Pergamon

Tetrahedron 54 (1998) 15227–15242

TETRAHEDRON

Simple and Condensed β-Lactams, Part 31.[1] Acid Catalyzed Ring Closures and Ring Transformations of Some 3-Aryloxy-4-oxoazetidine-2-carbaldehydes

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Received 25 June 1998; revised 28 September 1998; accepted 14 October 1998

Abstract

Carbaldehydes **1a** and **1b**, when treated with Lewis or Brønsted acids in non-aromatic solvents or in nitrobenzene afford dihydrochromeno[3,2-*b*]azet-2(1*H*)-ones of types **4-6** and **10**. In toluene, chloro- and fluoro-benzene related compounds of types **7-9** were obtained, in the last named two solvents accompanied by pyrrolidin-2-one derivatives **11-15**.

Keywords: Azetidinones; chromenes; diastereoselection; ring transformations

Racemic 3-aryloxy-4-oxoazetidine-2-carbaldehydes **1a** and **1b** were obtained, together with racemic (**2a, b**) and *meso*-4,4′-bi(azetidin-2-ones) (**3a, b**) as minor products, by allowing the ketenes generated *in situ* from the corresponding aryloxyacetyl chlorides to react with *N,N′*-di(4-methoxyphenyl)-ethanediimine, according to the published general method [2, 3]. Treatment of **1a** and **1b** with Lewis or Brønsted acids afforded, depending on the conditions used, products or mixtures of products of types **4-15** (Table 1). Two important points emerge from the data compiled in Table 1: first, that when compounds **1a** and **1b** are treated with $AlCl_3$

[1] For Part 30, see ref. [1]

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PII: S0040-4020(98)00951-X

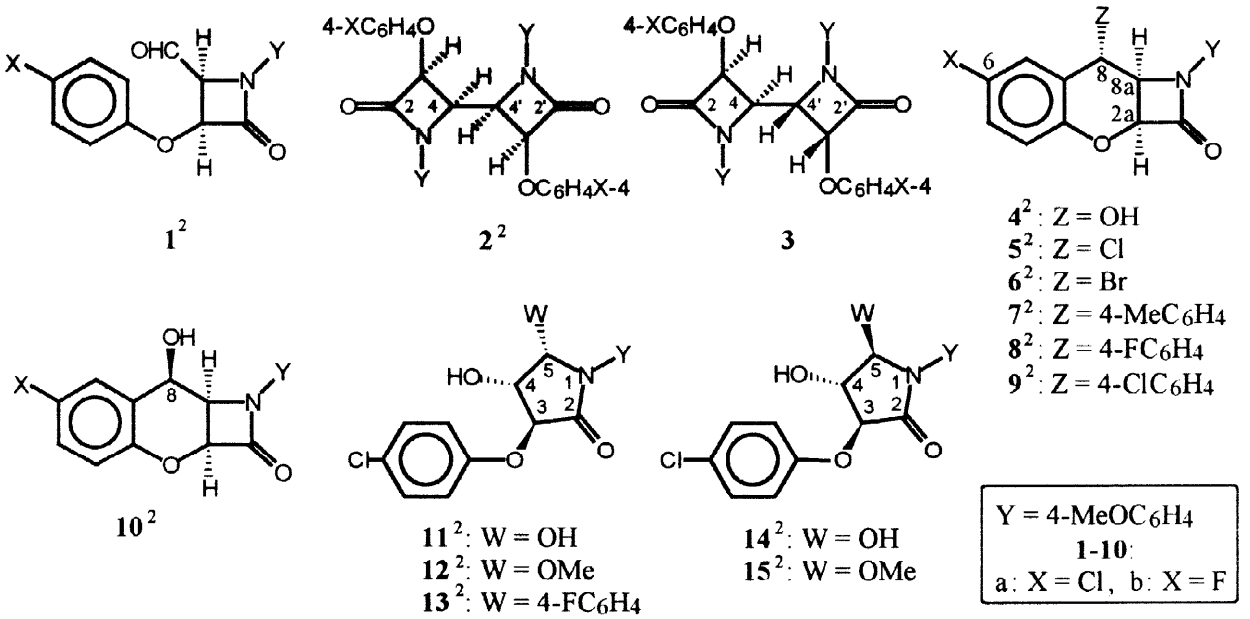


Table 1.

Reaction of 3-aryloxy-4-oxoazetidine-2-carbaldehydes **1a** and **1b** with Lewis or Brønsted acids in various solvents

	Starting compound	Reagent	Solvent[a]	Products (and yields,%)
1	**1a**	$AlCl_3$	Et_2O-DCM	**4a** (45) + **10a** (6) + **5a** (14)
2	**1b**	$AlCl_3$	Et_2O-DCM	**4b** (35) + **10b** (7) + **5b** (15)
3	**1a**	$AlCl_3$	$MeNO_2$	**5a** (46)
4	**1a**	$AlBr_3$	$MeNO_2$	**6a** (91)
5	**1a**	conc. H_2SO_4 +$SnCl_2 \cdot 2\ H_2O$	DCM	**5a** (47)
6	**1a**	$AlCl_3$	$PhNO_2$	**5a** (68)
7	**1a**	$AlCl_3$	toluene	**7a** (82)
8	**1b**	$AlCl_3$	toluene	**7b** (72)
9	**1a**	conc. H_2SO_4	toluene	**7a** (48)
10	**1a**	$AlCl_3$	PhF[b]	**8a** (41) + **11+14** (Σ20; 4:1)
11	**1a**	$AlCl_3$	PhF[c]	**8a** (56) + **11+14** (Σ3.5) + **12** (7) +**13** (6.6) + **15** (8.6)
12	**1a**	$AlCl_3$	PhCl[b]	**9a** (36) + **11+14** (Σ31)

[a] DCM = dichloromethane

[b] Reaction mixture quenched by pouring into water

[c] Reaction mixture quenched by pouring into methanol

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

in aromatic solvents such as **toluene**, **chloro-** and fluoro-benzene (but not in nitrobenzene), 1 molecule of the solvent is **incorporated** into the product; second, that when treatment of **compounds 1a** and **1b** with $AlCl_3$ **is carried** out in chloro- or fluoro-benzene (but not in toluene, nor in nitrobenzene), formation of the cyclization products **8** and **9**, respectively, is accompanied by ring transformation to afford mixtures of the pyrrolidinone derivatives **11-15**.

Except for the formation of the epimeric pairs of compounds **4a** and **10a**, and **4b** and **10b**, formation of all other dihydrochromeno[3,2-*b*]azet-2(1*H*)-ones was highly diastereoselective, affording chromane derivatives **5-9** monosubstituted diastereoselectively at each of the carbon atoms of the dihydropyran ring, without formation of their 8-epimers. (Studies aiming to exploit the potential of this method are in progress.)

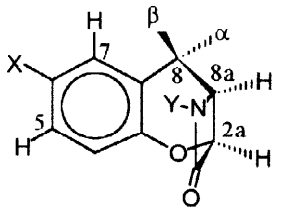
The constitutions of ring closure products **4b, 5b, 7b** and **10b** at once follow from an inspection of their ^{1}H NMR spectra: all of them display the signals of *three* aromatic protons coupled with fluorine, *i.e.* cyclization has taken place with participation of the fluorophenyl ring of substrate **1b**. By analogy, it may be assumed that the constitutions of compounds **4a, 5a, 6a, 7a, 8a, 9a** and **10a** are of the same type. Support for this view comes from the fact that compound **7a**, as shown by its ^{1}H and two-dimensional ^{1}H-^{1}H NMR spectra, contains 11 aromatic protons, four being part of the 4-methoxyphenyl group (AA′BB′ spectrum) which has remained intact in the course of the cyclization, and four of the newly incorporated 4-methylphenyl group (heavily distorted AA′BB′ spectrum). Consequently, the 4-chlorophenyl group has lost one of its four hydrogen atoms, *i.e.* cyclization has taken place with participation of the chlorophenyl group, analogously to the case of the fluorophenyl group discussed above.[3] Furthermore, the structural similarity of all products discussed so far is borne out by their NMR spectra.

The relative configurations of C-8 in the two epimeric pairs **4a** and **10a**, and **4b** and **10b** were established on the basis of NOE studies, and other evidence from NMR spectra. Two conformations are possible for these compounds, one compact, folded, the other more extended, as shown in **16** and **16A**, respectively. In the former the C-8-α bond in the flagpole position of the boat-shaped six-membered ring is close to perpendicular to the plane of the fused benzene ring. As shown by the values of the $J_{8\text{-H}/8a\text{-H}}$ coupling constants and by the occurring of certain long-range couplings in compounds **10a** and **10b**,[4] and their non-occurring in compounds **4a** and **4b**, of the two conformations of these compounds, the former is the only or the predominant one in solution. In agreement herewith, NOEs were observed on 2a-H on irradiation of 8α-H in compound **10a**, and on 7-H on irradiation of 8β-H in

[3] The assignment of the signals of the various aromatic protons is supported by the ^{1}H-^{13}C correlation spectra

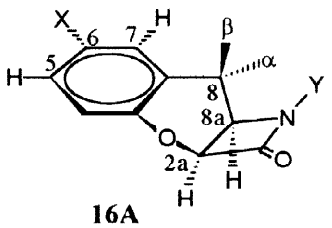
[4] Observed values, $J_{8\text{-H}/8a\text{-H}}$: **4a**, **4b**, 2.0, **10a** 4.0, **10b** 3.9 Hz; $J_{5\text{-H},8\text{-H}}$: **10a**, **10b** 1.0 Hz; $J_{7\text{-H},8\text{-H}}$: **10a**, **10b** 1.2 Hz.

compound **4a** and of the hydroxyl proton of 8β-OH in **10a**, whereas only a weak NOE was observed on 7-H on irradiation of **8α-H in 10a**. In agreement with these structure assignments, long-range couplings were observed between 8α-H and both 7-H and 5-H in the ^{1}H NMR spectrum of compound **10a** (where the C-8 – 8α-H bond is close to perpendicular to the plane of the condensed benzene ring), but no analogous long-range couplings were observed in the spectrum of compound **4a**.



16

Y = 4-MeOC$_6$H$_4$



16A

The stereochemistry of compounds **4a** and **4b**, and **10a** and **10b**, respectively, was proved by the identity or near-identity of the coupling constants $J_{8\text{-H}/8a\text{-H}}$ for both pairs of compounds,[4] the observation of long-range couplings in the spectrum of compound **10b** (with identical coupling constants as for **10a**[4]) and the absence of long range couplings in that of compound **4b**.

Since the $J_{8\text{-H}/8a\text{-H}}$ coupling constants of compounds **4a**, **4b** and **5-8** were similar[5] and long-range couplings between 8-H and either 7-H or 5-H were not observed, 8-H in all these compounds clearly occupies the same steric position (β). The observation of a NOE between 8-H and 7-H and of a *weak* NOE between 8-H and 8a-H in the ^{1}H NMR spectrum of compound **7a** is in agreement with these conclusions and serves as additional evidence for the stereochemistry of this compound.

By monitoring the reactions of compound **1a** with Brønsted and Lewis acids by t.l.c. valuable information concerning the mechanisms of the reactions leading to products **5a-9a** was obtained; *viz.* it was found that compounds **4a** and **10a**, complexed to the Lewis acid through, or protonated by the Brønsted acid at, their hydroxyl groups, are the intermediates of all these reactions. (The same should be true, by analogy, for the **b** series.) Thus, in the reaction of compound **1a** with $AlCl_3$ in toluene, the substrate was found to react rapidly affording initially two intermediates which are subsequently gradually transformed into final product **7a**. The R_f values of the two intermediates were found to be identical with those of the epimeric compounds **4a** and **10a**; clearly, hydrolysis of the intermediate $AlCl_3$ complexes has taken place during chromatography. The reaction of compound **1a** and $AlBr_3$ in nitromethane was similar. Thus, an examination by t.l.c. of samples taken from time to time from the

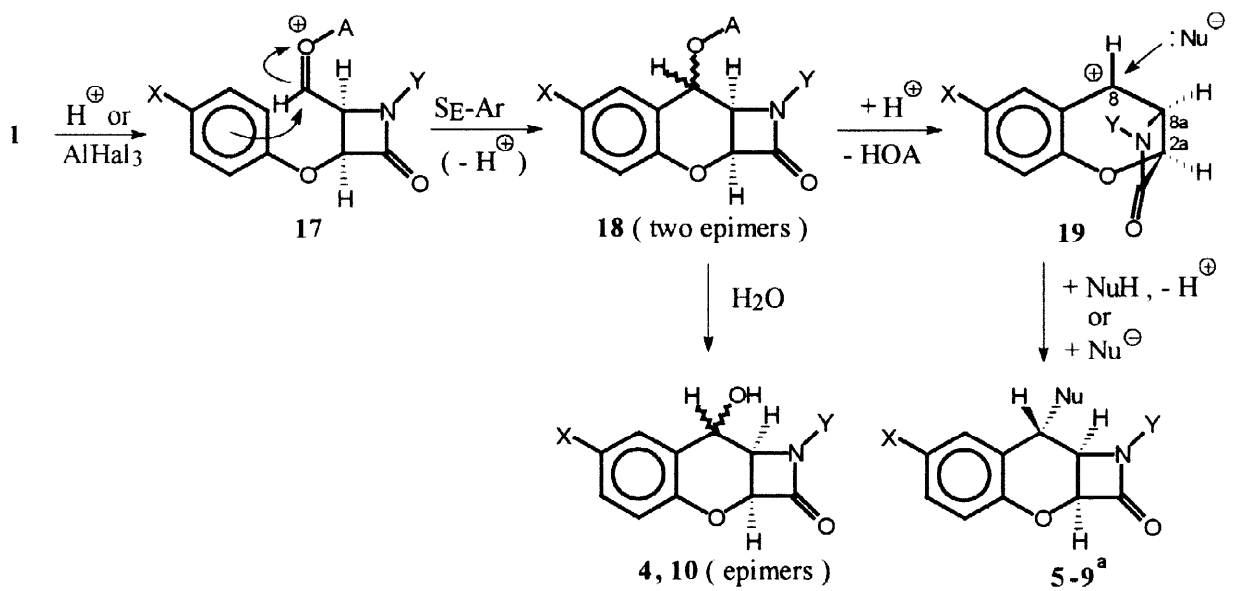
[5] $J_{8\text{-H}/8a\text{-H}}$, observed values, **5a**, **5b**, **6a**, 1.8 Hz; **7a**, **7b**, **8a**: 1.2 Hz.

reaction mixture has shown that the $AlBr_3$ complexes of intermediates **4a** and **10a** are rapidly formed and subsequently more slowly converted into the complex of final product **6a**. Of the two complexed compounds **4a** and **10a**, the former was found to disappear more rapidly from the reaction mixture, which suggests that, at least under these conditions, no equilibrium is set up between the complexed diastereoisomeric intermediates **4a** and **10a**, in other words that they are independently formed from carbaldehyde **1a** and $AlBr_3$. Support for this view comes from the observations that neither compound **4a**, nor compound **10a** is isomerized even partly into the other on treatment with conc. H_2SO_4, with toluene-sulfonic acid for 24 h in aqueous dioxane at 60-70°C (not even after addition of some TFA) or with 3 mol equivalents of $AlCl_3$ in DCM.

Taken together, all these observations suggest the mechanism shown in Scheme 1 for the formation of compounds **4-10**.

Scheme 1.

Suggested mechanism of reactions **1** → **4-10**.



A = H, $^{\ominus}AlCl_3$, $^{\ominus}AlBr_3$; X = Cl, F; Y = 4-$MeOC_6H_4$; Nu = Cl, Br, 4-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4.

[a] Reactions **19** $\xrightarrow{ArH}$ **7-9** are S_E-Ar reaction

The highly diastereoselective nature of transformations **19** → **5-9** and the identity of the configurations at C-8 in the products may be explained by assuming that the intermediate cation does exist in the folded conformation **19** shown, which is similar to conformation **16** of the products **5-9**. As a result, cation **19** is expected to be attacked by nucleophiles from outside as indicated, the entering ligand occupying the α-position and pushing 8-H into the β-position.

As shown by their IR spectra (ν_{max} around 1700 cm^{-1}), compounds **11-15** do not contain the azetidin-2-one ring of starting compound **1a** any more. On the other hand, both the IR and NMR spectra are in agreement with the ring-expanded structures shown. The relative configurations of the chiral carbon atoms of compounds **11-15** were deduced from the results of NOE studies (Table 2). These results clearly demonstrate the *trans* relation of 3-H and 4-H in all of the compounds **11-15,** the *cis* relation of 4-H and 5-H in compounds **11-13** and their *trans* relation in compounds **14** and **15,** as well as the *trans* relation of 3-H and 5-H in compounds **11-13** and their *cis* relation in compounds **14** and **15**.

Table 2.

NOE studies on compounds **11-15**.

Compound	Irradiated signal	NOEs[a] observed on
11[b]	5-H (5.36)	2-H+6-H, PMP (7.58); 4-OH (4.31); 4-H (4.41)
	3-H (5.06)	5-OH (5.87)
11[c]	5-H (5.30)	4-H (4.30); 2-H+6-H, PMP (7.52); 5-OH (6.39); 4-OH, very weak (5.76)
	3-H (5.14)	2-H+6-H, 4-ClC_6H_4 (7.13); 4-H (4.30); 4-OH (5.76); 5-OH (6.39)
12[d]	3-H (4.89)	2-H+6-H, 4-ClC_6H_4 (7.10); 4-H (4.49); 4-OH (3.03); 5-OMe (3.43)
	5-H (5.09)	5-OMe (3.43); 4-H (4.49); 2-H+6-H, PMP (7.30)
	4-OH (3.03)	3-H (4.89); 4-H (4.49); 5-OMe (3.43); 5-H (5.09); 2-H+6-H, 4-ClC_6H_4 (7.10)
13[d]	3-H (4.85)	2-H+6-H, 4-ClC_6H_4 (7.08); 2-H+6-H, 4-FC_6H_4 (7.24); 4-OH (2.07)
	5-H (5.24)	4-H (4.74); 2-H+6-H, PMP (7.36); 2-H+6-H, 4-FC_6H_4 (7.24)
14[b]	3-H (4.79)	5-H (5.35)
14[c]	3-H (4.95)	2-H+6-H, 4-ClC_6H_4 (7.14); 4-H (4.04); 4-OH (6.20); 5-H (5.21)
	5-OH (6.64)	5-H (5.21); 4-H (4.04)
	4-H (4.04)	4-OH (6.20); 5-OH (6.64); 3-H (4.95); 5-H, very weak (5.21)
15[d]	3-H (4.55)	2-H+6-H, 4-ClC_6H_4 (6.96); 4-OH (3.68); 4-H (4.20); 5-H (5.05)
	5-H (5.05)	2-H+6-H, PMP (7.26); 5-OMe (3.25); 4-OH (3.68); 4-H (4.20); 3-H (4.55)
	5-OMe (3.25)	5-H (5.05); 4-H (4.20); 2-H+6-H, PMP (7.26)

[a] Listed in the order of decreasing intensities [b] Solvent DMSO-d_6+$CDCl_3$ [c] Solvent DMSO-d_6 [d] Solvent $CDCl_3$

A related acid catalyzed ring transformation, that of azetidine-2-one **20** into pyrrolidine-2,4--dione **24** had been described by Alcaide *et al.* [4]. The key-step of the reaction was assumed to be an anionic 1,2-shift, *viz.* concerted cleavage of the C-3 — C-2 bond of the protonated starting substance **21a** and formation of a new bond between C-3 and the original aldehydic carbon atom to afford the intermediate carbenium ion **22a**. This was assumed to be followed by a second anionic 1,2-shift, this time of a hydride anion, to yield the protonated product **23**, which is finally transformed by loss of a proton into the end product **24** [4].

The key step of ring transformations **1a** → **11-15** is assumed to be an analogous 1,2 shift, leading from the $AlCl_3$ complex (**21b** = **17**, X = Cl, A = $^{\ominus}AlCl_3$) of the starting carbaldehyde **1a** to zwitter-ionic intermediate **22b**. Since the relative configurations of C-3 and C-4 are identical in all isolated products (**11-15**) of the ring transformation (3-H and 4-H being *trans* to each other), this 1,2-shift is clearly highly stereoselective. The correct stereochemistry of the products may be derived by assuming that the bond between C-2 and the carbon atom of the complexed aldehyde group at the moment of the shift adopts the conformation shown in Scheme 2 and that, consequently, the complexed aldehyde group of compound **21b** is attacked by the migrating C-3 atom from the *Si* face.

The stereochemistry of key step **21a** → **22a** of ring transformation **20** → **24** may be assumed to be identical; since, however, the two substituents at C-3 in the starting **20** are identical and the chirality of C-2 (which becomes C-4 in the product) is temporarily lost during the reaction, there is no stereochemical proof for this assumption.

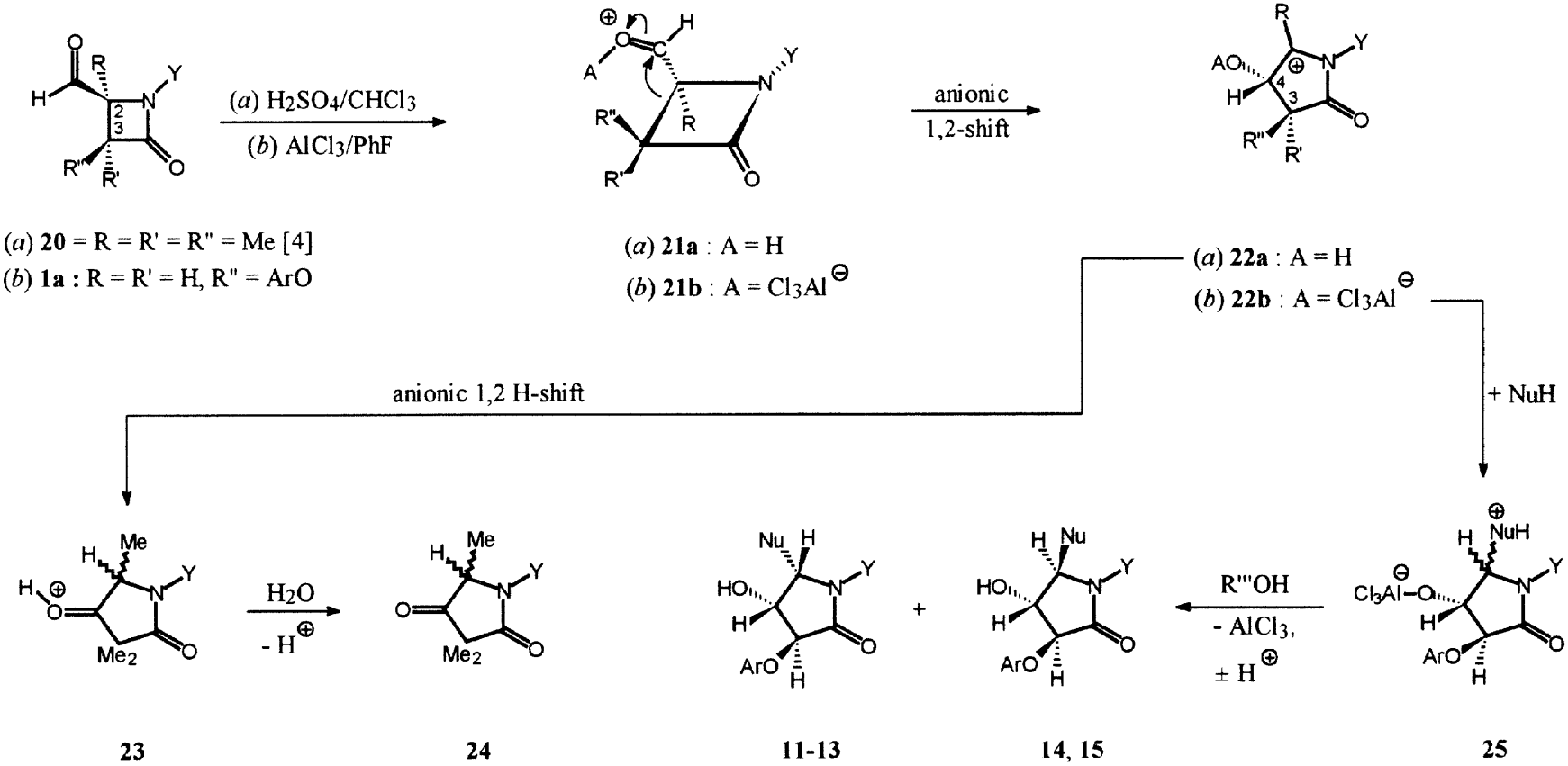
An important difference between the two related ring transformations is that, while in Alcaide's case, the anionic shift of C-3 is followed by an anionic 1,2-H-shift [which ultimately leads to the formation of a pyrrolidine-2,4-dione (**24**)], in our case the cationic center of intermediate **22b** is attacked by some nucleophile present in the reaction mixture to afford ultimately mixtures of several of the pyrrolidin-2-ones **11-15**. The reason for this difference is not clear. Depending on whether attack of the nucleophile takes place from the top or bottom face of the five-membered ring of intermediate **22b**, formation of two epimeric products is theoretically possible. Pairs of epimeric compounds (**11**, **14** and **12**, **15**) have indeed been obtained; on the other hand, the 5-epimer of the 4,5-*cis* product **13** was not obtained.

According to the mechanisms suggested for ring closures **1** → **4-10** (Scheme 1) and ring transformations **1a**→**11-15** (Scheme 2) the key-intermediates of the two reactions are identical (*e.g.* **21b** = **17**, X = Cl, A = $^{\ominus}AlCl_3$) or at least of identical types. This means that all these intermediates should be capable to proceed, ultimately, either to ring closure or ring transformation products. As shown by our experiments (Table 1), while the cyclizations appear to be general, ring transformations have been observed only with fluoro- or chlorobenzene used as solvents. The reluctance of compounds **1a** and **1b** to undergo ring transformations in toluene, nitrobenzene and in a series of non-aromatic solvents, both in the presence of H_2SO_4 and aluminium trihalides is not clear. Since, however, treatment of compounds **4a** or **10a** with excess $AlCl_3$ in dichloromethane (DCM) afforded compound **5a** in *ca* 60% yield with no detectable amounts (t. l.c.) of ring transformation products **11** and **14** being formed [6] and,

[6] When the solvent DCM was replaced by DCM-diethyl ether (1:1), compound **10a** did not change at all even after 24 h on treatment with 3 mol equivalents of $AlCl_3$. The latter is apparently complexed to the ether, rather than to the hydroxyl group of compound **10a**; as a result, reaction **10a** → **5a** is inhibited.

Scheme 2.

Mechanism of ring transformations



(*a*) **20** = R = R' = R" = Me [4]
(*b*) **1a** : R = R' = H, R" = ArO

(*a*) **21a** : A = H
(*b*) **21b** : A = $Cl_3Al^{\ominus}$

(*a*) **22a** : A = H
(*b*) **22b** : A = $Cl_3Al^{\ominus}$

(a) **20** → **24** [4] and *(b)* **1a** → **11-15**. Y = 4-$MeOC_6H_4$, Ar = 4-ClC_6H_4. Compounds **23** and **24** are racemic. Nu = H_2O, MeOH, PhF; R'''OH = H_2O, MeOH

furthermore, treatment of any of **compounds 4a**, **10a** or **5a** with excess $AlCl_3$ in fluorobenzene afforded compound **8a** in excellent yield, it is clear that once the chromane ring is formed, the reaction leads, in the presence of aromatics not too strongly deactivated towards electrophilic substitution, invariably to the formation of 8-aryl-8,8a-dihydro-2a*H*-chromeno-[3,2-*b*]azet--2(1*H*)-ones (**7-9**).

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 $CDCl_3$-DMSO-d_6 solutions, unless otherwise stated and using tetramethylsilane as the internal reference compound; J values are given in Hz. 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]. Exact molecular mass determinations were made at 70eV with a Finnigan MAT 95SQ instrument of reversed geometry equipped with a direct inlet system.

*(2*RS,*3*RS*)-3-(4-Chlorophenyl)- and (2*RS,*3*RS*)-3-(4-fluorophenyl)-1-(4-methoxyphenyl)--4-oxoazetidine-2-carbaldehydes* (**1a**, **1b**), *(2*RS,*3*RS,*2'*RS,*3'*RS*)- or* racemic *and (2*RS,*3*RS,*2'*SR,*3'*SR*)- or* meso-*3,3'-bis-(4-chlorophenyl)-* (**2a**, **3a**) and *-3,3'-bis(4-fluorophenyl)-1,1'-bis(4-methoxyphenyl)-4,4'-bi(azetidin-2-ones)* (**2b**, **3b**)

Solutions of 4-chloro- [5] and 4-fluoro-phenoxyacetyl chloride [6] (50 mmol) (freshly prepared from the corresponding acids) in DCM (250 cm^3) were dropwise added over 0.5 h to solutions of *N,N'*-di(4-methoxyphenyl)ethanediimine [7] (16.1 g, 60 mmol) and triethylamine (16.8 g, 120 mmol) in DCM (500 cm^3) with continuous stirring and ice-water

cooling. Stirring was continued for 1 h with the cooling bath removed. 1.5 N Hydrochloric acid (500 cm^3) was added and the mixture was stirred for further 1.5 h. The two phases were separated. The organic phases were dried and worked up by c.c. (DCM) to afford the title compounds.

1a: 40%; m.p. 135°C; found: C, 61.45; H, 4.35; Cl, 10.35; N, 4.15; $C_{17}H_{14}ClNO_4$ (331.75) requires: C, 61.55; H, 4.25; Cl, 10.7; N, 4.2%; ν_{max} (KBr) 1750, 1710 cm^{-1}; δ_H ($CDCl_3$) 4.75dd (5.3, 3.7; 2-H), 5.52d (5.3; 3-H), 7.02 + 7.30 (AA'BB'; 4-ClC_6H_4), 9.82d (3.7; CHO);

2a + 3a (*racemic* + *meso* form): 1.0%; m.p. 259°C; found: C, 63.3; H, 4.15; Cl, 11.9; N, 4.4; $C_{32}H_{26}Cl_2N_2O_6$ (605.5) requires: C, 63.5; H, 4.35; Cl, 11.7; N, 4.65%; ν_{max} (KBr) 1760 cm^{-1}; δ_H ($CDCl_3$) 4.99m (4-H + 4'-H), 5.49m (3-H + 3'-H), 6.55 + 7.01 + 7.05 + 7.44 (2 x 4-$MeOC_6F_4$ + 2 x 4-ClC_6H_4);

1b: 80%; m.p. 126°C; found: C, 65.0; H, 4.35; F, 5.8; N, 4.65; $C_{17}H_{14}FNO_4$ (315.3) requires: C, 64.75; H, 4.5; F, 6.05; N, 4.45%; ν_{max} (KBr) 1750, 1710 cm^{-1}; δ_H ($CDCl_3$) 4.71dd (5.4, 3.7; 2-H), 5.49d (5.4; 3-H), 6.95-7.1m (4-FC_6H_4), 9.82d (3.7; CHO);

2b + 3b (*racemic* + *meso* form): 8.0%; m.p. 251-252°C; found: C, 66.95; H, 4.7; F, 6.3; N, 4.75; $C_{32}H_{26}F_2N_2O_6$ (572.6) requires: C, 67.15; H, 4.6; F, 6.65; N, 4.9%; ν_{max} (KBr) 1740 cm^{-1}; δ_H ($CDCl_3$) 5.01m (4-H + 4'-H), 5.48m (3-H + 3'-H), 6.55 + 7.05 (2 x 4-$MeOC_6H_4$), 6.98 + 7.04 (2 x 4-FC_6H_4);

Because of the similarity of their R_f values, chromatographic separation of compounds **1b** and **2b + 3b** proved rather difficult. The crude mixture (obtained by evaporation to dryness of their DCM solution) was therefore boiled with methanol (*cf.* ref. [3]), whereby aldehyde **1b** was converted into a mixture of its diastereoisomeric hemiacetals. From the solution compound **2b + 3b** gradually separated on cooling while the two hemiacetals [70%; ratio of the stereoisomers according to the ^1H NMR spectrum *ca* 3:2; m.p. 117°C; ν_{max} (KBr) 3390, 1750 cm^{-1}; δ_H ($CDCl_3$), isomer *A*: 1.6 br s (OH), 3.46s (OMe, hemiacetal group), 4.38dd (5.1, 4.1; 4-H), 5.06d (4.1; 4-C*H*), 5.31d (5.1; 3-H), 6.95-7.16m (4-FC_6H_4); isomer *B*: 1.6 br s (OH), 3.41s (OMe, hemiacetal group), 4.45dd (5.4, 3.5; 4-H), 4.99d (3.5; 4-C*H*), 5.26d (5.4; 3-H), 6.95-7.16m (4-FC_6H_4)] separated on prolonged standing in a refrigerator. The hemiacetals proved quite unstable: when kept for some time at room temperature either in crystalline form or in $CDCl_3$ solution, gradual decomposition to the aldehydes took place. The resulting mixtures of the aldehydes and their hemiacetals, however, could be used instead of the pure aldehydes for the transformations described below.

Reaction of carbaldehydes **1a** *and* **1b** *with Lewis and Brønsted acids: preparation of 1-(4-methoxyphenyl)-8,8a-dihydro-2a*H*-chromeno[3,2-*b*]-azet-2(1*H*)-ones* (**I**) *and tetra-substituted pyrrolidin-2-ones*

(*a*) Carbaldehydes **1a** or **1b** (30 mmol) in DCM (60 cm^3) were stirred with $AlCl_3$ (16.0 g, 120 mmol) in dry diethyl ether (220 cm^3) for 40 h at room temperature, then poured into a mixture of ice-water (400 cm^3) and ethyl acetate (100 cm^3). The two phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were successively washed with saturated aqueous Na_2CO_3 solution and brine, dried and evaporated to dryness. The oily residue was worked up by flash-chromatography (toluene - EtOAc, 10:1 in the **a** and 10:0.5 in the **b** series) to afford *(2a*RS,*8*RS,*8a*SR*)-6-chloro-8-hydroxy-***I** (**4a**)[7] (4.5 g, 45%), its *(2a*RS,*8*SR,*8a*SR*)* epimer (**10a**)[7] (0.6 g, 6%) and *(2a*RS,*8*RS,*8a*RS*)-6,8-dichloro--***I** (**5a**)[7] (1.5 g, 14%), and *(2a*RS,*8*RS,*8a*SR*)-6-fluoro-8-hydroxy-***I** (**4b**)[7] (4.2 g, 35%), its *(2a*RS,*8*SR,*8a*SR*)* epimer **10b**[7] (0.9 g, 7%) and *(2a*RS,*8*RS,*8a*RS*)-8-chloro-6-fluoro-***I** (**5b**)[7] (1.9 g, 15%), respectively.

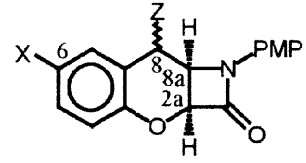
(*b*) $AlCl_3$ (5.3 g, 40 mmol) and $AlBr_3$ (8.0 g, 3.0 mmol), respectively, were added to carbaldehyde **1a** (3.3 g, 10 mmol) in nitromethane (70 cm^3) with continuous stirring at -15°C. The mixtures were allowed to warm up to room temperature, stirred for further 5 h, then poured into ice-water and EtOAc (100 cm^3, each) and worked up as described in (*a*) to afford compounds **5a** (1.6 g, 46%; m.p. 193°C), identical (m.p., IR) with the sample obtained as described in (*a*), and *(2a*RS,*8*RS,*8a*RS*)-8-bromo-6-chloro-***I** (**6a**)[7] (3.6 g, 91%), respectively.

(*c*) A mixture of carbaldehyde **1a** (6.6 g, 20 mmol) in DCM (400 cm^3) was stirred with $SnCl_2 \cdot 2\ H_2O$ (9.0 g, 40 mmol) and conc. H_2SO_4 (6 cm^3) for 20 h at room temperature. A resinuous precipitate was formed. The supernatant was decanted and the resin was washed with DCM (2x50 cm^3). The combined organic solutions were worked up as described in (*a*) to afford compound **5a** (3.3 g, 47%), identical (m.p., IR) with the sample obtained as described in (*a*).

(*d*) Carbaldehyde **1a** (0.33 g, 1 mmol) was added in one portion to a suspension of $AlCl_3$ (0.28 g, 2 mmol) in nitrobenzene (4 cm^3). The mixture was stirred for 3 h at room temperature and evaporated to dryness (35-40°C, *ca* 70 Pa). The residue was taken up in water and DCM, the two phases were separated and the aqueous phase was extracted with DCM. The combined organic phases were dried and evaporated to dryness. The residue was worked up by c.c. (toluene) to afford compound **5a** (0.24 g, 68%; m.p. 192-193°C) which proved identical (m.p., IR, R_f) with the sample obtained as described in (*a*).

[7] For the melting points, analyses, IR and ^1H NMR spectra, see Table 3

Table 3. Melting points, elemental analyses, IR (KBr) and ^{1}H NMR spectra ($CDCl_3$; TMS = 0) of compounds **4-10** [2]



(4-10, a: X = Cl; **b**: X = F)

Compound, Z	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 [a]
4a α-OH	169	$C_{17}H_{14}ClNO_4$ 331.75	61.3 61.55	4.4 4.25	10.95 10.7		4.35 4.2	3440 1730	4.68dd 5.0, 2.2	5.04dd 5.2, 2.2	5.39d 5.0	7.03d 8.6	7.15d 2.5	7.26dd 8.6, 2.5	b
4b α-OH	154	$C_{17}H_{14}FNO_4$ 315.3	64.65 64.75	4.45 4.5		6.05 6.05	4.45 4.45	3400 1730	4.68dd 5.0, 2.2	5.05dd 5.3, 2.2	5.38d 5.0	7.04dd 8.7, 4.6[c]	6.88dd 2.8, 7.5[c]	6.99ddd 8.7, 2.8, 7.9[c]	d
5a α-Cl	193	$C_{17}H_{13}Cl_2NO_3$ 350.2	58.1 58.3	3.7 3.75	20.45 20.25		3.85 4.00	1740	4.92dd 5.0, 1.8	5.30d 1.8	5.55d 5.0	7.08d 8.6	7.15d 2.5	7.32dd 8.6, 2.5	
5b α-Cl	167-170	$C_{17}H_{13}ClFNO_3$ 333.75	61.1 61.2	3.8 3.95	10.75 10.6	5.9 5.7	4.25 4.3	1750	4.90dd 4.9, 1.8	5.32d 1.8	5.53d 4.9	7.10dd 8.7, 4.6[c]	6.89m	7.06ddd 8.7, 2.8, 7.9[c]	
6a α-Br	200	$C_{17}H_{13}BrClNO_3$ 394.65	51.55 51.75	3.35 3.3	8.8 9.0	20.5[e] 20.25[e]	3.7 3.55	1770	5.04dd 5.0, 1.6	5.38d 1.6	5.56d 5.0	7.07d 8.6	7.14d 2.5	7.30dd 8.6, 2.5	
7a α-(4-MeC_6H_4)	138	$C_{24}H_{20}ClNO_3$ 405.9	71.1 71.0	5.0 4.95	9.2 8.75		3.3 3.45	1760	4.74dd 5.1, 1.4	4.47d 1.4	5.42d 5.1	7.07d 8.6	7.00d 2.5	7.18dd 8.6, 2.5	f
7b α-(4-MeC_6H_4)	88	$C_{24}H_{20}FNO_3$ 389.4	74.1 74.0	5.1 5.3		4.95 4.9	3.7 3.6	1770	4.74dd 5.0, 1.4	4.48 1.4	5.41d 5.0	7.10dd 8.8, 4.6[c]	6.73dd 3.0, 8.4[c]	6.92ddd 8.8, 3.0, 7.9[c]	g
8a α-(4-FC_6H_4)	183	$C_{23}H_{17}ClFNO_3$ 409.85	67.25 67.4	4.0 4.2	9.1 8.65	4.8 4.65	3.35 3.4	1750	4.73dd 5.2, 1.4	4.49d 1.4	5.44d 5.2	7.10d 8.6	7.00d 2.5	7.22dd 8.6, 2.5	h
9a α-(4-ClC_6H_4)	204-206	$C_{23}H_{17}Cl_2NO_3$	$M^{+\bullet}$ 425.05806 / 425.05855					1740	4.72dd 5.2, 1.3	4.47 br	5.43d 5.2	7.09d 8.6	6.99d 2.5	7.21dd 8.6, 2.5	i
10a β-OH	188	$C_{17}H_{14}ClNO_4$ 331.75	61.3 61.55	4.15 4.25	10.65 10.7		4.4 4.2	3400 1720	4.96dd 5.4, 4.0	5.09dddd 8.7, 4.0 1.3[k], ~1[k]	5.34d 5.4	7.01d 8.5	7.45dd 2.6, 1.3[k]	7.23ddd 8.5, 2.6,~1[k]	l, m
10b β-OH	182-185	$C_{17}H_{14}FNO_4$ 315.3	64.4 64.75	4.5 4.5		6.2 6.05	4.25 4.45	3350 1730	4.91dd[n] 5.4, 4.0	5.05 br dd[n] 6.3, 4.0	5.32d[n] 5.4	7.01dd[n] 8.6, 4.5[c]	7.25ddd[n] 3.0, ~1[k], 8.8[c]	6.92 br ddd[n] 8.6, 3.0, 7,8[c]	o, p

[a] The chemical shifts of the PMP (4-$MeOC_6H_4$) 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; 4xArH)] [b] Z: 2.31d (5.2) [c] $J_{H,F}$ [d] Z: 2.74d (5.3) [e] Br [f] Z: 2.33s, 7.15 br s (4xArH) [g] Z: 2.33s, 7.16s (4xArH) [h] Z: 7.04m + 7.23m (2x2 ArH) [i] Z: 7.19 + 7.32 (AA'BB', 8.5) [k] Long-range coupling [l] Z: 2.39d (8.7) [m] PMP: 3.76s, 6.81 + 7.48 (AA'BB') [n] Solvent: $CDCl_3$ + DMSO-d_6 [o] Z: 5.43d (6.3) [p] PMP: 3.75s, 6.80 + 7.59 (AA'BB')

(*e*) Carbaldehydes **1a** (10.0 **g, 30 mmol**) and **1b** (3.5 g, 11 mmol), respectively, in dry toluene (12 cm^3/mmol **1**) were added dropwise over 0.5 h to $AlCl_3$ (4 mol equivalents) in dry toluene (10 cm^3/mmol **1**) with continuous stirring at -5 – -10°C. Stirring was continued for further 4 h at -10°C. The mixture was then poured onto a mixture of ice-water (800 cm^3) and EtOAc (200 cm^3). The two phases were separated and the aqueous phase was extracted with EtOAc. The combined organic phases were washed successively with saturated aqueous Na_2CO_3 solution and water, dried and evaporated to dryness. The oily residue was triturated with methanol to afford crystalline *(2a*RS,*8*RS,*8a*RS*)-6-chloro-8-(4-methylphenyl)*-**I** (**7a**)[7] [10 g, 82%; δ_C ($CDCl_3$)[8] 21.04 (Ar-*Me*), 43.47 (C-8), 55.54 (OMe), 60.43 (C-8a), 79.68 (C-2a), 114.80 + 118.75 + 129.38* + 150.75† (C_{ar}s, PMP), 127.41 + 129.99 + 137.20 + 137.50 (C_{ar}s, Z), 120.46 (C-4), 126.99* (C-6), 128.62* (C-7a), 130.40 (C-7), 156.87† (C-3a), 161.62 (C-2)] and *(2a*RS,*8*RS,*8a*RS*)-6-fluoro-8-(4-methylphenyl)*-**I** (**7b**)[7] (3.1 g, 72%), respectively.

(*f*) Conc. H_2SO_4 (0.25 cm^3, 5 mmol) was dropwise added to compound **1a** (3.3 g, 10 mmol) in dry toluene (150 cm^3). The mixture was gently refluxed for 1 h, allowed to cool and washed successively with ice-water, saturated aqueous Na_2CO_3 and brine, dried and evaporated to dryness. The residue was purified by flash-chromatography (hexane-DCM 10:1 → 1:1) to afford compound **7a** (1.95 g, 48%), identical with the sample obtained as described in (*e*).

(*g*) A mixture of compound **1a** (5.3 g, 16 mmol), $AlCl_3$ (4.4 g, 33 mmol) and dry fluorobenzene (100 cm^3) was stirred for 20 h at room temperature. The excess fluorobenzene was distilled off at *ca* 2.5 kPa and the oily residue was taken up in EtOAc. The solution was washed with water, saturated aqueous Na_2CO_3 solution and brine, dried and evaporated to dryness. The oily residue was worked up by flash-chromatography (DCM) to afford *(2a*RS,*8*RS,*8a*RS*)-6-chloro-8-(4-fluorophenyl)*-**I** (**8a**)[7] (2.7 g, 41%) and a 4:1 mixture (^{1}H NMR) of the stereoisomeric ring transformation products *(3*RS,*4*RS,*5*RS*)*-* (**11**) and *(3*RS,*4*RS,*5*SR*)-3-(4-chlorophenoxy)-4,5-dihydroxy-1-(4-methoxyphenyl)pyrrolidin-2-one* (**14**) [Σ1.1 g, 20%; m.p. 170-175°C found: C, 58.15; H, 4.55; Cl, 10.05; N, 3.95; $C_{17}H_{16}ClNO_5$ (349.75) requires: C, 58.4; H, 4.6; Cl, 10.15; N, 4.00; ν_{max} (KBr) 3420, 1680 cm^{-1}; δ_H ($CDCl_3$ + DMSO-d_6), compound **11**, 3.81s (OMe), 4.41ddd (7.4, 7.4 and 5.5; 4-H), 4.91d (7.4; 4-OH), 5.06d (7.4; 3-H), 5.36dd (5.5 and 5.6; 5-H), 5.86d (5.6; 5-OH), 6.91 + 7.58 (2 x 2H, PMP), 7.14 + 7.23 (2 x 2H, chlorophenoxy), difNOE 3-H → 5-OH; compound **14**, 3.80s (OMe), 4.28ddd (5.3, 5.0 and 3.4; 4-H), 4.79d (5.3; 3-H), 5.35dd (7.5 and 3.4; 5-H), 5.59d (5.0; 4-OH), 5.94d (7.5; 5-OH), 6.92 + 7.44 (2 x 2H, PMP), 7.13 + 7.23 (2 x 2H, chlorophenoxy); difNOE 3-H → 5-H; δ_C[8] ($CDCl_3$ + DMSO-d_6), compound **11**, 55.14 (OMe), 71.80 (C-4), 79.99 (C-3), 81.78 (C-5), 113.70 + 123.84 + 130.39* + 157.21† (C_{ar}s, PMP), 117.46 + 128.79

[8] Assignment of the signals marked * and † is uncertain, other interpretations are possible.

+ 125.94* + 157.23† (C_{ar}s, chlorophenoxy), 168.55 (C-2); compound **14**, 55.14 (OMe), 77.33 (C-4), 81.24 (C-3), 86.55 (C-5), 113.70 + 125.65 + 130.39* + 156.94† (C_{ar}s, PMP), 117.35 + 128.85 + 125.94* + 157.55† (C_{ar}s, chlorophenoxy), 167.47 (C-2)][8].

(*h*) Carbaldehyde **1a** (5.3 g, 16 mmol) was added in one portion to a suspension of $AlCl_3$ (4.4 g, 33 mmol) in fluoro-benzene (70 cm^3) with continuous stirring at room temperature under argon. Stirring was continued under the same conditions. T.l.c. analysis (toluene - EtOAc, 8:2) of a sample taken after 20 min showed the presence of two products: the less polar compound **8a** and, as a result of hydrolysis during t.l.c., the more polar mixture of compounds **11** and **14**; the starting compound had already been consumed. The chromatograms of samples taken after 1, 3 and 20 h were identical with the first. The excess fluoro-benzene was distilled off at reduced pressure, the residue was stirred for 1 h with dry methanol (150 cm^3) and the mixture was evaporated to dryness. The residue was taken up in a mixture of DCM and water, the two phases were separated and the aqueous phase was re-extracted with DCM. The combined organic phases were dried and evaporated to dryness. The oily residue (6.1 g) was worked up by c.c. (toluene → toluene – EtOAc, 10:0.5) to afford the following products, which were eluted in this order: **8a** [3.65 g, 56%; identical (IR, t.l.c.) with the sample obtained as described in (*g*)], **13** [0.45 g, 6.6%; solid foam; found: $M^{+\cdot}$, 427.09793; $C_{23}H_{19}ClFNO_4$ requires $M^{+\cdot}$, 427.09866; ν_{max} (KBr) 3400, 1710/1695 cm^{-1}; δ_H ($CDCl_3$) 2.07d (6.2; 4-OH), 4.74ddd (7.3, 7.2, 6.2; 4-H), 4.85d (7.2; 3-H), 5.24d (7.3; 5-H), 7.08 + 7.22 (AA'BB', 9.0; 4-chlorophenoxy), 7.09dd + 7.24dd (2 x 2H, 4-fluorophenyl); NOE: see Table 2; δ_C ($CDCl_3$) 55.38 (MeO, PMP), 64.20 (C-5), 72.41 (C-4), 80.97 (C-3), 114.14 (C-3 + C-5, PMP), 116.18 ($^2J_{C,F}$ 21.7; C-3 + C-5, fluorophenyl), 117.96 (C-2 + C-6, chlorophenoxy), 123.12 (C-2 + C-6, PMP), 127.25* (C-1, PMP), 129.28 ($^3J_{C,F}$ 8.4; C-2 + C-6, fluorophenyl), 129.35 (C-3 + C-5, chlorophenoxy), 129.75 ($^4J_{C,F}$ 3.4; C-1, fluorophenyl), 130.42* (C-4, chlorophenoxy), 156.96† (C-4, PMP), 157.30† (C-1, chlorophenoxy), 162.81 ($^1J_{C,F}$ 248.3; C-4, fluorophenyl), 168.50 (C-2)[8]], **12** [purity 77% (^{1}H NMR);[9] 0.55 g, 7%; solid foam; main component, found: $M^{+\cdot}$, 363.08728; $C_{18}H_{18}ClNO_5$ requires: $M^{+\cdot}$, 363.08735; ν_{max} (KBr) 3400, 1720/1710 cm^{-1}; δ_H ($CDCl_3$) 3.03 br (4-OH), 3.43s (5-OMe), 4.49 br dd (7.5, 5.6; 4-H), 7.10 + 7.22 (AA'BB', 9.0; chlorophenoxy); NOE: see Table 2], **15** [0.5 g, 8.6%; m.p. 138°C; found: $M^{+\cdot}$, 363.08724; $C_{18}H_{18}ClNO_5$ requires: $M^{+\cdot}$, 363.08735; ν_{max} (KBr) 3400, 1695 cm^{-1}; δ_H ($CDCl_3$) 3.25s (5-OMe), 3.68d (6.6; 4-OH), 4.20ddd (6.6, 3.7, 2.3; 4-H), 4.55d (3.7; 3-H), 5.05d (2.3; 5-H), 6.96 + 7.20 (AA'BB', 8.9; chlorophenoxy); NOE: see Table 2] and a mixture of epimers **11** and **14** [Σ0.2 g, 3.5%; identical (IR, t.l.c.) with the product obtained as described in (*g*)].

[9] The main part (15%) of the impurities (total 23%) was shown (^{1}H NMR) to be very likely identical with the 5-epimer **15**; the rest was made up of several unindentified compounds

(*i*) Carbaldehyde **1a** (5.65 g, 17 mmol) was added in one portion to a suspension of $AlCl_3$ (5.3 g, 40 mmol) in dichlorobenzene (80 cm^3) at room temperature. Stirring was continued for 3 h and the solvent was distilled off. The residue was taken up in a mixture of EtOAc and water. The organic phase was washed with water, dried and evaporated to dryness. The residue was worked up by c.c. (toluene - EtOAc, 10:0.5 → 10:3) to afford compound **9a**[7] (2.65 g, 36%) and two fractions [Σ1.85 g, 31%] of mixtures of epimers **11** and **14** [*first fraction:* 0.1 g, m.p. 181-183°C (^{1}H NMR) 92:8 ($CDCl_3$ + DMSO-d_6) which changed to 54:46 in DMSO-d_6, indicating epimerization at C-5 in the latter solvent; δ_H (DMSO-d_6), compound **11**, 3.762s MeO, PMP), 4.30ddd (8.2, 5.3, 7.0; 4-H), 5.14d (8.2; 3-H), 5.30dd (5.3, 7.5; 5-H), 5.76d (7.0; 4-OH), 6.39d (7.5; 5-OH), 6.97 + 7.52 (AA'BB', 9.0; PMP), 7.13 + 7.35 (AA'BB', 9.0; 4-ClC_6H_4O), NOE: see Table 2; compound **14**, 3.757s (OMe, PMP), 4.04ddd (6.3, 4.0, 5.6; 4-H), 4.95d (6.3; 3-H), 5.21dd (4.0, 8.0; 5-H), 6.20d (5.6; 4-OH), 6.64d (8.0; 5-OH), 6.97 + 7.355 (AA'BB', 9.0; PMP), 7.14 + 7.35 (AA'BB', 9.0; 4-ClC_6H_4O), NOE: see Table 2; *second fraction:* 1.75 g; m.p. 170-175°C; identical (IR, t.l.c., m.p.) with the sample obtained as described in (*g*)].

Monitoring the reaction of compound **1a** *with* $AlBr_3$

Carbaldehyde **1a** (2 mmol) was added in one portion to $AlBr_3$ (6 mmol) in nitromethane (15 cm^3) at -15 – -20°C. Stirring was continued for 25 min at this temperature and then for *ca* 1.5 h with the cooling bath removed. From time to time samples were taken from the mixture and examined by t.l.c. (toluene – EtOAc, 8:2; detection: UV light or 5% ethanolic molybdophosphoric acid). In the chromatogram of the sample taken after 1 min fair amounts of compounds **4a** and **10a** (formed by hydrolysis of their $AlBr_3$ complexes in the course of t.l.c.), together with unchanged starting compound **1a** and minute amounts of product **6a** were detected. After 5 min the starting compound was consumed; after 50 min compound **4a** could not be detected any more in the chromatogram, but compound **10a** was detected even after 60 min. After 2 h product **6a** was the only compound detected in the chromatogram.

Reaction of compounds **4a, 5a** *and* **10a** *with fluorobenzene in the presence of* $AlCl_3$

(*a*) Compound **4a** (166 mg, 0.5 mmol) or compound **10a** (166 mg, 0.5 mmol) were added in one portion to suspensions of $AlCl_3$ (200 mg, 1.5 mmol) in fluorobenzene (3 cm^3) with continuous stirring at room temperature. Within *ca* 15 sec clear yellow solutions (containing minute amounts of insoluble impurities) were formed. Stirring was continued for 90 min and the mixtures were evaporated to dryness. The residues were taken up in water and extracted

with EtOAc at *ca.* 35 °C. The combined organic phases were washed with water, dried and evaporated to dryness. The oily residues gradually crystallized to afford compound **8a** [187 mg, 92%; m.p. 184-185°C, and 170 mg, 84%; m.p. 185°C, respectively; identical with the sample obtained as described above in (*g*)].

(*b*) By similar treatment of compound **5a** for 3 h with $AlCl_3$ (3 mol equivalent) in fluorobenzene at room temperature compound **8a** was obtained in 99% yield.

Acknowledgments. The authors thank Dr. Medzihradszky-Schweiger and her staff for the microana;yses and Miss K. Ófalvi for the IR spectra. F. B., J. F. and K. L. are grateful also 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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