Pergamon

Tetrahedron 55 (1999) 5567–5580

TETRAHEDRON

Simple and Condensed β-Lactams. Part 33.[1] $AlCl_3$ Catalyzed Ring Closures of Some 3-Aryloxy-4-oxoazetidine-2-carboxylic Chlorides to 1*H*-chromeno[3,2-*b*]azete-2,8(2a*H*,8a*H*)-diones and Some Reactions of the Products

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Received 10 November 1998; revised 15 February 1999; accepted 4 March 1999

Abstract

Carboxylic chlorides **3a-3c**, when treated with $AlCl_3$, afforded the tricyclic compounds **17a-17c**. $NaBH_4$ reduction of **17a** and **17b** afforded compounds **11a** and **11b**. The latter and the related known compounds **4a**, **5b**, **6a** and **7a** were used for the preparation of various dihydrochromeno[3,2-*b*]azet-2(1*H*)-ones and of a 3,4-disubstituted chromane-2-carboxylic ester (**26**) of fixed stereochemistry. Catalytic reduction of 8-chloro compound **5b** afforded compounds **10b** and **25**, the products of simple hydrodechlorination and of azetidinone ring cleavage with concomitant hydrodechlorination, respectively.

Keywords: Azetidin-2-ones; ring cleavage; condensed chromanes; diastereoselection

In Part 31 [2] of the present series the Lewis and Brønsted acid catalysed ring closure of (2*RS*,3*RS*)-3-aryloxy-4-oxoazetidine-2-carbaldehydes **1a** and **1b** leading to (2a*RS*,8*RS*,2a*RS*)-(**4a**, **b**) and (2a*RS*,8*SR*,8a*RS*)-8-hydroxy-1-(4-methoxyphenyl)-8,8a-dihydro-2a*H*-chromeno-[3,2-*b*]azet-2(1*H*)-ones (**11a, 11b**) and transformation products (**5a,b-7a,b**) was described. Here we report the extension of these studies to the $AlCl_3$ catalysed ring closure of (2*RS*,3*RS*)--3-aryloxy-4-oxoazetidine-2-carboxylic chlorides (**3a-3c**) and some reactions of the resulting (2a*RS*,8a*RS*)-1-(4-methoxyphenyl)-1*H*-chromeno[3,2-*b*]azete-2,8(2a*H*,8a*H*)-diones (**17a-17c**).

[1] For Part 32, see ref. [1]

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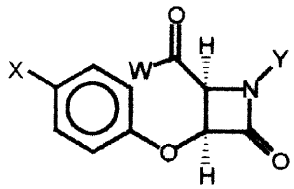
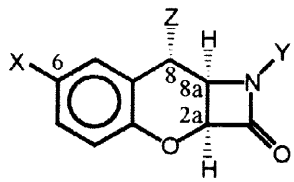
PII: S0040-4020(99)00222-7

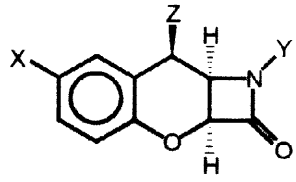


1^2: W = H
2^2: W = OH
3^2: W = Cl

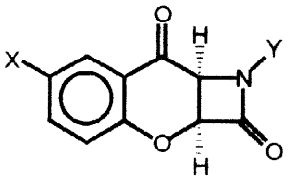
Y = 4-MeOC$_6$H$_4$
a: X = Cl
b: X = F
c: X = MeO



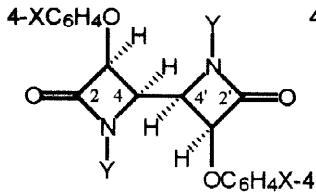
4^2: Z = OH
5^2: Z = Cl
6^2: Z = Br
7^2: Z = aryl
8^2: Z = OMe
9^2: Z = O_2CNH_2
10^2: Z = H



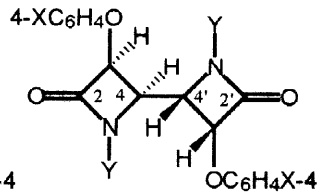
11^2: Z = OH
12^2: Z = OSO_2Me
13^2: Z = N_3
14^2: Z = NH_2
15^2: Z = NHAc
16^2: Z = OAc



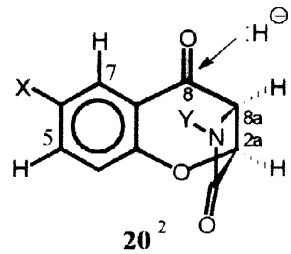
17^2



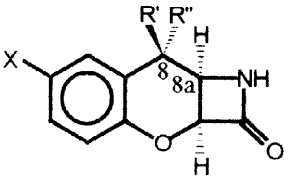
18^2



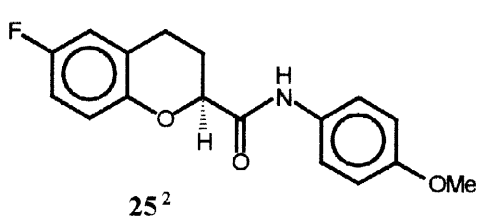
19^2



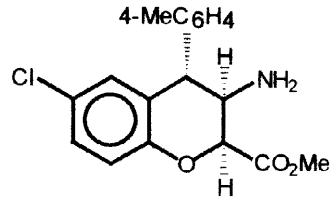
20^2



21^2: R' = H, R'' = 4-MeC$_6$H$_4$
22^2: R' = AcO, R'' = H
23^2: R' + R'' = O
24^2: R' = OH, R'' = H



25^2



26^2

The starting carboxylic acid chlorides **3a-3c** were prepared by $KMnO_4$ oxidation of aldehydes **1a-1c** and treatment of the resulting carboxylic acids **2a-2c** with thionyl chloride. Carbaldehyde **1c** was obtained [together with a mixture of the racemic (**18c**) and *meso*-4,4'-bi(azetidin-2-ones) (**19c**) as minor products] similarly as the analogous compounds of the **a** and **b** series [2].

When carboxylic chlorides **3a** and **3b** were treated with $AlCl_3$ in dichloromethane the expected diones **17a** and **17b**, respectively, were obtained in 80-90% yields. In the methoxy

[2] Racemic compounds; for convenience only one enantiomer is shown.

series, however, the yield of the desired dione **17c** was much lower (17%) because, as shown by the ^{1}H NMR spectra of the products (which were separated by chromatography), the partially *O*-demethylated derivative (or a mixture of the isomeric partially *O*-demethylated derivatives) (25%) and the totally *O*-demethylated derivative (2%) were also formed Methylation of the *O*-demethylated products with ethereal diazomethane afforded compound **17c**.

The structure of product **17b** was at once clear from an inspection of its ^{1}H NMR spectrum whose aromatic part displayed signals of *three* protons coupled with fluorine which proves that the fluorophenyl group of the starting **3b** was involved in the cyclization. In addition, the (relative to that of the starting compound practically unchanged) MeO signal and the AA'BB' spectrum of the 4-methoxyphenyl group were present in the spectrum, which was true also for the cyclization products **17a** and **17c**. Further proof of structure for products **17a** and **17b** came from $NaBH_4$ reduction experiments which afforded the known compounds **11a** (97%) and **11b** (92%) [2] and none of their 8-epimers **4a** and **4b**. Similarly, $NaBH_4$ reduction of dione **23c** (see below) afforded compound **24c**, again with 8-H and 8a-H in *cis* position relative to one another.

The stereospecificity of the $NaBH_4$ reductions may be understood by assuming that compounds **17a** and **17b** do exist in solution predominantly or even exclusively in the folded compact conformations shown in **20** (*cf.* ref. [2]). As a consequence, the reducing agent approaches the surfaces of the diones from outside and transfer of the hydride anion takes place as indicated in **20**, with the result that the oxygen atom is pushed into the β-position (*trans* relative to 8a-H) while the newly introduced 8-H ligands will occupy the α-position in the products.

Since compounds **11a** and **11b** were obtained as single diastereoisomers, and both their known 8-epimers **4a** and **4b** as well as derivatives of types **5-7** of the latter were also available as single diastereoisomers [2], a study was undertaken to explore the suitability of these compounds as starting compounds for the preparation of various other dihydrochromeno-[3,2-*b*]azet-2(1*H*)-ones and, possibly, of 2,3,4-trisubstituted chromane derivatives of fixed stereochemistry.

The hydrogen atoms in positions 2a and 8a of all products obtained in the course of these studies were shown by their ^{1}H NMR spectra to be *cis* relative to one another. This follows from the values of the coupling constants $J_{2a\text{-}H/8a\text{-}H}$ (4.9-5.6 Hz) characteristic for 3,4-*cis* disubstituted azetidin-2-ones. The relative configuration of C-8, on the other hand, was established on the basis of two rules [2], *viz.* (i) that the value of the coupling constant $J_{trans\ 8\text{-}H/8a\text{-}H}$ is about 2 Hz while $J_{cis\ 8\text{-}H/8a\text{-}H}$ is about 4 Hz and (ii) that long-range couplings $J_{5\text{-}H/8\text{-}H}$ and $J_{7\text{-}H/8\text{-}H}$ (0.8-0.9 and 1.0-1.3 Hz, respectively) are observed only when 8-H and

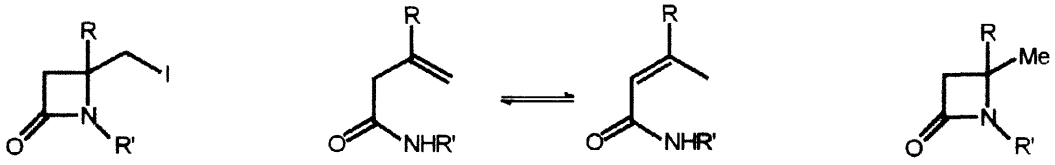
8a-H are *cis*, but no such couplings are observed when 8-H and 8a-H are *trans*.[3]

Treatment of compounds **11a** and **11b** at 0°C with $MeSO_2Cl$ in pyridine afforded crude *O*-methylsulfonyl derivatives **12a** and **12b** in high yields if care was taken that the temperature during work-up did not exceed 50°C until chloride ions, the co-products were present. When, however, the temperature was raised to 70°C, reaction with chloride ions took place to afford the known compounds **5a** and **5b** [2], respectively, with inversion at C-8 in high yields. When crude compounds **12a** and **12b** were refluxed with methanol, methoxy derivatives **8a** and **8b** were obtained, again with inversion at C-8, in *ca* 70% yields.

Treatment of compound **6a** [2] with sodium azide in DMF afforded 8-azido derivative **13a** in excellent yield with inversion at C-8. Reduction of compound **13a** with H_2S, followed by acetylation with acetic anhydride afforded the 8-acetylamino derivative **15a**. 8-Acyloxy derivatives **9a** and **16b** were obtained by treatment of the 8-hydroxy derivative **4a** with sulfuryl chloride isocyanate, followed by treatment with $Na_2S_2O_5$, and by acetylation of compound **11b** with acetic anhydride, respectively.

N-Demethoxyphenylation with CAN according to the published procedure [3] of the two dihydrochromeno[3,2-*b*]azet-2-ones (**7a**, Z = 4-methylphenyl; **16b**) and the two chromeno-[3,2-*b*]azete-2,8-diones (**17b**, **c**) tested afforded the desired products **21a**, **22b** and **23b**, **c**, respectively, in medium to good yields.

Catalytic reduction (H_2/Pd-C, NaOAc, MeOH + CH_2Cl_2) of the 8-chloroderivative **5b** afforded, in addition to the expected product **10b** of hydrodechlorination, chromane-2--carboxanilide **25** as a result of cleavage of the azetidinone ring with concomitant hydrodechlorination. Compound **10b** was found not to be an intermediate en route to compound **25**, since the ratio of the two products did not change on prolonged hydrogenation. Compound **10b** being essentially a 4-benzylazetidin-2-one, this result could be anticipated: although the N(1)-C(4) bond of 4-phenyl- and other 4-arylazetidin-2-ones is readily cleaved by hydrogenolysis (Raney-Ni, H_2/Pd-C) [4a-e], the N(1)-C(4) bond of 4-benzylazetidin-2-ones is stable to these conditions.



27 **28** **29** **30**

A closely related reaction, **27** → **28** + **29**, accompanied in some cases by the formation of traces to considerable amounts of simple reductive deiodination products **30**, has been found

[3] In the case of compound **10b** at most very weak long range coupling ($J < 0.5$ Hz) was observed for 8β-H which is *trans* to 8a-H

to take place on treatment of a series of 4-(iodomethyl)azetidin-2-ones **27** with disodium or dipotassium [tetracarbonylferrate(-II)], lithium [tetracarbonyl(pentanoyl)ferrate(-II)] or butyl lithium [5]. A reasonable multistep mechanism, assuming radicals and anions as intermediates has been suggested for this reaction [5]. Whether the mechanisms of the heterogeneous reaction **5b** → **10b** + **25** and of the homogeneous reaction **27** → **28** + **29** + **30** are similar, remains to be seen.

A different type of cleavage of the azetidin-2-one ring, *viz.* cleavage of the NH-CO bond of compound **21a**, resulting in the formation of the 3-aminochromane-2-carboxylic ester **26**, was brought about by treatment with methanolic sodium methoxide.

Experimental

Dichloromethane is abbreviated as DCM. $MgSO_4$ was invariably used as the drying agent. Evaporations to dryness were carried out at reduced pressures (*ca* 2.5 kPa). Separations of product mixtures by column chromatography (c.c.) were mostly carried out at reduced pressures (10-25 kPa) using Kieselgel G 60 (Merck) as the adsorbent. For preparative t.l.c. separations 20 x 20 cm glass plates coated with Kieselgel $PF_{254-366}$ (Merck; thickness of adsorbent layer 1.5 mm) were used. The solvents used are given in parentheses. The purity of the products was checked, in combination with IR spectroscopy, by t.l.c. on DC-Alufolien 60 F_{254} (Merck); the individual compounds were detected by UV irradiation or by using iodine, 5% ethanolic molybdo- or tungsto-phosphoric acids as the reagents.

Melting points were determined on a Kofler hot-stage m.p. apparatus. IR spectra were recorded on a Specord-75 (Zeiss, Jena) spectrometer, ^1H and ^{13}C n.m.r. spectra were obtained with a Varian VXR-400 spectrometer in $CDCl_3$ solutions, unless otherwise stated, and using tetramethylsilane as the internal reference compound; J values in Hz are given in parentheses. The chemical shifts of the 4-methoxyphenyl groups are given only if differing by more than 0.1 ppm from the usual values in the present series [*ca* 3.8 ppm (MeO) and 6.9 + 7.3 ppm (AA'BB'), *J ca* 9; 4 x ArH].

*(2*RS,*3*RS*)-3-(4-Methoxyphenoxy)-1-(4-methoxyphenyl)-4-oxoazetidine-2-carbaldehyde* (**1c**), *(2*RS,*3*RS,*2'*RS,*3'*RS*)- or racemic* (**18c**) *and (2*RS,*3*RS,*2'*SR,*3'*SR*)- or* meso-*3,3'-bis-(4-methoxyphenoxy)-1,1'-bis(4-methoxyphenyl)-4,4'-bi(azetidin-2-one)* (**19c**)

Treatment of (4-methoxyphenoxy)acetyl chloride [6] in the presence of triethylamine (2.4 mol equivalent) in DCM with *N,N'*-di(4-methoxyphenyl)ethanediimine [7] (1.2 mol equivalent), followed by hydrolysis with dilute hydrochloric acid of the resulting

4-methoxyphenylimine of carbaldehyde **1c** as described for the analogous reactions in the **a** and **b** series [2] afforded compound **1c** [53 %, colourless crystals; m.p. 120°C; found: C, 66.15; H, 5.3; N, 4.45; $C_{18}H_{17}NO_5$ (327.35) requires: C, 66.05; H, 5.25; N, 4.3 %; ν_{max} (KBr) 1760, 1730 cm^{-1}; δ_H 3.77s + 3.80s (2 x OMe), 4.70dd (5.3, 3.6; 2-H), 5.48d (5.3; 3-H), 6.84 + 7.01 (AA'BB') and 6.89 + 7.30 (AA'BB') (2 x PMP), 9.81d (3.6; CHO)] and a mixture of stereoisomers **18c** and **19c** [Σ 2.4 %, colourless crystals; m.p. 222°C; found: C, 68.25; H, 5.2; N, 4.65; $C_{34}H_{32}N_2O_8$ (596.65) requires: C, 68.45; H, 5.4; N, 4.7 %; ν_{max} (KBr) 1770 cm^{-1}; δ_H 3.68s + 3.77s (2 x 2 MeO), 4.99m (4-H + 4'-H), 5.41m (3-H + 3'-H), 6.56 + 7.07 (AA'BB') and 6.81 + 7.02 (AA'BB') (2 x PMP)].

(2RS,3RS)-1-(4-Methoxyphenyl)-4-oxo-3-(4-substituted phenoxy)azetidine-2-carboxylic acids (**2a-c**)

(*a*) A mixture of carbaldehyde **1b** (15.7 g, 50 mmol), acetone, water (650 cm^3, each) and $KMnO_4$ (11.9 g, 75 mmol) was stirred for 10 h at room temperature. The excess oxidant was removed by adding $Na_2S_2O_5$ until the violet colour disappeared. The MnO_2 was filtered off and the acetone component of the filtrate was distilled off. The residual aqueous solution was extracted with DCM. The aqueous phase was acidified (pH 2) by adding conc. HCl with ice-water cooling to afford the colourless crystals of fluorophenoxy compound **2b** [12.6 g, 76 %; m.p. 191°C (from EtOAc-hexane); found: C, 61.7; H, 4.4; F, 5.35; N, 4.35; $C_{17}H_{14}FNO_5$ (331.3) requires: C, 61.65; H, 4.25; F, 5.75; N, 4.25 %; ν_{max} (KBr) 3300-2900, 1750, 1730 cm^{-1}; δ_H ($CDCl_3$ + DMSO-d_6) 3.79s (OMe), 4.87d (5.2; 2-H), 5.3br (CO_2H + H_2O), 5.45d (5.2; 3-H), 6.88 + 7.34 (AA'BB'; PMP), 6.99m + 7.08m (fluorophenoxy)].

(*b*) Similarly obtained were, starting with carbaldehydes **1a** and **1c**, carboxylic acids **2a** [71 %, colourless crystals; m.p. 186°C (from EtOAc-hexane); found: C, 58.9; H, 4.2; Cl, 10.45; N, 3.9; $C_{17}H_{14}ClNO_5$ (347.75) requires: C, 58.7; H, 4.05; Cl, 10.2; N, 4.05; ν_{max} (KBr) 3400-2900, 1760, 1730 cm^{-1}; δ_H ($CDCl_3$ + DMSO-d_6) 3.79s (OMe), 4.88d (5.2; 2-H), 5.49d (5.2; 3-H), 6.88 + 7.34 (AA'BB'; PMP), 7.05 + 7.25 (AA'BB'; chlorophenoxy), 7.6br (CO_2H + H_2O)] and **2c** [64.5 %, colourless crystals; m.p. 187°C; found: C, 62.85; H, 4.75; N, 4.22; $C_{18}H_{17}NO_6$ (343.35) requires: C, 62.95; H, 5.00; N, 4.1 % ; ν_{max} (KBr) 3300-2900, 1760, 1750 cm^{-1}; δ_H ($CDCl_3$ + DMSO-d_6) 3.68s + 3.70s (2 x MeO), 4.78br d (4.8; 2-H), 5.33d (4.8; 3-H), 6.4br (CO_2H + H_2O), 6.74 + 6.96 (AA'BB'; methoxyphenoxy), 6.80 + 7.26 (AA'BB'; PMP)], respectively.

Conversion into carboxylic acid chlorides **3a-c**

Carboxylic acids **2a-c** were stirred with 4 parts of $SOCl_2$ (w/w) for 1 h at 80°C. The mixtures were evaporated to dryness. The crude carboxylic acid chlorides were used without any purification in the subsequent ring closure steps.

Ring closure of compounds **3a-c**

(*a*) $AlCl_3$ (32.6 g, 245 mmol) was added to crude acyl chloride **3a** (29.3 g, 80 mmol) in dry DCM (450 cm^3) with continuous stirring and ice-water cooling. Stirring was continued for 2 h with the cooling bath removed. A yellow precipitate separated gradually. The mixture was poured onto ice (300 g), the two phases were separated and the aqueous phase was extracted with DCM. The combined organic phases were successively washed with 0.1 N HCl, water and brine, dried and evaporated to dryness. The crystalline residue was triturated with diethyl ether to afford *(2a*RS,*8a*RS*)-6-chloro-1-(4-methoxyphenyl)-1*H*-chromeno[3,2-*b*]azete-2,8-(2a*H,*8a*H*)-dione* (**17a**) [26.1 g, 79 %, colourless crystals; m.p. 149°C (from MeOH); found: C, 62.1; H, 3.7; Cl, 10.95; N, 4.35; $C_{17}H_{12}ClNO_4$ (329.75) requires: C, 61.9; H, 3.65; Cl, 10.75; N, 4.25 %; ν_{max} (KBr) 1760, 1670 cm^{-1}; δ_H 3.79s (OMe), 4.84d (5.2; 8a-H), 5.68d (5.2; 2a-H), 6.88 + 7.53 (AA'BB'; PMP), 7.11d (8.7; 4-H), 7.52dd (8.7, 2.7; 5-H), 7.80d (2.7; 7-H)].

(*b*) $AlCl_3$ (38.3 g, 287 mmol) was added to crude acyl chloride **3b** (34.7 g, 99 mmol) in dry DCM (500 cm^3) with ice-water cooling and continuous stirring. Strirring was continued for 2 h at room temperature. When the evolution of gas had ceased, the mixture was poured onto ice (1000 g) and acidified with *conc.* HCl. The two phases were separated and the aqueous phase was extracted with DCM. The combined organic phases were successively washed with 1N HCl, water and brine, dried and evaporated to dryness to afford *(2a*RS,*8a*RS*)-6-fluoro--1-(4-methoxyphenyl)-1*H*-chromeno[3,2-*b*]azete-2,8(2a*H,*8a*H*)-dione* (**17b**) [28 g, 90 %, which proved homogeneous (t.l.c.); colourless crystals, m.p. 162-163°C (MeCN); found: C, 65.3; H, 3.6; F, 6.1; N, 4.4; $C_{17}H_{12}FNO_4$ (313.3) requires: C, 65.2; H, 3.85; F, 6.05; N, 4.45 %; ν_{max} (KBr) 1770, 1690 cm^{-1}; δ_H 3.78s (OMe), 4.83d (5.2; 8a-H), 5.66d (5.2; 2a-H), 6.88 + 7.53 (AA'BB'; PMP), 7.14dd (9.1, 4.2[4] ; 4-H), 7.30ddd (9.1, 3.2, 7.5[4]; 5-H), 7.49dd (3.2, 7.9[4]; 7-H)].

(*c*) A mixture of crude acyl chloride **3c** (27.8 g, 77 mmol), dry DCM (25 cm^3) and $AlCl_3$ (30.8 g, 231 mmol) was refluxed for 10 h. Since starting compound **3c** was not consumed at this point, another portion of $AlCl_3$ (10.3 g, 77 mmol) was added and the mixture was refluxed for another 10 h. The starting substance was thereby consumed, however at the expense of severe tar formation. The mixture was poured onto ice and extracted with EtOAc. The

[4] $J_{H,F}$

combined organic phases were washed with water and 0.1 N HCl, dried and evaporated to dryness. The residue was worked up by c.c.; (DCM → DCM-acetone, 10:0.5 → 10:1) to afford *(2a*RS,*8a*RS*)-6-methoxy-1-(4-methoxyphenyl)-1*H*-chromeno[3,2-*b*]azete-2,8(2a*H*, 8a*H*)-dione* (**17c**) [4.2 g, 17 %, colourless crystals; m.p. 158°C; found: C, 66.7; H, 4.55; N, 4.45; $C_{18}H_{15}NO_5$ (325.3) requires: C, 66.45; H, 4.65; N, 4.3 %; ν_{max} (KBr) 1770, 1680 cm^{-1}; δ_H 3.77s + 3.78s (2 x OMe), 4.82d (5.2; 8a-H), 5.63d (5.2; 2a-H), 6.88 + 7.55 (AA'BB'; PMP), 7.08d (9.0; 4-H), 7.17dd (9.0, 3.1; 5-H), 7.23d (3.1; 7-H)], the partially *O*-demethylated (^{1}H NMR) product (or a mixture of the two isomeric partially *O*-demethylated products) of compound **17c** [6.0 g, 25 %, colourless crystals; m.p. 200-203°C; ν_{max} (KBr) 3400, 1740, 1685 cm^{-1}] and the totally *O*-demethylated (^{1}H NMR) product of compound **17c** [0.6 g, 2 %, colourless crystals; m.p. >275°C (dec); ν_{max} (KBr) 3380, 3280, 1730, 1680 cm^{-1}].

Methylation of both the partially and the totally *O*-demethylated products with ethereal diazomethane afforded compound **1c**.

Sodium [tetrahydridoborate] reduction of compounds **17a**, **17b** *and* **23c**

(*a*) $NaBH_4$ (1.45 g, 38 mmol) was added to a suspension of compound **17a** (14.5 g, 44 mmol) in methanol (240 cm^3) with continuous stirring and ice-cooling. Stirring was continued for 2 h with the cooling bath removed. The mixture was acidified with *conc.* HCl and evaporated to dryness at reduced pressure. The residue was triturated with water to afford compound **11a** [14.2 g, 97 %, colourless crystals; m.p. 188-189°C (from MeOH)] which proved identical (m.p., IR, ^{1}H NMR) with one of the minor products obtained by ring closure of carbaldehyde **1a** with $AlCl_3$ in diethyl ether-DCM [2].

(*b*) Starting with compound **17b** (6.3 g, 20 mmol), compound **11b** [5.8 g, 92 %, colourless crystals; m.p. 184-186°C (from MeOH)] was obtained by an essentially identical procedure. The product proved identical with one of the minor products obtained by ring closure of carbaldehyde **1b** with $AlCl_3$ in diethyl ether-DCM [2].

(*c*) $NaBH_4$ (20 mg, 0.5 mmol) was added to compound **23c** (see below; 0.22 g, 1 mmol) in MeOH (10 ml) at 0°C. The mixture was stirred for 1 h and acidified at this temperature by adding conc. HCl. The residue, obtained by evaporation to dryness of the mixture, was taken up in water (3 cm^3). From the initial clear solution the colourless crystals of *(2a*RS,*8*SR,*8a*SR*)-8-hydroxy-6-methoxy-8,8a-dihydro-1*H*-chromeno[3,2-*b*]azet-2(2a*H*)-one* (**24c**) (0.14 g, 63 %)[5] gradually separated.

[5] For the m.p., elemental analyses and spectra, see Table

Methylsulfonylation of compounds **11a** *and* **11b** *and reaction of the resulting 8-methylsulfonyloxy derivatives* **12a** *and* **12b** *with some nucleophiles*

(*a*) $MeSO_2Cl$ (1.5 cm^3, 19 mmol) was added dropwise to compound **11a** (3.3 g, 10 mmol) in pyridine (50 cm^3) with continuous stirring and ice-water cooling. Stirring was continued for 1 h at room temperature and for 1/2 h at 50°C, and the mixture was evaporated to dryness at 0.2 kPa (bath temperature below 50°C), the residue was triturated with ice-cold water to afford crude compound **12a** (3.7 g).[5] This was refluxed for 2 h with methanol (60 cm^3) to afford the colourless crystals of *(2a*RS,*8*RS,*8a*SR*)-6-chloro-8-methoxy-1-(4-methoxyphenyl)--8,8a-dihydro-1*H*-chromeno[3,2-*b*]azet-2(2a*H*)-one* (**8a**) (2.1 g, 70 %)[5] which separated on cooling.

(*b*) $MeSO_2Cl$ (16.0 cm^3, 202 mmol) was added dropwise to compound **11b** (21.5 g, 68.2 mmol) in pyridine (350 cm^3) with continuous stirring and ice-water cooling. Stirring was continued for 3 h with the cooling bath removed and the mixture was poured onto ice-water (1000 g) to afford the crystals of crude compound **12b** (26.4 g, 98 %).[5] Crude compound **12b** (13 g, 33 mmol) was refluxed for 2.5 h with methanol (300 cm^3). The colourless crystals (6.4 g) of *(2a*RS,*8*RS,*8a*SR*)-6-fluoro-8-methoxy-1-(4-methoxyphenyl)-8,8a-dihydro-1*H*--chromeno-[3,2-*b*]azet-2(2a*H*)-one*[5] (**8b**) separated on cooling; a second fraction of the same product (total yield 7.4 g, 68 %) was obtained by concentration of the filtrate of the first.

(*c*) A solution of compound **12b** (and of the excess $MeSO_2Cl$ used) in pyridine, obtained from compound **11b** (21.2 g, 67.2 mmol) as described in (*b*), was evaporated to dryness at 0.2 kPa (bath temperature 70°C). The residue was triturated with water to afford crude compound **5b** (22.3 g, 100 %; colourless crystals) which was recrystallized from methanol and proved identical (m.p., IR, ^1H NMR) with one of the minor products obtained by ring closure of carbaldehyde **1b** with $AlCl_3$ in diethyl ether-DCM [2].

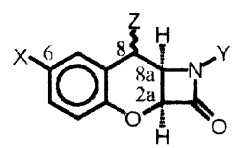
(*d*) Starting with compound **11a**, compound **5a** (colourless crystals), identical (m.p., IR, ^1H NMR) with one of the minor products obtained by ring closure of carbaldehyde **1a** with $AlCl_3$ in diethyl ether-DCM [2] was obtained similarly.

*(2a*RS,*8*SR,*8a*SR*)-8-Azido-6-chloro-1-(4-methoxyphenyl)-8,8a-dihydro-1*H*-chromeno-[3,2-*b*]-azet-2(2a*H*)-one* (**13a**)

A mixture of compound **6a** [2] (4.3 g, 11 mmol), dry DMF (40 cm^3) and NaN_3 (2.1 g, 33 mmol) was stirred for 2 h at 80°C and poured onto ice-water (500 g) to afford the crude colourless crystalline title compound (3.8 g, 97 %) which was recrystallized from EtOAc.[5]

Table Melting points, elemental analyses, IR (KBr) and ^{1}H NMR spectra ($CDCl_3$; TMS = 0) of some compounds **8-10**, **12**, **13**, **15**, **16**, **21**, **22**, and **24**[a] (**a**: X = Cl; **b**: X = F; **c**: X= MeO)

Compound, Z Y	Mp, °C	Molecular formula, mol. mass	Found / required, %					ν_{max} (KBr), cm^{-1}	δ_H, ppm / *J*, Hz						
			C	H	Cl	F	N		8a-H	8-H	2a-H	4-H	7-H	5-H	Other [b]
8a α-MeO PMP	140	$C_{18}H_{16}ClNO_4$ 345.8	62.55 62.5	4.7 4.65	10.2 10.25		4.2 4.05	1770	4.77dd 5.0, 2.0	4.60d 2.0	5.42d 5.0	7.08d 8.8	7.09d 2.5	7.31dd 8.8, 2.5	c
8b α-MeO PMP	125-126	$C_{18}H_{16}FNO_4$ 329.3	65.55 65.65	4.8 4.9		5.6 5.75	4.35 4.35	1760	4.76dd 5.0, 2.0	4.61d 2.0	5.42d 5.0	7.11dd 8.6, 4.6[d]	6.84dd 2.8, 7.6[d]	7.05ddd 8.6, 2.8, 8.0[d]	e
9a α-H_2NCO_2 PMP	197	$C_{18}H_{15}ClN_2O_5$ 374.8	57.5 57.7	4.0 4.0	9.5 9.45		7.35 7.45	f	4.78dd 5.0, 1.7	6.05d 1.7	5.43d 5.0	7.06d 8.5	7.23d 2.5	7.32dd 8.5, 2.5	g
10b H PMP	127	$C_{17}H_{14}FNO_3$ 299.3	68.3 68.2	4.55 4.7			4.55 4.7	1740	4.77ddd 5.3, 4.2, 1.5	h	5.35d 5.3	7.02dd 8.8, 4.7[d]	6.71ddd 3.0, 1.0[i], 8.2[d]	6.90dddd 8.8, 3.0 0.8[i], 8.2[d]	h
12a [j] β-$MeSO_3$ PMP	134-135							1750 1370 1180	5.24dd 5.3, 3.9	6.00ddd 3.9, 1.3[i], 0.8[i]	5.44d 5.3	7.10d 8.5	7.29dd 2.5, 1.3[i]	7.32ddd 8.5, 2.5, 0.8[i]	k
12b [j] β-$MeSO_3$ PMP	135-137							1750 1370 1190	5.23dd 5.4, 4.0	5.99dm 4.0	5.44d 5.4	7.02-7.15m			l
13a β-N_3 PMP	169	$C_{17}H_{13}ClN_4O_3$ 356.75	57.15 57.25	3.7 3.65	9.95 9.95		15.5 15.7	2110 1750	5.05dd 5.3, 3.7	4.94ddd 3.7, 1.0[i], 0.8[i]	5.42d 5.3	7.07d 8.5	7.38dd 2.6, 1.0[i]	7.30ddd 8.5, 2.6, 0.8[i]	
15a [m] β-AcNH PMP	248	$C_{19}H_{17}N_2O_4$ 372.8	61.0 61.2	4.7 4.6	9.55 9.5		7.35 7.5	3320 1750 1645	5.15dd 5.6, 4.2	5.54dddd 8.8, 4.2, 1.3[i], 0.8[i]	5.42d 5.6	7.3d	7.40dd	7.25dd	n
16b β-AcO PMP	154	$C_{19}H_{16}FNO_5$ 357.35	64.05 63.85	4.4 4.5		4.9 5.3	4.1 3.9	o	5.14dd 5.4, 3.9	6.12dddd 3.9, 1.2[i], 0.9[i], 0.9[d]	5.42d 5.4	7.10dd 8.8, 4.6[d]	6.93ddd 3.0, 1.2[i], 8.5[d]	7.01dddd 8.8, 3.0, 0.9[i], 8.0[d]	p
21a [q] α-(4-MeC_6H_4) H	120-125	$C_{17}H_{14}ClNO_2$ +0.5 C_7H_8 345.8	70.95 71.2	5.0 5.25	10.1 10.25		4.3 4.05	3220 1760	4.37dd 4.9, 1.6	4.18d 1.6	5.34dd 4.9, 2.9[r]	7.03d 8.5	7.10d 2.5	7.18dd 8.5, 2.5	s
22b β-AcO H	155-156	$C_{12}H_{10}FNO_4$ 251.2	57.6 57.35	4.15 4.0		7.25 7.55	5.75 5.6	t	4.55dd 5.1, 4.2	5.99dddd 4.2, 1.3[i], 0.8[i], 0.9[d]	5.33dd 5.1, 2.6[r]	7.04dd 8.6, 4.7[d]	6.95ddd 3.0, 1.3[i], 8.5[d]	6.99 dddd 8.6, 3.0, 0,8[i], 7.8[d]	u
24c [m] β-HO H	179-180	$C_{11}H_{11}NO_4$ 221.2	59.8 59.75	4.95 5.0			6.15 6.35	3380 br 1760	4.37dd 4.9, 4.3	4.81d 4.3	5.21dd 4.9, 1.8[r]	6.92d	7.16d	6.75dd	v



8-10, **12**, **13**, **15**, **16**, **21**, **22**, **24**

[a] All compounds are racemic [b] The chemical shifts of the PMP (4-$MeOC_6H_4$) groups are not given separately since their appear in all compounds listed at about 3.8 (s, MeO) and 6.9 + 7.3 ppm (AA'BB', *J ca* 9; *Ar*-H's) [c] Z: 3.27s [d] $J_{H,F}$ [e] Z: 3.28s [f] 3500, 3280, 1760, 1730, 1250, 1030 cm^{-1} [g] Z: 4.90br s [h] 8α-H: 3.03dddd (*J* 16.3, 4.2, 1.0,[i] 0.8[i]), 8β-H: 3.24dd (*J* 16.3, 1.5; <0.5[i]) [i] long-range coupling [j] crude product [k] Z: 3.11s [l] Z: 3.10s [m] ^{1}H NMR spectrum taken in solvent $CDCl_3$+DMSO-d_6 [n] Z: 2.05s [o] 1750, 1730sh, 1240, 1210, 1045 cm^{-1} [p] Z: 2.13s [q] containing 0.5 mol of toluene [r] long-range coupling with the NH proton [s] Z: 2.30s and 7.06 + 7.11 (AA'BB'); NH: 6.54br [t] 3290, 1805, 1760, 1250, 1050 cm^{-1} [u] Z: 2.26s; NH: 6.53br [v] 6-MeO: 3.78s; Z: ~0.5br; NH: 7.39br

*(2a*RS,*8*SR,*8a*SR*)-8-Acetylamino-6-chloro-1-(4-methoxyphenyl)-8,8a-dihydro-1*H--*chromeno[3,2-*b*]azet-2(2a*H*)-one* (**15a**)

A vigorous stream of H_2S was introduced for 15 min. into a solution of compound **13a** (3.6 g, 10 mmol) in dry DCM (100 cm^3) with continuous stirring and ice-water cooling. The introduction of H_2S was stopped, triethylamine (17 cm^3) was added and stirring was continued for 1 h. The mixture was evaporated to dryness. the residue was triturated with warm ethyl acetate (200 cm^3), the insoluble material was filtered off and the filtrate was evaporated to dryness to afford crude 8-amino derivative (**14a**) which was stirred for 18 h at room temperature with acetic anhydride (3.5 cm^3, 37 mmol) in dry DCM (80 cm^3). The resulting suspension was evaporated to dryness and the residue was recrystallized from acetonitrile to afford the title compound (2.5 g, 60 %, colourless crystals).[5]

*(2a*RS,*8*RS,*8a*SR*)-8-Carbamoyloxy-6-chloro-1-(4-methoxyphenyl)-8,8a-dihydro-1*H--*chromeno[3,2-*b*]azet-2(2a*H*)-one* (**9a**)

Sulfuryl chloride isocyanate (0.83 cm^3, 9.5 mmol) was dropwise added to compound **4a** [2] (2.5 g, 7.5 mmol) in dry THF (50 cm^3) with continuous stirring and ice-water cooling. Stirring was continued for 1.5 h at 0°C. An aqueous (38 cm^3) solution of $Na_2S_2O_5$ (4.3 g) was added and the mixture was stirred for 4 days at room temperature. EtOAc (100 cm^3) was added and the two phases were separated. The aqueous phase was extracted with EtOAc. The combined organic phases were washed with water, dried and evaporated to dryness. The oily residue crystallized when triturated with diethyl ether to afford the title compound (2.7 g, 96 %, colourless crystals).[5]

*(2a*RS,*8*SR,*8a*SR*)-8-Acetoxy-6-fluoro-1-(4-methoxyphenyl)-8,8a-dihydro-1*H-*chromeno-[3,2-*b*]azet-2(2a*H*)-one* (**16b**)

Acetic anhydride (5.3 cm^3, 56 mmol) was added dropwise to compound **11b** [2] (9.8 g, 31 mmol) in pyridine (100 cm^3) with continuous stirring at 0°C. Stirring was continued for 6 h at 50°C. The mixture was evaporated to dryness. The colourless crystalline residue was triturated with water to afford the crude title compound (10.3 g, 96 %) which was recyrstallized from toluene.[5]

N-*De(4-methoxyphenylations)*

(*a*) CAN (36 g, 66 mmol) in water (250 cm^3) was dropwise added within 20 min. to compound **7a** (Z = 4-methylphenyl) [2] (10.5 g, 26 mmol) in acetonitrile (220 cm^3) with

continuous stirring at -10°C. Stirring was continued for 20 min. EtOAc (200 cm^3) was added, the two phases were separated and the aqueous phase was extracted with EtOAc. The combined organic phases were successively washed with 10 % aqueous $NaHSO_3$, water and brine, dried and evaporated to dryness. The residue was worked up by flash chromatography (toluene-EtOAc, 10:1), followed by recrystallization from toluene to afford *(2a*RS, *8*RS,*8a*SR*)-6-chloro-8-(4-methylphenyl)-8,8a-dihydro-1*H*-chromeno[3,2-*b*]azet-2(2a*H*)-one* (**21a**), containing 1/2 mol of crystal-toluene (4.9 g, 63 %, colourless crystals).[5]

(*b*) Compound **16b** (6.2 g, 17.35 mmol) was allowed to react similarly with CAN, except that the crude product was isolated by extraction with DCM and purified by trituration with methanol to afford crystalline *(2a*RS,*8*SR,*8a*SR*)-8-acetoxy-6-fluoro-8,8a-dihydro-1*H*-chromeno[3,2-*b*]azet-2(2a*H*)-one* (**22b**) (2.8 g). A second fraction (1.5 g; total yield 69 %, colourless crystals) of this product was obtained by subjecting the methanolic filtrate to flash chromatography. The combined fractions were recrystallized from toluene to afford pure compound **22b**.[5]

(*c*) Treatment of compound **17c** (0.32 g, 1 mmol) with CAN as described in (*a*), except that DCM-acetone (10:0.5) was used for purification of the crude product, afforded *(2a*RS,*8a*RS*)-6-methoxy-1*H*-chromeno[3,2-*b*]azete-2,8(2a*H*,8a*H*)-dione* (**23c**) [70 mg, 32 %, colourless crystals; m.p. 175-176°C (from MeOH); found: C, 60.1; H, 4.35; N, 6.45; $C_{11}H_9NO_4$ (219.2) requires: C, 60.3; H, 4.15; N, 6.4 %; ν_{max} (KBr) 3340, 1770, 1690 cm^{-1}; δ_H ($CDCl_3$ + DMSO-d_6) 3.81s (6-MeO), 4.38d (4.9; 8a-H), 5.55dd (4.9, 1.6;[6] 2a-H), 7.02d (4-H), 7.16dd (5-H), 7.27d (7-H), 8.93br (NH).

(*d*) *(2a*RS,*8a*RS*)-6-fluoro-1*H*-chromeno[3,2-*b*]azete-2,8(2a*H*,8a*H*)-dione* (**23b**) [29 %, colourless crystals; m.p. 203-205°C (from MeOH); found: C, 57.7; H, 3.15; N, 6.5; $C_{10}H_6FNO_3$ (207.15) requires: C, 58.0; H, 2.9; N, 6.75 %; ν_{max} (KBr): 3290, 1780/1760d, 1690 cm^{-1}; δ_H ($CDCl_3$ + DMSO-d_6) 4.39d (5.0; 8a-H), 5.59d (5.0, 1.7;[6] 2a-H), 7.11dd (9.1, 4.3;[4] 4-H), 7.30ddd (9.1, 3.1, 7.6;[4] 5-H), 7.52dd (3.1, 8.0;[4] 7-H), 8.94br (NH)] was obtained from compound **17b** according to the procedure described in (*c*).

Catalytic reduction of compound **5b**

A mixture of compound **5b** (5.0 g, 15 mmol), NaOAc (2.0 g, 24 mmol), methanol (50 cm^3), DCM (50 cm^3) and a 10 % Pd-C catalyst (1.0 g) was vigorously stirred for 2 h under hydrogen. The catalyst was filtered off and the filtrate was evaporated to dryness. The residue was triturated with 3 % aqueous $NaHCO_3$ (50 cm^3) and the mixture was extracted with DCM.

[6] Long-range coupling with the NH proton

The combined organic phases were dried and evaporated to dryness. The residue (2.1 g) was worked up by c.c. (hexane-EtOAc, 4:0.5 → 4:1) to afford *(2RS)-6-fluoro-4'-methoxychromane-2-carboxanilide* (**25**) [0.3 g, 6.7 %, colourless crystals; m.p. 137°C (apparently with change of the crystal structure at 132-133°C; from MeOH); found: C, 67.5; H, 5.25; N, 4.75; $C_{17}H_{16}FNO_3$ (301.3) requires: C, 67.75; H, 5.35; N, 4.65 %; ν_{max} (KBr) 3220, 1770 cm^{-1}; δ_H 2.06dddd + 2.48dddd (J_{gem} 13.5, J_{vic} 9.7 + 10.5 + 5.5 and 2.8 + 6.0 + 4.0, respectively; 3-H_2), 2.79ddd + 2.89ddd (J_{gem} 16.5, J_{vic} 5.5 + 4.0 and 10.5 + 6.0, respectively; 4-H_2), 3.79s (4'-OMe), 4.57dd (9.7, 2.8; 2-H), 6.79dd (3.0, 8.6,[4] 5-H), 6.85m (7-H), 6.87 + 7.48 (AA'BB'; *Ar*-H's, PMP), 6.90dd (8.7, 4.8;[4] 8-H)] and *(2aRS,8aSR)-6-fluoro-1-(4-methoxyphenyl)-8,8a-dihydro-1H-chromeno-[3,2-b]azet-2(2aH)-one* (**10b**) (0.6 g, 13.4 %, colourless crystals)[5] in the order of increasing polarities, and a mixture (0.6 g) of these two products as the intermediate fraction.

Methyl (2RS,3SR,4RS)-3-amino-6-chloro-4-(4-methylphenyl)chromane-2-carboxylate (**26**)

1 M methanolic NaOMe (30 cm^3) was added to a methanolic (20 cm^3) suspension of compound **21a** (4.5 g, 15 mmol) with continuous stirring at 0°C. Stirring was continued for 2 h. The crystalline title compound [2.9 g, 59 %, colourless crystals; m.p. 174°C; found: C, 65.1; H, 5.7; Cl, 10.6; N, 4.15; $C_{18}H_{18}ClNO_3$ (331.8) requires: C, 65.15; H, 5.45; Cl, 10.7; N, 4.2 %; ν_{max} (KBr) 3410, 3330, 1770, 1210, 1060 cm^{-1}; δ_H 1.40br (NH_2), 2.33s and 6.94 + 7.14 (AA'BB'; 4-MeC_6H_4), 3.55dd (3.5, 2.3; 3-H), 3.79s (CO_2Me), 4.01d (3.5; 4-H), 4.60d (2.3; 2-H), 6.94d (2.5; 5-H), 7.04d (8.6; 8-H), 7.18dd (8.6, 2.5; 7-H)] was filtered off and washed with cold methanol.

Acknowledgments. The authors are grateful to Dr. Medzihradszky-Schweiger for the microanalyses and to Miss K. Ófalvi for the IR spectra. F.B., J.F. and K.L. are grateful to OTKA (Hungarian Scientific Research Fund; Grant No. T-023742), to the Hungarian Ministry of Education (Grant FKFP 0349/1997) and to EGIS Pharmaceuticals, LTd., Budapest, for financial assistance.

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