Pergamon

Tetrahedron 57 (2001) 5843–5850

TETRAHEDRON

Seven-membered ring formation through Grewe-cyclization

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Received 15 February 2001; revised 17 April 2001; accepted 3 May 2001

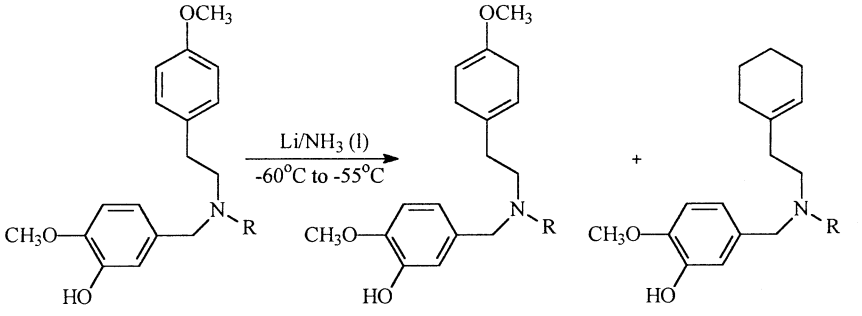
Abstract—The first example of seven-membered ring formation using Grewe-cyclization of cyclohexene derivatives (**3b** and **c**) yielding spiro-substituted benzo[*c*]azepines (**9b** and **c**) is presented.

1. Introduction

The acid-catalyzed cyclization of *N*-benzyloctahydroisoquinolines resulting in morphinan derivatives was first presented by Grewe.[1,2] This type of ring closure reaction has become known as the 'Grewe-cyclization' and has been widely used as a classical method in the synthesis of opium alkaloids.[3–7] The Grewe-cyclization was performed under different acidic reaction conditions (e.g. cc. phosphoric acid, cc. sulphuric acid and their mixture, 48% hydrobromic acid, $NH_4F{\cdot}HF$ in triflic acid) and as a result six-membered ring closure occurred. A seven-membered ring-closure under the conditions of the Grewe-cyclization was attempted only in one case, but failed.[8] In the course of our work aimed at synthesizing some natural products, we encountered the problem of cyclizing compounds **4** into the ring system **9** using Grewe's method.[1]

2. Results and discussion

The starting materials were prepared as follows. Condensation of 4-methoxy-phenethylamine with 3-hydroxy-4-methoxybenzaldehyde, followed by reduction by sodium borohydride of the formed imine, gave amine **1a**. Methylation of **1a** to **1c** was carried out with formylation and subsequent reduction of the intermediate *N*-formyl compound **1b** with lithium aluminium hydride. Alternatively, **1c** was prepared by allowing **1a** to react with formaldehyde and sodium borohydride.[9]



1a; R= H
1b, R= CHO
1c; R= CH_3

2a; R= H (72%)
2b; R= CHO (63%)
2c; R= CH_3

3a; R= H
3b; R= CHO (8%)
3c; R= CH_3

Scheme 1.

Keywords: reduction; rearrangement; cyclization; benzazepines.
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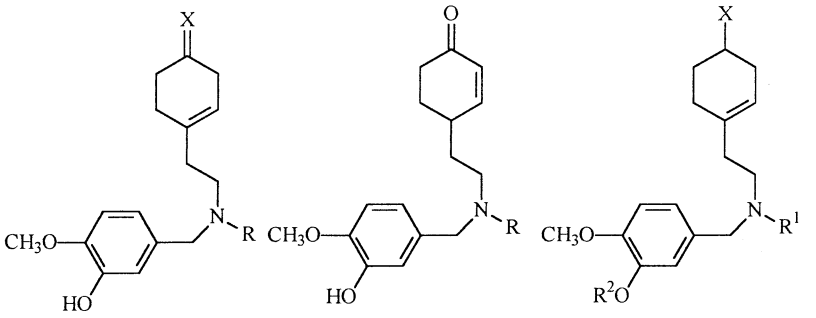
0040–4020/01/$ - see front matter
PII: S0040-4020(01)00497-5

Birch reduction of amines **1a** and **1c** was performed with lithium metal in liquid ammonia in the presence of *t*-butanol as the proton source. The reaction gave enolethers **2a** and **2c** and the unexpected derivatives **3a** and **3c**, respectively (Scheme 1). The overreduction of *p*-substituted anisole to a cyclohexene derivative has precedent in the literature.[10] Enolether **2a** and cyclohexene **3a** were conveniently separated by column chromatography as *N*-formyl derivatives (**2b** and **3b**) prepared by formylation with phenyl formate. Birch reduction of the *N*-methyl tertiary amine **1c** gave similar results. After demethylation of enol ether **2c** by treatment with aqueous formic acid, ketone **4a** and the cyclohexene derivative **3c** were isolated by column chromatography. Similarly, the *N*-formyl enolether **2b** was transformed into ketone **4b**.

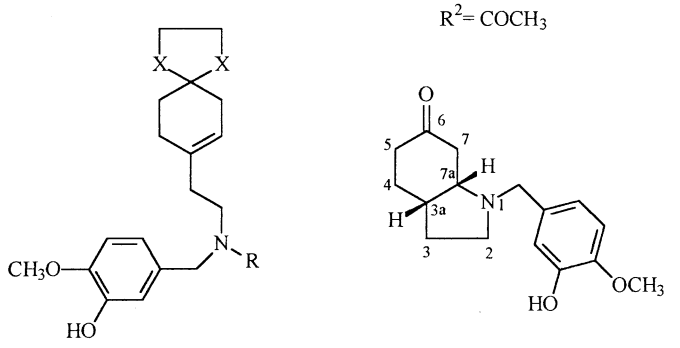
The next step should have been the acidic cyclization of ketones **4** under the conditions of the Grewe-cyclization. We were, however, unsuccessful in that respect although several acidic systems mentioned above were investigated. Instead of ring closure, the double bond moved to the thermodynamically more stable conjugated position, forming compound **5**. Rice[4] encountered a similar problem during his synthesis of morphine. His solution to the problem was the application of a 'super-acid' system (trifluoromethanesulfonic acid+ammonium fluoride). In



4a; R= CH_3, X= O
4b; R= CHO, X= O
4c; R= CH_3, X= NOH

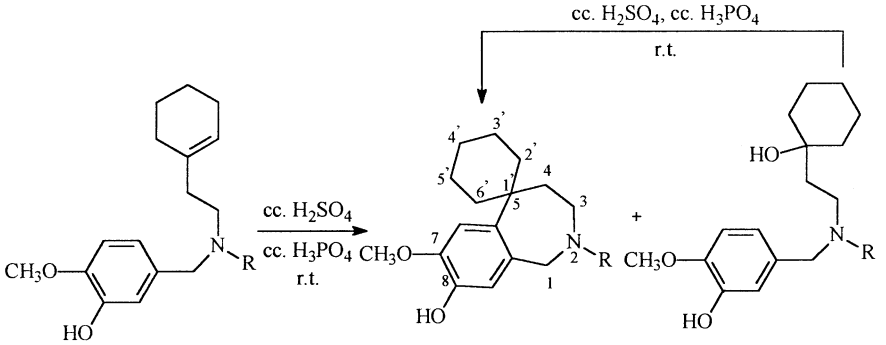
5a; R= H
5b; R= CHO

6a; X= OH, R^1= CH_3, R^2= H
6b; X= OH, R^1= CHO, R^2= H
6c; X= NH_2, R^1=CHO, R^2= H
6d; X= $NHCOCH_3$, R^1= CHO, R^2= $COCH_3$



7a; X= O, R= CH_3
7b; X= O, R= CHO
7c; X= S, R= CHO
7d; X= S, R= H

8



3b; R= CHO
3c, R= CH_3

9a; R= H (40%)
9b; R= CHO (21%)
9c; R= CH_3 (21.5%)

10b; R= CHO (37%)
10c; R= CH_3 (16%)

Scheme 2.

such a system the carbonyl oxygen is assumed to be highly protonated, thus eliminating the thermodynamic driving force towards formation of the conjugated system. Unfortunately, in our case the above system did not work: either the starting material was recovered or the conjugated ketones **5a** and **b** were obtained. Further on we tried to mask the keto group by using standard procedures in order to prepare several derivatives such as oxime **4c**, hydroxy derivatives **6a** and **b**, ketals **7a** and **b** and dithioketal **7c**. In order to prevent the isomerization of the β,γ-double bond, ketone **4b** was allowed to react with 1,2-ethanedithiol in the presence of borontrifluoride etherate[11] to give dithiolane **7c** in good yield. Because of the poor solubility of compound **7c** in the mixture of cc. sulphuric acid and cc. phosphoric acid, it was transformed with aqueous sodium hydroxide into the amino compound **7d**. Under acidic conditions, however, **7d** became deprotected, and subsequently isomerized to **5a** which, after basification, cyclized to **8**[12] isolated as crystalline hydrobromide salt.

Subsequently, we investigated the behavior of the amino compound **6c** under similar conditions. The amino compound **6c** was prepared from ketone **4b** applying reductive amination.[13,14] The purification of **6c** proved to be difficult, therefore **6c** was transformed into the diacetyl derivative **6d** by refluxing in acetic anhydride. Unfortunately, neither the amine **6c** nor its diacetyl derivative **6d** could be cyclized under the mentioned conditions. All these failures can be rationalized by assuming that: (a) the strained seven-membered ring does not form under Grewe's conditions (excepting one failed attempt,[8] we could not find any example of a similar reaction in the literature); (b) the isomerization of the double bond in ketone **4** is much faster than the slow seven-membered ring formation, unlike in the case of the faster six-membered ring formation.

To investigate the problem we repeated the reaction using compounds **3** (Scheme 2). Performing Grewe-cyclization both with *N*-formyl (**3b**) and *N*-methyl cyclohexenes (**3c**) in the proven acidic system (a 1:1 vol/vol mixture of cc. phosphoric acid and cc. sulphuric acid) the ring closure occurred and we could isolate the spiro-substituted benzo-[*c*]azepines **9b** (21%) and **9c** (21.5%) in addition to the tertiary alcohols **10b** (37%) and **10c** (16%). Alcohols **10b** and **c** were transformed into **9b** (55%) and **9c** (9.3%), respectively, under the same conditions. Deformylation of **9b** by refluxing under alkaline conditions yielded benzo-[*c*]azepine **9a** (40%).

Thus we found the first case of seven-membered ring formation using Grewe-cyclization. In the literature only a few relatives of compound **9** are described with analgetic[15] or cholinesterase inhibition activity.[16] Derivatives of benzo-[*c*]azepine **9** could be a good precursor for the synthesis of new derivatives with useful biological activity.

3. Experimental

3.1. General

Melting points are uncorrected. IR spectra were recorded on ZEISS IR 75 and 80 instruments. ^{1}H NMR spectra were recorded on a Bruker DRX 500 (compounds **1a–c**) and a Varian INOVA 300 spectrometer (all other compounds). Mass spectrometric measurements were performed on a VG-Trio-2 (EI 70 eV) spectrometer. High-resolution MS measurements were performed on a Finnigan MAT 95SQ hybrid tandem mass spectrometer. TLC was carried out using Kieselgel 60 F_{254} (Merck) plates.

3.1.1. 2-Methoxy-5-{[2-(4-methoxy-phenyl)-ethylamino]-methyl}-phenol (1a). To a solution of isovanillin (10.00 g, 66 mmol) in dry ethanol (330 ml), 4-methoxyphenethylamine (10 g, 66 mmol) and 4 Å molecular sieves (62 g) were added. After stirring overnight the molecular sieves were filtered and washed with dry methanol (330 ml). Sodium borohydride (5 g, 132.2 mmol) was added to the filtrate at 0°C in 6–8 portions, then the reaction mixture was stirred for 3 h at room temperature. The solvent was removed in vacuo, the residue was suspended in saturated NaCl solution (410 ml), adjusted to pH 8 with 5% aq. HCl solution (ca. 80 ml) and was extracted with ethyl acetate (3×200 ml). The combined organic extracts were washed with 5% aq. HCl solution (2×200 ml) and the combined acidic extracts were made alkaline (pH 8) with 40% (120 ml) and then with 15% (50 ml) aq. NaOH solutions. After extraction with dichloromethane (4×100 ml), the combined organic phase was dried over $MgSO_4$, concentrated in vacuo giving **1a** (16.9 g, 89%) as a white solid, mp 83–84°C (ethyl acetate). TLC (dichloromethane–methanol 10:1) R_f 0.4; IR (KBr) 3420, 3285, 1605–1585 cm^{-1} ^{1}H NMR ($CDCl_3$, δ_{TMS}=0.00 ppm): 2.78 (2H, m, –CH_2CH$_2$N–); 2.85 (2H, m, –CH$_2$CH_2N–); 3.71 (2H, s, –NCH_2Ph); 3.76 (3H, s, OCH$_3$); 3.80 (3H, s, OCH$_3$); 4.65 (2H, broad, OH+NH); 6.74 (2H, m, Ar-H-3,4) and 6.86 (1H, m, Ar-H-6); 6.79 (2H, dm) and 7.07 (2H, dm) (H-*o*,*o*′-PhOMe, H-*m*,*m*′-PhOMe). MS *m*/*z* (%): 288 (0.1, MH$^+$), 287 (M$^+$), 166 (43.0), 137 (100.0), 121 (19.0), 94 (15.0), 77 (12.0), 65 (7.0). Anal. Calcd for $C_{17}H_{21}NO_3$ (287.36): C, 71.06; H, 7.37; N, 4.87. Found C, 71.00; H, 7.51; N 5.03.

3.1.2. 2-Methoxy-5-({[2-(4-methoxy-phenyl)-ethyl]-methyl-amino}-methyl)-phenol (1c). *Method A.* A solution of **1a** (12.38 g, 43.14 mmol) in a mixture of formamide (111 ml) and formic acid (81 ml) was refluxed for 2.5 h. The excess formic acid was removed in reduced pressure and the solution was poured into ice-water (300 ml). The precipitate was filtered, washed with water and dried in a vacuum desiccator, yielding 12.6 g (93%) of *N*-formyl derivative **1b** as a crystalline substance, mp 100–101°C (ethyl acetate). TLC (dichloromethane–methanol 20:1) R_f 0.6; IR (KBr) 3100, 1635, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ_{TMS}=0.00 ppm) (a 1:1 mixture of formyl rotamers A and B): 2.71 and 2.72 (2H, t, *J*=7.0 Hz, –CH_{2A}CH$_2$N–⇌–CH_{2B}CH$_2$N–); 3.32 and 3.40 (2H, t, *J*=7.0 Hz, –CH$_{2A}$CH_2N–⇌–CH$_2$CH_{2B}N–); 3.77 (3H, s, OCH$_3$); 3.87 (3H, s, OCH$_3$); 4.12 and 4.44 (2H, s, –NCH_{2A}Ph ⇌–NCH_{2B}Ph); 5.93 (1H, broad, OH); 6.60–7.10 (7H, m, ArH); 7.92 and 8.23 (1H, s, NCHO$_A$⇌NCHO$_B$); MS *m*/*z* (%) 315 (2.0, M$^+$), 181 (48.0), 137 (100.0), 121 (38.0), 94 (11.0), 77 (8.0), 65 (7.0). Anal. Calcd for $C_{18}H_{21}NO_4$ (315.37): C, 68.55; H, 6.71; N, 4.44. Found C, 68.80; H, 6.75; N, 4.75. To a suspension of lithium aluminum hydride (5.86 g, 149 mmol) in diethyl ether (120 ml) a solution of *N*-formyl

derivative (**1b**) (12 g, 38 mmol) in THF (200 ml) was added under argon at −10°C with stirring and was heated at 55–60°C oil-bath temperature for 2 h. The reaction mixture was then decomposed by ethyl acetate (30 ml) and a saturated solution of Seignette salt (140 ml) with ice-cooling. After decantation from solid precipitate the residue was washed with ethyl acetate (200 ml). The combined organic solutions were dried over magnesium sulfate and after evaporation **1c** was obtained (11.2 g, 98%) as white crystals, mp 83–85°C. TLC (dichloromethane–methanol 10:1) R_f 0.5; IR (KBr) 3400, 1605, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, δ_{TMS}= 0.00 ppm): 2.25 (3H, s, NMe); 2.59 (2H, m) and 2.76 (2H, m) (–CH_2CH_2N–); 3.46 (2H, s, –NCH_2-Ph); 3.77 (3H, s, C(4′)–OCH_3); 3.86 (3H, s, C(2)–OCH_3); 5.88 (1H, broad, OH); 6.75 (2H, m H-3,4); 6.87 (1H, m, H-6); 6.81 (2H, dm) and 7.09 (2H, dm) (H-*o*,*o*′-PhOMe, H-*m*,*m*′-PhOMe); MS *m*/*z* (%) 301 (0.1, M^+), 300 (0.2), 180 (58.0), 137 (100.0), 121 (12.0), 94 (11.0), 77 (10.0), 65 (7.0). Anal. Calcd for $C_{18}H_{23}NO_3$ (301.39): C, 71.73; H, 7.69; N, 4.65. Found C, 72.91; H, 7.65; N, 4.71.

Method B. Secondary amine **1a** (144 mg, 0.5 mmol) was dissolved in acetonitrile (7 ml) under argon and cooled to 0°C. To the solution acetic acid (2 ml) was added and stirred for 5 min, then sodium borohydride (76 mg, 2 mmol) was added and the mixture was stirred for 15 min at the above temperature. The mixture was treated with formaldehyde (3 ml, 37% solution in water) and stirred for 30 min. The mixture was diluted with water (10 ml) and the pH was adjusted to 7–8 with saturated aqueous sodium carbonate, then extracted with chloroform (3×30 ml). The organic phase was washed with water (20 ml) and dried over magnesium sulfate. The filtrate was evaporated under reduced pressure to give **1c** (158 mg, 95%) as a crystallizable oil identical with the compound obtained above.

3.1.3. Birch-reduction of secondary amine 1a. To a flask containing absolute THF (45 ml), absolute *t*-butanol (45 ml) and liquid ammonia (280 ml), lithium metal (2.66 g, 0.384 mol) was added portionwise at −78°C under argon. After stirring for 10 min, compound **1a** (4.88 g, 17 mmol) was added in one portion then the reaction mixture was stirred between −55 and −60°C for 4 h. The deep blue color was discharged by addition of solid ammonium chloride (41 g, 0.75 mol) and after evaporation of the greater part of ammonia the reaction mixture was poured into saturated aqueous ammonium chloride solution (200 ml). The separated oil was extracted with chloroform (2×100 ml) and the organic layer washed with water (2×50 ml). The combined organic phase was dried over magnesium sulfate and after filtration the solvent was evaporated in vacuo. From the crude product (3.5 g, 72%) a pure sample of **2a** was obtained after repeated recrystallizations from ethyl acetate as a white solid, mp 92°C. TLC (dichloromethane–methanol 10:2) R_f 0.2; IR (KBr) 3290, 1695, 1670, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, δ_{TMS}= 0.00 ppm): 2.21 (2H, t, *J*=7.0 Hz, –CH_2CH_2N–); 2.71 (2H, t, *J*=7.0 Hz, –CH_2CH_2N–); 2.71 (4H, m, H_2-3′,6′); 3.30 (1H, broad, NH); 3.54 (3H, s, C(4′)–OCH_3); 3.69 (s, 2H, –NCH_2Ph); 3.86 (3H, s, C(2)–OCH_3); 4.60 (1H, m, H-5′); 5.42 (1H, m, H-2′); 6.74–6.81 (2H, m, H-3,4); 6.86 (1H, m, H-6); MS *m*/*z* (%): 289(1) M, 274(4), 166(26), 137(100), 122(11), 120(9), 94(17), 77(12). Anal. Calcd for $C_{17}H_{23}NO_3$ (289.38): C, 70.56; H, 8.01; N, 4.84. Found: C, 70.54; H, 8.03; N, 4.86.

3.1.4. *N*-(3-Hydroxy-4-methoxy-benzyl)-*N*-[2-(4-methoxy-cyclohexa-1,4-dien-1-yl)-ethyl]-formamide (2b) and *N*-(2-cyclohex-1-enyl-ethyl)-*N*-(3-hydroxy-4-methoxy-benzyl)-formamide (3b). Crude product of Birch reduction of **1a** (3.945 g, ~13 mmol) in a solution of dry ethyl acetate (40 ml) was refluxed under Ar with phenyl formate (2.5 g, 20.5 mmol) for 45 min. Reaction mixture was then diluted with ethyl acetate (30 ml), washed with 2.5% aq. sodium hydroxide solution (2×40 ml), with water (40 ml) and with saturated sodium chloride solution (40 ml). After drying over magnesium sulfate, the solvent was evaporated in vacuo and products were separated on silica gel by column chromatography with slight pressure (ca. 2 bar) using ethyl acetate–hexane (1:1) yielding **2b** (2.45 g, 63%) as white crystals, mp 90–92°C (ethyl acetate–isopropyl ether 2:5) and **3b** (289 mg, 8%) as a viscous oil. **2b**: TLC (ethyl acetate–methanol 1:1) R_f 0.5; IR (KBr) 3440, 1688, 1644, 1536 cm^{-1}; ^1H NMR (DMSO-D_6, δ_{TMS}=0.00 ppm) (a 1:1 mixture of formyl rotamers A and B): 2.07 and 2.13 (2H, t, *J*=7.0 Hz, –$CH_{2A}CH_2N$–⇌–$CH_{2B}CH_2N$–); 2.55–2.70 (4H, m, H_2-3′,6′); 3.15 and 3.20 (2H, t, *J*=7.0 Hz, –$CH_{2A}CH_2N$–⇌–$CH_{2B}CH_2N$–); 3.45 and 3.46 (3H, s, C(4′)OCH_{3A}⇌C(4′)OCH_{3B}); 3.74 and 3.75 (3H, s, C(4)OCH_{3A}⇌C(4)OCH_{3B}); 4.28 and 4.31 (2H, s, –NCH_{2A}Ph ⇌–NCH_{2B}Ph); 4.61 and 4.62 (1H, m, H_A-5′⇌H_B-5′); 5.33 (1H, m, H-2′); 6.63–6.90 (3H, m, ArH); 8.08 and 8.23 (1H, s, $NCHO_A$⇌$NCHO_B$); 8.93 and 9.00 (1H, s, OH_A⇌OH_B); MS *m*/*z* (%): 317(1) M, 181(2), 137(100), 123(34), 94(7). Anal. Calcd for $C_{18}H_{23}NO_4$ (317.39): C, 68.11; H, 7.31; N, 4.41. Found C, 68.09; H, 7.31; N, 4.43. **3b**: TLC (ethyl acetate–hexane 1:1) R_f 0.55; IR (film) 3288, 1656, 1592, 1512 cm^{-1}; ^1H NMR ($CDCl_3$, δ_{TMS}=0.00 ppm) (a 1:1 mixture of formyl rotamers A and B): 1.47–2.13 (10H, m, H_2-3′,4′,5′,6′, –CH_2CH_2N–); 3.18 and 3.29 (2H, t, *J*=7.0 Hz, –$CH_2CH_{2A}N$–⇌–$CH_2CH_{2B}N$–); 3.88 and 3.89 (3H, s, OCH_{3A}⇌OCH_{3B}); 4.27 and 4.43 (2H, s, –NCH_{2A}Ph⇌NCH_{2B}Ph); 5.42 (1H, m, H-2′); 5.77 and 5.80 (1H, broad, OH_A⇌OH_B); 6.66–6.83 (3H, m, ArH); 8.11 and 8.22 (1H, s, $NCHO_A$⇌$NCHO_B$); MS *m*/*z* (%): 289(7) M, 271(2), 181(28), 137(100), 122(9), 94(7), 79(6); HRMS calcd 289.16779, found 289.16790.

3.1.5. Birch reduction of tertiary amine (1c). The reduction of amine (**1c**) (10.24 g, 34 mmol) was performed as in the case of **1a**. Crude product of **2c** (10.41 g) as a viscous oil obtained. IR (KBr) 3400, 1695, 1670, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, δ_{TMS}=0.00 ppm): 2.22 (3H, s, NCH_3); 2.22 (2H, t, *J*=7.0 Hz, –CH_2CH_2N–); 2.50 (2H, t, *J*=7.0 Hz, –CH_2CH_2N–); 2.72 (4H, m, H_2-3′,6′); 3.44 (2H, s, –NCH_2Ph); 3.54 (3H, s, C(4′)–OCH_3); 3.88 (3H, s, C(2)–OCH_3); 4.61 (1H, m, H-5′); 5.40 (1H, m, H-2′); 6.77–6.81 (2H, m, H-3,4); 6.90 (1H, m, H-6); MS *m*/*z* (%): 304(1) [M+H], 180(93), 137(100), 122(17), 94(14). HRMS calcd 304.19127 (MH^+), found 304.19133.

3.1.6. 4-{2-[(3-Hydroxy-4-methoxy-benzyl)-methyl-amino]-ethyl}-cyclohex-3-enone (4a) and 5-{[(2-cyclohex-1-enyl-ethyl)-methyl-amino]-methyl}-2-methoxy-phenol (3c). The crude product of the Birch reduction of **1c** (4.95 g, ~14 mmol) was stirred at room temperature in a mixture

of formic acid–water 5:1 (80 ml) for 1 h. 10% aqueous sodium hydrogen carbonate (150 ml) was then added and the pH was adjusted to ~7.5 with addition of solid sodium hydrogen carbonate. The alkaline mixture was extracted with chloroform (3×50 ml), the combined organic phases washed with water (30 ml), dried over magnesium sulfate and evaporated to dryness. After column chromatography of the residual oil on silica gel (benzene–methanol 14:3) with slight pressure (ca. 2 bar), ketone **4a** (3.05 g, 74%) and cyclohexene **3c** (423 mg, 11%) were separated as oily substances. **4a**: TLC (benzene–methanol 14:3) R_f 0.4; IR (film) 3350, 1715, 1690, 1600 cm^{-1}; MS *m/z* (%): 289(12) M, 180(36), 137(100), 122(11), 94(7). Ketone **4a** was used without any further purification for the next reaction steps. **3c**: TLC (benzene–methanol 14:3) R_f 0.5; IR (film) 2928, 1620, 1592, 1410, 1270 cm^{-1}; ^1H NMR ($CDCl_3$, δ_{TMS}=0.00 ppm): 1.49–1.67 (4H, m, H_2-4′,5′); 1.87–2.02 (4H, m, H_2-3′,6′); 2.15 (2H, m, $-CH_2CH_2N-$); 2.20 (3H, s, NCH_3); 2.46 (2H, m, $-CH_2CH_2N-$); 3.42 (2H, s, $-NCH_2Ph$); 3.87 (3H, s, OCH_3); 5.41 (1H, m, H-2′); 6.78 (2H, m, H-3,4); 6.89 (1H, s, H-6); MS *m/z* (%): 275(2) M, 180(42), 137(100), 122(9), 94(11); HRMS calcd 275.18852, found 275.18865.

3.1.7. *N*-(3-Hydroxy-4-methoxy-benzyl)-*N*-[2-(4-oxocyclohex-1-enyl)-ethyl]-formamide (4b). The solution of enolether **2b** (3.26 g, 10.35 mmol) in a mixture of formic acid (22.0 ml) and water (4.4 ml) was allowed to stand at room temperature. When the hydrolysis was complete the reaction mixture was poured into 10% aqueous sodium hydrocarbonate solution (100 ml). Under external ice-water cooling the pH was adjusted to 8 with concentrated ammonium hydroxide and extracted with chloroform (3x30 ml). After drying over magnesium sulfate, filtering and evaporation in vacuo, the residual oil (3.30 g) was purified with flash-chromatography (70.0 g of Kieselgel-PF_{254}, elution with 400 ml of ethylacetate) to give the title compound (2.49 g, 79%) as a crystalline product, mp 50–52°C. IR (KBr) 3312 (OH), 1712 (CO), 1692 (NCHO) 1652 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, δ_{TMS}=0.00 ppm) (a 3:2 mixture of formyl rotamers A and B): 2.20–2.50 (6H, m, $-CH_2CH_2N-$,5′,6′); 2.80–2.86 (2H, m, H_2-3′); 3.35 and 3.25 (2H, t, J=7.0 Hz, $-CH_2CH_{2A}N-\rightleftharpoons-CH_2CH_{2B}N-$); 3.90 and 3.88 (3H, s, $OCH_{3A}\rightleftharpoons OCH_{3B}$); 4.29 and 4.46 (2H, s, $-NCH_{2A}Ph \rightleftharpoons -NCH_{2B}Ph$); 5.44 (1H, m, H-2′); 5.84 and 5.81 (1H, s, $OH_A\rightleftharpoons OH_B$); 6.67–6.84 (3H, m, ArH); 8.25 and 8.15 (1H, s, $NCHO_A\rightleftharpoons NCHO_B$). MS *m/z* (%): 303(1) M, 285(0.5), 181(9), 137(100), 122(27), 94(13); HRMS calcd 303.14706, found 303.14721.

3.1.8. 4-{2-[(3-Hydroxy-4-methoxy-benzyl)-methyl-amino]-ethyl}-cyclohex-3-enone oxime (4c). Ketone **4a** (294 mg, 1 mmol) was dissolved in dry ethanol (3 ml), then hydroxylamine hydrochloride (141 mg, 2 mmol) was added in a solution of water (0.5 ml). After stirring for 1 h at room temperature, water (10 ml) was added and the pH was adjusted to 8 by 10% saturated aqueous sodium hydrogencarbonate with ice cooling. After extraction with dichloromethane (3×10 ml) the organic phase was dried over magnesium sulfate and the solvent was evaporated under reduced pressure. After preparative layer chromatography on silica gel (chloroform–methanol 7:2, R_f 0.49) 276 mg (89%) of the product (**4c**) was obtained as an oil. IR (film) 3400–3300 broad, 1590, 1505, 1430, 1270, 790, 750 cm^{-1}; ^1H NMR ($CDCl_3$, δ_{TMS}=0.00 ppm) (a 4:1 mixture of oxime isomers); major isomer: 2.13–2.24 (4H, m, H_2-5′,6′); 2.21 (3H, s, NCH_3); 2.39 (2H, t, J=7.0 Hz, $-CH_2CH_2N-$); 2.46 (2H, m, $-CH_2CH_2N-$); 3.06 (2H, m, H_2-3′); 3.43 (2H, s, $-NCH_2Ph$); 3.87 (3H, s, OCH_3); 5.38 (1H, m, H_2-2′), 6.75–6.90 (3H, m, ArH); MS *m/z* (%): 304(6) M, 180(88), 137(100), 122(21), 94(37); HRMS calcd 304.17869, found 304.17860.

3.1.9. *N*-(3-Hydroxy-4-methoxy-benzyl)-*N*-[2-(4-oxo-cyclohex-2-enyl)-ethyl]-formamide (5b). In a hard polyethylene vessel $NH_4F{\cdot}HF$ (1.40 g, 25.9 mmol) was dissolved in trifluoromethanesulphonic acid (5 ml, 8.61 g, 57.3 mmol) under external ice-water cooling and stirring, then enolether **2b** (0.41 g, 1.30 mmol) was added to the super-acidic mixture; stirring was continued at the same temperature for 48 h. Thereafter the reaction mixture was poured into concentrated ammonium hydroxide (20 ml) containing ice-water and extracted at pH=8.5 with chloroform (3×20 ml). The combined organic extracts were dried (magnesium sulfate), filtered and evaporated to dryness under reduced pressure. The residue (0.32 g) was purified by preparative layer chromatography (Kieselgel $PF_{254+366}$, dichloromethane–methanol 20:2). From the least polar layer 120 mg (30.5%) of the title compound was isolated as a crystalline substance, mp 100–102°C (ethylacetate). IR (KBr) 3384 (OH), 1680 ($CO_{conj.}$), 1664 (NCHO) cm^{-1}; ^1H NMR ($CDCl_3$, δ_{TMS}=0.00 ppm) (a 2:1 mixture of formyl rotamers A and B): 1.48–2.52 (7H, m, $-CH_2CH_2N$,5′,6′ and H-1′); 3.25 and 3.34 (2H, m, $H_{2A}-CH_2CH_{2A}N-\rightleftharpoons-CH_2CH_{2B}N-$); 3.90 and 3.88 (3H, s, $OCH_{3A}\rightleftharpoons OCH_{3B}$); 4.31 s and 4.44 d+4.50 d (2H, $-NCH_{2A}Ph\rightleftharpoons NCH_{xB}Ph+NCH_{yB}Ph$); 5.82 (1H, d, J=11.7 Hz, H-3′); 5.98 (1H, m, H-2′); 6.66–6.85 (3H, m, ArH); 8.28 and 8.21 (1H, s, $NCHO_A\rightleftharpoons NCHO_B$); MS *m/z* (%): 303(1) M, 286(1), 245(2), 182(5), 143(3), 137(100), 122(93), 94(14); HRMS calcd 303.14706, found 303.14726.

3.1.10. 5-({[2-(4-Hydroxy-cyclohex-1-enyl)-ethyl]-methyl-amino}-methyl)-2-methoxy-phenol (6a). *N*-Methyl-ketone **4a** (2 g, 7 mmol) was dissolved in a mixture of dichloromethane (21 ml) and methanol (21 ml) and was treated with sodium borohydride (0.53 g, 14 mmol) under ice-cooling. After stirring at room temperature for 30 min, the reaction was quenched by adding a few drops of acetic acid, and the solvent was evaporated under reduced pressure. Water (30 ml) was added to the residue and the pH was adjusted to 8 by adding 10% aqueous sodium hydrogencarbonate. The aqueous phase was extracted with chloroform (30 ml), the organic layer was dried over magnesium sulfate, filtered and evaporated to dryness. After preparative layer chromatographic separation on silica gel (chloroform–methanol 7:2, R_f 0.2) 1.8 g (88%) of oily product **6a** was obtained. IR (film) 3400 broad, 2920, 2840, 1585, 1505, 1435, 1275, 790, 750 cm^{-1}; ^1H NMR ($CDCl_3$, δ_{TMS}= 0.00 ppm) (characteristic signals): 2.23 (3H, s, NCH_3); 2.47 (2H, t, J=7.0 Hz, $-CH_2CH_2N-$); 3.47 (2H, s, $-NCH_2Ph$); 3.88 (3H, s, OCH_3); 4.20 (1H, s, H-4′); 5.66 (1H, m, H-2′); 6.80 (2H, m, H-3,4); 6.91 (1H, s, H-6); MS *m/z* (%): 291(1) M, 180(18), 137(100), 122(8), 94(9); HRMS calcd 291.18344, found 291.16351.

3.1.11. *N*-[2-(4-Hydroxy-cyclohex-1-enyl)-ethyl]-*N*-(3-hydroxy-4-methoxy-benzyl)-formamide (6b). *N*-Formyl-ketone (**4b**) (1.55 g, 5 mmol) was reduced by sodium borohydride (377 mg, 10 mmol) in a mixture of dichloromethane (15 ml) and methanol (15 ml) as described above. Product (**6b**) (1.05 g, 69%) was obtained as an oil. TLC (ethyl acetate–methanol 10:1), R_f 0.5; IR (KBr) 3400 broad, 1640, 1505, 1435, 1270, 795, 750 cm^{-1}; ^1H NMR ($CDCl_3$, δ_{TMS}=0.00 ppm) (a ca. 4:3 mixture of formyl rotamers A and B): 1.20–2.40 (8H, m, $-CH_2CH_2N-$,3′,5′,6′); 3.16–3.46 (2H, m, $-CH_2CH_2N-$); 3.89 and 3.88 (3H, s, $OCH_{3A}\rightleftharpoons OCH_{3B}$); 3.93 (1H, m, H-4′); 4.44 s and 4.24 d+4.29 d (2H, $-NCH_{2B}Ph \rightleftharpoons -NCH_{xA}Ph+-NCH_{yA}Ph$); 5.29 (1H, m, H-2′); 5.73 and 5.69 (1H, s, $OH_A\rightleftharpoons OH_B$); 6.66–6.84 (3H, m, ArH); 8.22 and 8.11 (1H, s, $NCHO_A\rightleftharpoons NCHO_B$); MS *m/z* (%): 305(2) M, 287(1), 181(11), 137(100), 122(6), 94(6); HRMS calcd 305.16279, found 305.16260.

3.1.12. *N*-(3-Hydroxy-4-methoxy-benzyl)-*N*-[2-(4-amino-cyclohex-1-enyl)-ethyl]-formamide (6c). A solution of ketone **4b** (1.00 g, 3.30 mmol), ammonium acetate (2.50 g, 31.9 mmol) and $NaBH_3CN$ (0.26 g, 4.14 mmol) in 30 ml of absolute methanol was stirred for 24 h at 25°C. Concentrated hydrochloric acid was added (pH 2) and the methanol was removed under reduced pressure. Water (20 ml) was added to the residue and the acidic solution was extracted with dichloromethane (3×10 ml). The acidic aqueous phase was basified with concentrated ammonium hydroxide, then with 10% aqueous sodium hydrogencarbonate solution (pH 9) and extracted with dichloromethane (4×20 ml). The combined organic extracts were dried (magnesium sulfate), filtered and evaporated to dryness under reduced pressure to give 0.65 g (64.8%) of the title compound as a solid foam. IR (KBr) 3440 (NH_2, OH), 1664 (NCHO) cm^{-1}; ^1H NMR ($CDCl_3$, δ_{TMS}=0.00 ppm) (a ca. 1:1 mixture of formyl rotamers A and B): 1.32–3.20 (12H, m, $-CH_2CH_2N-$,3′,5′,6′, NH_2); 3.16–3.46 (2H, m, $-CH_2CH_2N-$); 3.32 (1H, m, H-4′); 3.89 and 3.88 (3H, s, $OCH_{3A}\rightleftharpoons OCH_{3B}$); 4.44 and 4.28 (2H, s, $-NCH_{2A}Ph \rightleftharpoons -NCH_{2B}Ph$); 5.32 (1H, m, H-2′); 6.65–6.84 (3H, m, ArH); 8.22 and 8.11 (1H, s, $NCHO_A\rightleftharpoons NCHO_B$); MS *m/z* (%): 304(16) M, 181(12), 137(100), 122(11), 94(10); HRMS calcd 304.17869, found 304.17855.

3.1.13. *N*-(3-Acetoxy-4-methoxy-benzyl)-*N*-[2-(4-acetamino-cyclohex-1-enyl)-ethyl]-formamide (6d). The solution of **6c** amine (0.45 g, 1.16 mmol) in acetic anhydride (4.1 ml) was refluxed at 140°C for 20 min. After cooling, water (8.2 ml) was added to the mixture and heated at 140°C for 5 min to decompose the excess anhydride. Thereafter under ice-water cooling the mixture was basified with concentrated ammonium hydroxide to pH 9 and extracted with dichloromethane (3×20 ml). The combined organic extracts were dried (magnesium sulfate), filtered, evaporated to dryness under reduced pressure and the residue was purified by preparative layer chromatography (Kieselgel $PF_{254+366}$, dichloromethane–methanol 20:2) to give 133 mg (29.56%) of the title compound as a viscous oil. IR (KBr) 3320 (NH), 1768 (ester CO), 1664 (broad, NCHO and amide CO) cm^{-1}; ^1H NMR ($CDCl_3$, δ_{TMS}=0.00 ppm) (a ca. 2:1 mixture of rotamers A and B); characteristic signals: 2.02 and 1.95 (3H, s, $NHCOCH_{3A}\rightleftharpoons NHCOCH_{3B}$); 2.31 and 2.30 (3H, s, $OCOCH_{3A}\rightleftharpoons OCOCH_{3B}$); 3.84 and 3.81 (3H, s, $OCH_{3A}\rightleftharpoons OCH_{3B}$); 4.25+4.39 and 4.39+4.53 (2H, d, *J*=11.7 Hz, $-NCH_{xA}Ph+-NCH_{yA}Ph \rightleftharpoons -NCH_{xB}Ph+-NCH_{yB}Ph$); 5.28 and 5.35 (1H, m, H_A-2′$\rightleftharpoons H_B$-2′); 6.29 and 5.48 (1H, broad $NH_A\rightleftharpoons NH_B$); 6.90–7.13 (3H, m, ArH); 8.22 and 8.10 (1H, s, $NCHO_A\rightleftharpoons NCHO_B$); MS *m/z* (%): 389(7) MH^+, 329(4), 238(7), 224(8), 209(8), 179(69), 137(100), 122(7), 106(41); HRMS calcd 389.20765 (MH^+), found 389.20782.

3.1.14. 5-({[2-(1,4-Dioxa-spiro[4.5]dec-7-en-8-yl)-ethyl]-methyl-amino}-methyl)-2-methoxy-phenol (7a). Enol-ether (**2c**) (1.165 g, 3.845 mmol) was dissolved in tetrahydrofuran (24 ml) and the pH was adjusted to 5 by addition of methanesulfonic acid (0.34 ml). Ethylene glycol (0.715 g, 11.5 mmol) was then added. After allowing to stand for 3 h at room temperature the reaction mixture was made alkaline with cc. ammonium hydroxide and the solvent was removed in vacuo. The residue was shared between water (15 ml) and chloroform (30 ml), after separation the organic phase was extracted with chloroform (2×15 ml). The combined organic phase was dried over magnesium sulfate, filtered and evaporated to dryness. The product (**7a**) (276 mg, 89%) was isolated by preparative layer chromatography on silica gel (benzene–methanol 14:5) as a viscous oil, R_f 0.5. IR (film) 3400, 1590, 1510, 1440, 1270, 1230, 850, 795, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.79 (2H, t, *J*=7.0 Hz, $-CH_2CH_2N-$); 2.17–2.32 (6H, m, H_2-3′,5′,6′); 2.24 (3H, s, NMe); 2.50 (2H, t, *J*=7.0 Hz, CH_2CH_2N-); 3.44 (2H, s, $-NCH_2Ph$); 3.90 (3H, s, OMe); 4.01 (4H, s, $-OCH_2CH_2O-$); 5.35 (1H, m, H-2′); 6.76–6.84 (2H, m, H-3,4); 6.94 (1H, m, H-6); MS *m/z* (%): 333(0.3) M, 180(48), 137(100), 122(7), 94(4); HRMS calcd 333.19401, found 333.19422.

3.1.15. *N*-{2-(1,4-Dioxa-spiro[4.5]dec-7-en-8-yl)-ethyl}-*N*-(3-hydroxy-4-methoxy)-formamide (7b). Enolether **2b** (1.0 g, 3.15 mmol) was dissolved in tetrahydrofuran (20 ml) containing methanesulfonic acid (0.2 ml) and ethylene glycol (0.59 g, 9.5 mmol) was added. The reaction mixture was allowed to stand at room temperature for 1 h, the pH was made alkaline (pH=8) with concentrated ammonium hydroxide under cooling and evaporated. To the residue water (20 ml) was added, after extraction with chloroform (2×20 ml) the combined organic phase was washed with water, dried over magnesium sulfate, filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silicagel, eluent dichloromethane–methanol 20:1) under slight pressure (ca. 2 bar) and 901 mg (91.5%) of title compound was obtained as an oil. IR (film) 3350, 1670, 1620, 1595, 1505, 1280 cm^{-1}; ^1H NMR ($CDCl_3$) (a ca. 1:1 mixture of formyl rotamers A and B): δ 1.73–1.76 (2H, m, $-CH_2CH_2N-$); 2.12–2.24 (6H, m, H_2-3′,5′,6′); 3.21 and 3.30 (2H, t, *J*=7.0 Hz, $-CH_2CH_{2A}N-\rightleftharpoons -CH_2CH_{2B}N-$); 3.88 and 3.89 (3H, s, $OCH_{3A}\rightleftharpoons OCH_{3B}$); 3.97 (4H, s, $-OCH_2CH_2O-$); 4.28 and 4.44 (2H, s, $-NCH_{2A}Ph \rightleftharpoons -NCH_{2B}Ph$); 5.31 and 5.33 (1H, m, H_A-2′$\rightleftharpoons H_B$-2′); 5.78 and 5.82 (1H, s, $OH_A\rightleftharpoons OH_B$); 6.67–6.82 (3H, m, ArH); 8.13 and 8.22 (1H, s, $NCHO_A\rightleftharpoons NCHO_B$); MS *m/z* (%): 347(26) M, 245(8), 216(12), 181(12), 166(65), 137(100), 122(21), 86(27); HRMS calcd 347.17327, found 347.17320.

3.1.16. *N*-{2-(1,4-Dithia-spiro[4.5]dec-7-en-8-yl)-ethyl}-*N*-(3-hydroxy-4-methoxy-benzyl)-formamide (7c). To a solution of ketone **4b** (1.97 g, 6.50 mmol) in dichloromethane (27 ml) 1,2-ethanedithiol (0.90 ml, 1.01 g, 10.74 mmol) and borontrifluoride etherate (0.174 ml, 0.20 g, 1.41 mmol) were added and the mixture was allowed to stand at room temperature for 14 h. The reaction mixture was basified with concentrated ammonium hydroxide (pH 8–9) and evaporated to dryness in vacuum. The residue was purified by flash chromatography (60 g of Kieselgel-PF_{254}, elution with 400 ml of ethylacetate) to yield 1.88 g (76.3%) of the title compound as white crystals, mp 65–68°C. IR (KBr) 3280 (OH), 1664 (NCHO) cm^{-1}; ^1H NMR ($CDCl_3$) (a ca. 1:1 mixture of formyl rotamers A and B): δ 2.07–2.24 (6H, m, $-CH_2CH_2N$,5′,6′); 2.64 (2H, m, H_2-3′); 3.18–3.38 (6H, m, $-CH_2CH_2N-$, $-SCH_2CH_2S-$); 3.88 and 3.89 (3H, s, $OCH_{3A} \rightleftharpoons OCH_{3B}$); 4.29 and 4.45 (2H, s, $-NCH_{2A}Ph \rightleftharpoons -NCH_{2B}Ph$); 5.36 and 5.39 (1H, m, H_A-2′$\rightleftharpoons H_B$-2′); 5.67 and 5.71 (1H, s, $OH_A \rightleftharpoons OH_B$); 6.67–6.84 (3H, m, ArH); 8.14 and 8.23 (1H, s, $NCHO_A \rightleftharpoons NCHO_B$); MS *m/z* (%): 379 (5.2) M, 351 (5.0), 198 (11), 181 (14), 137 (100), 118 (18); HRMS calcd 379.12759, found 379.12767.

3.1.17. 5-{[2-(1,4-Dithia-spiro[4.5]dec-7-en-8-yl)-ethyl-amino]-methyl}-2-methoxy-phenol (7d). The solution of *N*-formyl-derivate **7c** (0.79 g, 2.08 mmol) in 5% aqueous sodium hydroxide (17 ml) was heated at 110°C under nitrogen for 20 h. After cooling the reaction mixture was adjusted to pH 6 with acetic acid, thereafter basified with concentrated ammonium hydroxide to pH=8.5 and extracted with chloroform (3×10 ml). The combined organic extracts were dried (magnesium sulfate), filtered, evaporated under reduced pressure and the residue (0.67 g) was separated by preparative layer chromatography (Kieselgel $PF_{254+366}$, benzene–methanol 14:3, elution with dichloromethane–methanol 20:4, R_f=**7c**>**7d**) to give 0.41 g (56%) of the title compound as an oil. IR (KBr) 3300 (broad, OH, NH), 1592, 1512 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.01–2.17 (6H, m, $-CH_2CH_2N-$,5′,6′); 2.58 (2H, m, H_2-3′); 2.64 (2H, t, J=7.0 Hz, $-CH_2CH_2N-$); 3.18–3.32 (4H, m, $-SCH_2CH_2S-$); 3.65 (2H, s, $-NCH_2Ph$); 3.80 (3H, s, OCH_3); 5.37 (1H, m, H-2′); 6.73 (2H, m, H-3,4); 6.83 (1H, m, H-6); MS *m/z* (%): 351(1) M, 323(1), 166(51), 151(11), 137(100), 122(27), 105(12), 94(17); HRMS calcd 351.13267, found 351.13288.

3.1.18. 1-(4-Methoxy-3-hydroxy-benzyl)-octahydro-indole-6-one (8). The solution of compound **7d** (0.98 g, 2.79 mmol) in a 1:1 mixture of concentrated sulfuric acid and 80% phosphoric acid (52 ml) was allowed to stand at room temperature for 3 h. The reaction mixture was poured into ice-water (420 ml) and basified with concentrated ammonium hydroxide to pH 9 and extracted with chloroform (3×240 ml). The combined organic layers were dried (magnesium sulfate), filtered and evaporated under reduced pressure. The residue (0.59 g) was separated by preparative layer chromatography (Kieselgel $PF_{254+366}$, dichloromethane–methanol 20:2, elution 20:4). From the least polar layer 95 mg (12.4%) of the title compound could be isolated as a viscous oil. ^1H NMR ($CDCl_3$): δ 1.49 (1H, m, H_x-3); 1.74 (1H, m, H_x-5); 1.94 (1H, m, H_y-5); 1.97 (1H, m, H_y-3); 2.07 (1H, m, H_x-2]; 2.18 (1H, ddd, J=18.0 Hz, 6.9 Hz, 4.5 Hz, H_x-4); 2.42–2.52 (2H, m, H-3a, H_y-4); 2.52 (1H, dd, J=15.3 Hz, 4.8 Hz, H_x-7); 2.59 (1H, dd, J=15.3 Hz, 4.5 Hz, H_y-7); 2.79 (1H, dt, J=9.0 Hz, 4.5 Hz, 4.5 Hz (H-7a); 2.89 (1H, m, H_y-2); 3.04 (1H, d, J=13.2 Hz, $-NCH_xPh$); 3.84 (1H, d, J=13.2 Hz, $-NCH_yPh$); 3.86 (3H, s, OCH_3); 6.69–6.83 (3H, m, ArH); MS *m/z* (%): 275(37) M, 218(56), 204(8), 138(94), 137(100), 122(38), 94(52); HRMS calcd 275.15214, found 275.15238. Hydrobromide salt of **8**, mp 190–192°C (1,2-dichloroethane and 1–2 drops of methanol). IR (KBr) 3300 (OH), 1704 (CO) cm^{-1}.

3.2. General method for the Grewe-cyclization of cyclohexenes (3b, c) and tertiary alcohols (10b, c)

Cyclohexene (**3b** and **c**) or cyclohexanol (**10b** and **c**) (2 mmol), respectively, was dissolved in a 1:1 (vol/vol) mixture of cc. sulfuric acid and cc. phosphoric acid (40 ml; 20 ml/mmol). After stirring at room temperature for 2–3 h the reaction mixture was poured into cold cc. ammonium hydroxide with ice cooling. The alkaline mixture was then extracted with chloroform, the combined organic phase was washed with water, dried over magnesium sulfate and after filtering the solvent was evaporated at reduced pressure. Products were isolated by preparative layer chromatography on silica gel.

3.2.1. 8-Hydroxy-7-methoxy-spiro[2,3,4,5-tetrahydro-1*H*-benzo(*c*)azepin-5,1′-cyclohexane]-2-carbaldehyde (9b). Viscous oil, yield 21% from (**3b**) and 55% from (**10b**). TLC (benzene–methanol 14:3), R_f 0.5; IR (film) 3240, 2936, 1660, 1610, 1584, 1516, 1452, 1264, 1200, 1108, 1040, 872, 736 cm^{-1}; ^1H NMR ($CDCl_3$) (a ca. 4:3 mixture of formyl rotamers A and B): δ 1.22–1.92 (10H, m, H_2-2′,3′,4′,5′,6′); 2.07 and 1.96 (2H, m, H_{2A}-4$\rightleftharpoons H_{2B}$-4); 3.70 and 3.58 (2H, m, H_{2A}-3$\rightleftharpoons H_{2B}$-3); 3.89 and 3.88 (3H, s, $OCH_{3A} \rightleftharpoons OCH_{3B}$); 4.49 and 4.62 (2H, s, H_{2A}-1$\rightleftharpoons H_{2B}$-1); 5.56 (1H, broad, OH); 6.66 and 6.86 (1H, s, H_A-9$\rightleftharpoons H_B$-9); 6.99 and 6.94 (1H, s, H_A-6$\rightleftharpoons H_B$-6); 8.10 and 8.03 (1H, s, $NCHO_A \rightleftharpoons NCHO_B$); MS *m/z* (%): 289(100) M, 260(22), 246(14), 232(17), 216(13), 201(33), 189(24), 175(21), 137(36), 115(34); HRMS calcd 289.16779, found 289.16795.

3.2.2. *N*-[2-(1-Hydroxy-cyclohexyl)-ethyl]-*N*-(3-hydroxy-4-methoxy-benzyl)-formamide (10b). Viscous oil, yield 37%. TLC (benzene–methanol 14:3) R_f 0.45; IR (film) 3392, 2928, 2866, 1660, 1592, 1440, 1276, 1132, 1028, 972, 808, 788, 760 cm^{-1}; ^1H NMR ($CDCl_3$) (a ca. 4:3 mixture of formyl rotamers A and B): δ 1.16–1.6 (10H, m, H_2-2′,3′,4′,5′,6′); 1.61 and 1.65 (2H, m, $-CH_{2A}CH_2N- \rightleftharpoons -CH_{2B}CH_2N-$); 3.29 and 3.55 (2H, m, $-CH_2CH_{2A}N- \rightleftharpoons -CH_2CH_{2B}N-$); 3.87 and 3.89 (3H, s, $OCH_{3A} \rightleftharpoons OCH_{3B}$); 4.29 and 4.43 (2H, s, $-NCH_{2A}Ph \rightleftharpoons -NCH_{2B}Ph$); 5.86 and 5.80 (1H, broad $OH_A \rightleftharpoons OH_B$); 6.67–6.83 (3H, m, ArH); 8.19 and 8.20 (1H, s, $NCHO_A \rightleftharpoons NCHO_B$); MS *m/z* (%): 307(14) M, 289(9), 271(7), 192(13), 181(35), 164(16), 152(11), 137(100), 122(9), 94(12); HRMS calcd 307.17836, found 307.17821.

3.2.3. 2-Methyl-7-methoxy-spiro[2,3,4,5-tetrahydro-1*H*-benzo(*c*)azepin-5,1′-cyclohexan]-8-ol (9c). Colorless oil, yield 21.5% from **3c**, 9.3% from **10c**. TLC (benzene–methanol 14:3) R_f 0.4; IR (KBr) 3400, 2930, 2905 2830, 1600, 1580, 1505, 1450, 1285, 1115, 1030, 880, 770 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.20–1.76 (10H, m,

H_2-2′,3′,4′,5′,6′); 1.89 (2H, m, H_2-4); 2.30 (3H, s, NCH_3); 2.92 (2H, m, H_2-3); 3.86 (2H, s, H_2-1); 3.88 (3H, s, OCH_3); 5.60 (1H, broad, OH); 6.61 (1H, s, H-9); 6.95 (1H, s, H-6); MS *m/z* (%): 275(72) M, 274(56), 260(42), 232(12), 192(43), 178(74), 137(100), 115(12); HRMS calcd 275.18853, found 275.18865.

3.2.4. 5-({[2-(1-Hydroxy-cyclohexyl)-ethyl]-methyl-amino}-methyl)-2-methoxy-phenol (10c). Viscous oil, yield 16%. TLC (benzene–methanol 14:3) R_f 0.45; IR (KBr) 3400, 2910, 2840, 1590, 1510, 1280, 1020, 760 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.72–2.00 (12H, m, $-CH_2CH_2N-$,2′,3′,4′,5′,6′); 2.32 (3H, s, $-NCH_3$); 2.56 (2H, m, $-CH_2CH_2N-$); 3.61 (2H, s, $-NCH_2$-Ph); 3.88 (3H, s, OCH_3); 6.80–7.03 (3H, m, ArH); MS *m/z* (%): 293(1) M, 180(19), 137(100), 122(10), 94(13); HRMS calcd 293.1991, found 293.2005.

3.2.5. 7-Methoxy-spiro[2,3,4,5-tetrahydro-1*H*-benzo(*c*)-azepin-5,1′-cyclohexan]-8-ol (9a). Compound (**9b**) (74 mg, 0.256 mmol) was dissolved in a freshly prepared 5% aqueous solution of sodium hydroxide and under Ar was refluxed for 2 h in an oil bath at 110–115°C. After cooling the pH was adjusted to 6 with diluted acetic acid, then made alkaline (pH 8–8.5) by cc. ammonium hydroxide. After extraction with chloroform (3×5 ml) the combined organic phase was dried over magnesium sulfate, filtered and evaporated to dryness. The crystalline residue was rubbed with chloroform. After filtering and drying in a vacuum desiccator 27 mg (40%) of product (**9a**) was obtained as a crystalline substance, mp 212–213°C (chloroform); TLC (chloroform–methanol 1:1) R_f 0.2; IR (KBr) 3440, 3240, 2920, 2840, 1600, 1512, 1312, 1208, 864, 760 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.20–1.86 (10H, m, H_2-2′,3′,4′,5′,6′); 1.73 (2H, m, H_2-4); 2.88 (2H, m, H_2-3); 3.73 (3H, s, OCH_3); 3.78 (2H, s, H_2-1); 6.48 (1H, s, H-9); 6.85 (1H, s, H-6); 6.60 (1H, broad, OH); MS *m/z* (%): 261(89) M, 244(7), 232(11), 218(33), 189(31), 178(65), 164(97), 137(100), 124(22), 115(32), 91(31); HRMS calcd 261.17288, found 261.17270.

Acknowledgements

The authors thank Gedeon Richter Ltd for financial support. We are grateful for the MS data provided by J. Brlik and Dr G. Czira, as well as for the NMR technical assistance of A. Fürjes.

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