (m, 8H, H_2-2',3',4',6'), 3.18 (q, *J*=6.6 Hz, 2H, H_2-3), 6.74 (br t, *J*=6.6 Hz, 1H, N(2)H), 7.39-7.55 (m, 3H, H-6,7,8), 7.79 (m, 1H, H-9). MS *m/z* (%): 243(93.6), 226(5.1), 214(8.3), 200(100), 186(15.3), 172(28.7), 158(52.9), 144(47.1), 128(28.7), 115(33.8), 30(40.1); HRMS: calcd 243.1254, found 243.1253 (delta: -0.3 ppm).

Method B. To a solution of 9.15 g (30.4 mmol) of keto ester (**4**) in DMF (141 mL) 1.1 mL (1.1 g, 60.35 mmol) of water and 1.77 g (30.4 mmol) of sodium chloride was added. The reaction mixture was heated at 150°C for 3 h under argon, then was evaporated to dryness under vacuum. The residue was shared between dichloromethane (480 mL) and brine (150 mL), the organic phase was washed with dichloromethane (3x320 mL) and the combined organic layers were after drying ($MgSO_4$) evaporated to dryness under reduced pressure. The residue was treated with ether and the product (**15**) was obtained by filtration. From the ethereal mother liquor further product could be isolated by preparative layer chromatography on silica gel (CH_2Cl_2-MeOH 20:1). Yield: 6.378 g (86.45%). Product proved to be identical with **15** obtained according to *Method A*.

3,4-Dihydrodispiro[benzo[*c*]azepin-5,1'-cyclohexane-4',2"-[1,3]-dioxolan]-1(2*H*)-on (16)

Ketone (**15**) (1.39 g, 5.7 mmol) was dissolved in dichloromethane (40 mL), 0.53 mL (589 mg, 9.4 mmol) of ethylene glycol and 0.16 mL (176 mg, 1.24 mmol) boron trifluoride diethyl etherate were added and the solution was allowed to stand at rt for 10 d. Then the reaction mixture was evaporated to dryness under vacuum, the residue was taken up in dichloromethane (100 mL), 100 mL of water was added and the mixture was made to alkaline (pH 8-9) with some drops of concd ammonia. The water phase was washed with dichloromethane (100 mL), the combined organic layers were dried with $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was chromatographied by silica gel column (benzene-methanol 14:0.5) to give 1.513 g (92.26%) of ketal (**16**), mp 188-189°C. TLC (benzene-MeOH 14:3) R_f 0.4; IR (KBr) 3200, 2950, 1670, 1640, 1450, 1100, 925, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.55-2.22 (m, 8H, H_2-2',3',4',6'), 1.98 (t, *J*=6.3 Hz, 2H, H_2-4), 3.11 (q, *J*=6.3 Hz, 2H, H_2-3), 3.87-3.97 (m, 4H, dioxolane), 6.61 (br t, *J*=6.3 Hz, 1H, N(2)H), 7.32-7.46 (m, 3H, H-6,7,8), 7.72 (m, 1H, H-9). MS *m/z* (%): 287(8.3), 259(0.7), 243(2.1), 144(3.4), 128(6.9), 115(10.0), 99(100), 86(75.2); HRMS: calcd

287.1516, found 287.1512 (delta: -1.2 ppm).

1,2,3,4-Tetrahydrodispiro[benzo[*c*]azepin-5,1'-cyclohexane-4',2"-[1,3]-dioxolane] (17)

3.04 g (80.27 mmol) of lithium aluminum hydride was suspended under Ar in THF (80 mL) with stirring, azepinon (**16**) (2.05 g, 7.14 mmol) was added dropwise in THF (112 mL) solution, the mixture was refluxed for 58 h and then was quenched with saturated aqueous solution of Seignette salt. The solution layer was decanted and this procedure was repeated three times with THF (3x120 mL). The combined THF layers were evaporated in vacuum, the residue was taken up in dichloromethane (100 mL), after washing with water (100 mL) and drying ($MgSO_4$) solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (benzene-MeOH 14:3) to give 1.3 g (66.7%) of azepine (**17**) as an oil. TLC (benzene-MeOH 14:3) R_f 0.34; IR (film) 2950, 1450, 1100, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70-2.22 (m, 8H, H_2-2',3',4',6'), 1.73 (t, *J*=6.5 Hz, 2H, H_2-4), 3.29 (t, *J*=6.5 Hz, 2H, H_2-3), 3.96 (s, 4H, dioxolane), 4.31 (s, 2H, H_2-1), 6.22 (br s, 1H, N(2)H), 7.14-7.50 (m, 4H, H-6,7,8,9). MS *m/z* (%): 273(17.9), 256(2.1), 245(11.0), 228(26.2), 212(2.4), 200(5.5), 172(13.8), 158(19.3), 144(32.8), 129(34.5), 119(54.5), 99(100), 86(33.8); HRMS: calcd 273.1723, found 273.1718 (delta: -1.9 ppm).

2-Methyl-1,2,3,4-Tetrahydrospiro[benzo[*c*]azepin-5,1'-cyclohexan]-4'-one (19)

To a solution of ketal (**17**) (722 mg, 2.64 mmol) in acetonitrile (37 mL) 10.5 mL of acetic acid was added dropwise at 0°C. After stirring for 5 min sodium cyanoborohydride (662 mg, 10.52 mmol) was added in three parts, stirred at 0°C for 15 min and 15.8 mL of 37% aqueous formaldehyde solution was added dropwise. After stirring at this temperature for 24 h the reaction mixture was diluted with water (40 mL), made alkaline to pH 8 by 10% aqueous sodium carbonate solution and the layers were separated. The organic phase was washed with dichloromethane (3x70 mL) and the combined dichloromethane layers after drying ($MgSO_4$) were evaporated to dryness in vacuum to give the intermediate *N*-methylketal (**18**) as a crude product which was not isolated. Therefore the residue was taken up in dichloromethane (60 mL) and was stirred with 1N hydrochloric acid for 30 min at rt. After separating aqueous phase was made to alkaline (pH 9) with solid sodium hydrogencarbonate and was extracted with dichloromethane (3x100 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by preparative layer chromatography on silica gel ($CHCl_3$-MeOH 7:3) to give 420 mg (65.3%) of **19** as an oil. TLC ($CHCl_3$-MeOH 7:3) R_f 0.55; IR (film) 2940, 1710, 1450, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.07 (m, 2H, H_2-4), 2.30-2.58 (m, 8H, H_2-2',3',4',6'), 2.35 (s, 3H, NCH_3), 3.02 (m, 2H, H_2-3), 3.96 (s, 2H, H_2-1), 7.10-7.41 (m, 4H, H-6,7,8,9). MS *m/z* (%): 243(39.3), 228(33.8), 215(8.3), 200(11.0), 186(26.9), 174(71.0), 158(42.8), 142(58.6), 132(100), 115(80.0), 91(32.4), 42(70.3); HRMS: calcd 243.1618, found 243.1609 (delta: -3.5 ppm).

Spiro[benzo[*c*]azepin-5,1'-cyclohexane]-2'-ene-1(2*H*),3(4*H*),4'-trione (20)

2.472 g (10.16 mmol) of lactam (**15**) was dissolved in a mixture of fluorobenzene (34 mL) and DMSO (68 mL) and 11.1 g (39.63 mmol) of *o*-iodoxybenzoic acid[7] were added. The reaction mixture was heated at 85°C with stirring under argon for 76 h. Then the solvent was evaporated under vacuum, the residue was taken up in dichloromethane (500 mL), washed with saturated aqueous sodium hydrogencarbonate (2x150 mL), with water (250 mL) and with saturated aqueous sodium chloride solution (2x150 mL). The organic layer after drying ($MgSO_4$) was evaporated to dryness under reduced pressure and the residue was purified by column chromatography on silica gel (dichloromethane-methanol 30:1) to yield 1.306 g (50.3%) of olefin (**20**), mp 131-134°C. TLC (CH_2Cl_2-MeOH 20:1) R_f 0.50; IR (KBr) 3450, 3090, 2950, 1694, 1675, 1667, 1316, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.10-2.53 (m, 4H, H_2-5',6'), 3.02 (d, *J*=15.9 Hz, 1H, H_x-4), 3.24 (d, *J*=15.9 Hz, 1H, H_y-4), 6.30 (d, *J*=10.2 Hz, 1H, H-3'), 6.79 (d, *J*=10.2 Hz, 1H, H-2'), 7.34 (m, 1H, H-6), 7.48-7.60 (m, 2H, H-7,8), 8.35 (m, 1H, H-9), 8.74 (br s, 1H, N(2)H). MS *m/z* (%): 255(8.9), 227(14.1), 213(100), 199(35.3), 185(21.2), 171(26.9), 156(25.0), 141(19.2), 128(53.2), 115(26.9), 102(16.7); HRMS: calcd 255.0890, found 255.0884 (delta: -2.1 ppm).

Spiro[benzo[*c*]azepin-5,1'-cyclohexane]-2',5'-diene-1(2*H*),3(4*H*),4'-trione (21)

To a solution of cyclohexenone (**20**) (955 mg, 3.74 mmol) in *tert*-butanol (63 mL) 0.63 mL of glacial acetic acid and 623 mg (5.61 mmol) of selenium dioxide were added. After refluxing under argon for 24 h an other part of selenium dioxide (623 mg, 5.61 mmol) was added. The reaction mixture was refluxed for 24 h, then adding of SeO_2 (623 mg, 5.61 mmol) was repeated and reflux was going on for further 24 h. The hot solution was decanted and 60 mL of *tert*-butanol and then dichloromethane (60 mL) were added to wash solid precipitation again. After decantation of solutions the organic layers were combined and evaporated under reduced pressure. The residue was dissolved in dichloromethane (150 mL), washed with saturated aqueous sodium carbonate (4x100 mL), dried ($MgSO_4$) and evaporated to dryness under vacuum. The residue was purified by preparative layer chromatography on silica gel (dichloromethane-methanol 20:1) to give 360 mg (38%) of dienone (**21)**, mp 198-200°C. TLC Kieselgel (CH_2Cl_2-MeOH 20:1) R_f 0.50, Aluminiumoxid $60F_{254}$ (DC Alufolien) (CH_2Cl_2-MeOH 20:1) R_f 0.8; IR (KBr) 3450, 3095, 2930, 1700, 1675, 1667, 1310, 860, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.16 (s, 2H, H_2-4), 6.46 (d, *J*=6.0 Hz, 2H, H-2',6'), 7.12 (d, *J*=6.0 Hz, 2H, H-3',5'), 7.30 (m, 1H, H-6), 7.50-7.59 (m, 2H, H-7,8), 8.43 (m, 1H, H-9), 8.54 (br s, 1H, N(2)H). MS *m/z* (%): 253(22.3), 236(5.4), 225(56.8), 210(100), 196(38.5), 181(46.6), 168(26.9), 153(40.5), 139(23.6), 128(20.9), 115(10.8), 102(10.8); HRMS: calcd 253.0733, found 253.0729 (delta: -1.6 ppm).

ACKNOWLEDGEMENTS

The authors are grateful to Dr. H. Medzihradszky-Schweiger and her staff for the microanalyses, to Dr. G. Czira for providing part of the MS data, to A. Fürjes and I. Sinka for their NMR technical assistance and

to OTKA (Hungarian Academic Research Found Grant T 042491) and to Richter Gedeon Rt for financial assistance. Moreover one of the authors (Á. G.) is indebted to József Varga Foundation for financial support.

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