181. Synthesis of *trans*-10,11-Dihydro-10,11-dihydroxy-5*H*-dibenz[*b*,*f*]azepine-5-carboxamide, a Major Metabolite of Carbamazepine

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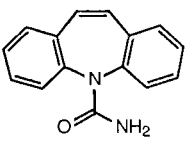
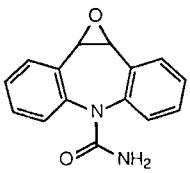
The stereoselectivity of the reduction of 5-carbamoyl-10,11-dihydro-11-oxo-5*H*-dibenz[*b*,*f*]azepine-10-yl acetate (**6**), prepared in two steps from 10,11-dihydro-10-oxo-5*H*-dibenz[*b*,*f*]azepine-5-carboxamide (**4**), has been studied. Among the reagents used, diisobutylaluminum hydride (DIBAH) was found to give the highest *trans*/*cis* diol ratio. This allowed the preparation of the important *trans*-diol metabolite **3** of carbamazepine (**1**).

1. Introduction. – Carbamazepine (5*H*-dibenz[*b*,*f*]azepine-5-carboxamide (**1**)) – a widely used drug for the treatment of epilepsy and trigeminal neuralgia – is metabolized mainly *via* oxidation to the 10,11-epoxide **2** [1] *(Scheme 1)*. Enzymatic cleavage of the epoxide ring leads to the major urinary metabolite *trans*-10,11-dihydro-10,11-dihydroxy-5*H*-dibenz[*b*,*f*]azepine-5-carboxamide (**3**). This compound, which is also a metabolite of the new antiepileptic development drug oxcarbazepine (**4**) [2], is used worldwide in clinics and research institutes as a reference substance. Thus it became desirable to devise a reasonable synthesis. In this paper, we describe our efforts in order to reach that goal.



1

Carbamazepine



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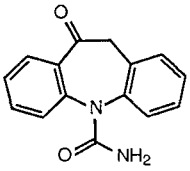

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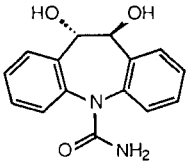
Oxcarbazepine

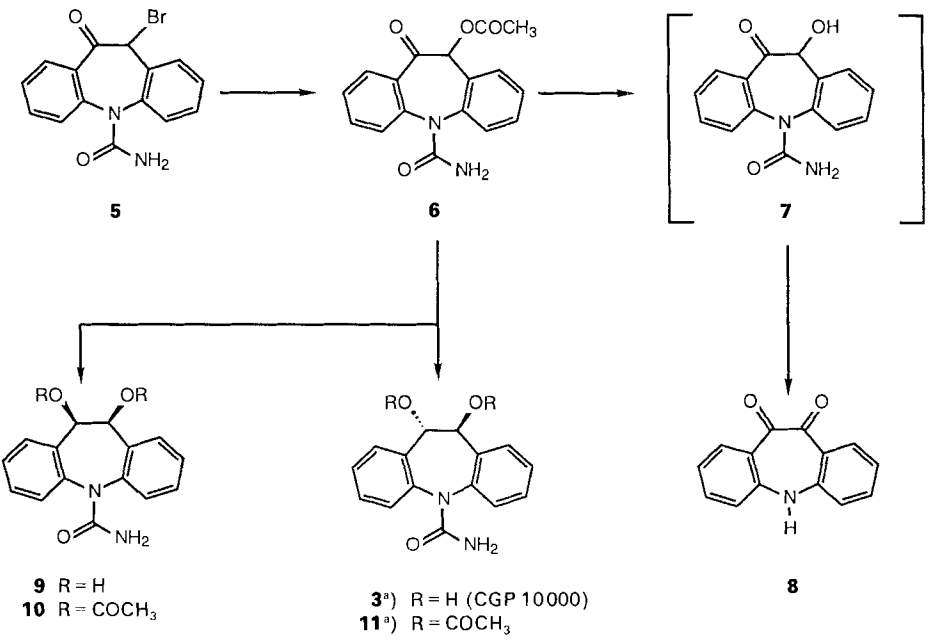


3[a])

[a]) Diol **3** isolated from human urine is optically active. The (10*S*,11*S*)-configuration drawn has recently been established by CD measurements of the bis(4-(dimethylamino)benzoate) of **3** [5].

2. Synthetic Approaches and Results. – An attractive route to the *trans*-diol **3** would obviously consist in the acid-catalyzed hydrolytic cleavage of the epoxide function of **2**. Some years ago *Lertratanangkoon* and *Horning* [1c] claimed to have synthesized **3** in this way. However, no data concerning the yield or the purity of the product were given. In our hands, epoxide **2** [3] – under the conditions reported (THF/H_2O/trace of AcOH, r.t.) – was slowly transformed into a number of products of which only a very minor component (about 5% according to TLC) corresponded to the *trans*-diol **3** isolated from biological material. We were unable to increase the diol yield by varying the solvent systems (*e.g.* H_2O/dioxane, H_2O/acetone) and by using different types of acid catalysts. More recently, *Hirobe* and coworkers [4] determined the acid hydrolysis rate of the epoxide **2**. Yet, no mention was made about the products of this reaction, although *N*-acyldibenz[*b,f*]azepine 10,11-oxides generally furnished the expected 10,11-*trans*-diols. Very recently *Marioni et al.* [5] showed that **2** is mainly transformed into 9-formyl-10-carbamoylacridan and 9-formylacridine upon acid-catalyzed hydrolysis. In order to prevent contraction of the 7-membered ring, they consequently replaced the carbamoyl group by the chlorocarbonyl substituent which is a better electron acceptor. This led to the first preparatively useful synthesis of *trans*-diol **3**. As the corresponding *cis*-diol **9** *(Scheme 1)* – which is not a metabolite of carbamazepine in man [1b] [2a] – is well known and easily prepared [6] by osmium-tetroxide oxidation of **1**, we also considered a catalytic *cis* to *trans* diol isomerization. Such processes are documented for certain bicyclic vicinal diols [7] and are thought to occur *via* dehydrogenation/reduction processes, leading in each case to the thermodynamically more stable *trans*-diols. However, diol **9** proved to be totally unreactive under such conditions.

Scheme 1



a) Compounds **3** and **11** are racemic. For convenience, just one enantiomer is drawn.

Another synthetic plan for the synthesis of *trans*-diol **3** called for the reduction of the α-hydroxyketone **7** *(Scheme 1)*. Our expectations were based on the work done by *Brown* and *Vogel* [8] who showed that the reduction of 2-hydroxycyclohexanone with $NaBH_4$ in THF gave predominantly *trans*-cyclohexane-1,2-diol (only 24% of *cis*-diol). Furthermore, it is well known [9] that phenanthrene-9,10-quinone, which is reduced by $LiAlH_4$ *via* an intermediate acyloin complex [10], also yields mainly (> 80%) *trans*-9,10-dihydro-

phenanthrene-9,10-diol. Thus, oxcarbazepine (**4**) [11] was monobrominated to give the α-bromo ketone **5**. Nucleophilic displacement of the Br substituent with AcOK in AcOH afforded the α-acetoxy ketone **6** in good yield. As a minor side product, the known 5*H*-dibenz[*b*,*f*]azepine-10,11-dione **8** [12] could easily be removed during workup owing to its extreme insolubility. Attempts to convert **6** into the desired α-hydroxyketone **7** by hydrolysis met with failure. Even very mild conditions, *e.g.* heating of **6** in H_2O containing $BaCO_3$, led invariably to reaction mixtures from which **7** could not be isolated. Instead, substantial amounts of the intensely colored insoluble diketone **8** were obtained. The same product **8** was formed almost instantaneously, when a methanolic solution of **6** was treated at room temperature with a catalytic amount of $NaOCH_3$. This may be rationalized by the assumption that the intermediate acyloin **7** is unstable under the reaction conditions. Facile oxidation by air to the corresponding α-diketone followed by cleavage of the now very labile carbamoyl moiety leads to **8**.

In view of these findings, we focussed our attention on the direct reduction of **6** although contemplation of molecular models of **6** prompted us to surmise that the formation of the *cis*-diol **9** might be favored. The reaction of **6** with an excess of $NaBH_4$ in CH_3OH/THF afforded polar products which were investigated by TLC. Using Al_2O_3-coated plates, we could see 2 separate albeit longish spots. The faster-moving one corresponded to synthetically prepared *cis*-diol **9**, and the slower, more polar component showed the same R_f value as a sample of *trans*-diol **3** obtained from biological material. The *cis* to *trans* ratio was estimated to be roughly 3:2. It is important to note that the diols **3** and **9**, even in different solvent systems, have identical R_f values on silica-gel-coated plates. Subsequent scaling up of this reaction allowed the separation and isolation of pure

Table 1. *Selected Physicochemical Data*[a]) *and for the Diols* **3** *and* **9** *and the Diacetates* **10** *and* **11**

	cis		*trans*	
	Diol **9**	Diacetate **10**	Diol **3**	Diacetate **11**
Melting point (recrystallization solvent)	244–246° dec. (CH_3OH)	143–145° (Et_2O/hexane)	228–231° dec. ($(CH_3)_2CHOH$) 201–203° (CH_2Cl_2/CH_3OH 9:1)	191–192° ($(CH_3)_2CHOH$)
Solubility in H_2O at 20°	1.7 g/l	< 0.1 g/l	3.8 g/l	< 0.1 g/l
^{1}H-NMR ((D_6) DMSO)[b])	5.01 (*d*, *J* = 4.3[c]), H–C(10), H–C(11))	2.05 (*s*, 2 CH_3CO)	4.0–5.2 (very br. H–C(10), H–C(11))	2.10 (*s*, 2 CH_3CO)
	5.37 (*d*, *J* = 4.3[d]), 2 OH)	5.92 (br. *s*[d]), NH_2)	5.74 (*d*, *J* = 4.2[d]), 2 OH)	6.00 (br. *s*[d]), NH_2)
	5.73 (br. *s*[d]), NH_2)	6.32 (*s*[e]), H–C(10), H–C(11))	5.81 (br. *s*[d]), NH_2)	6.24 (*s*[e]), H–C(10), H–C(11))
	7.20–7.60 (*m*, 8 arom. H)	7.20–7.55 (*m*, 8 arom. H)	7.15–7.60 (*m*, 8 arom. H)	7.20–7.55 (*m*, 8 arom. H)

[a]) See *Exper. Part* for complete data.
[b]) δ in ppm, *J* in Hz.
[c]) Becomes *s* after exchange with D_2O.
[d]) Exchangeable with D_2O.
[e]) Slightly broadened.

3 and **9** as we took advantage of the different H_2O solubility of these diols which were further characterized by their diacetates **10** and **11** (see *Table 1*).

Since the yield of pure *trans*-diol **3** never exceeded 20% of the theoretical amount, the reduction of **6** with various other reagents was examined in more detail. The result of this study is summarized in *Table 2*. The reducing agents utilized were of the aluminum-hydride and the borohydride type. Also included was a hydrosilane, recently introduced by *Miyama* and *Fujita* [13] for the diastereocontrolled reduction of acyclic α-functionalized ketones, and a *Meerwein-Ponndorf-Verley*-type reduction. Whereas reductions with $LiAlH_4$, $NaBH_4$, $Zn(BH_4)_2$ [14], as well as Bu_4NBH_4 [15] proceeded relatively cleanly to give the product diols **3** and **9** in moderate to good yields *(Entries 1–6)*, very slow reduction of **6** took place when AlH_3 [16] or the combination $NaBH_4/COCl_2$, known to be source of 'BH_3' [17], was used *(Entries 7* and *12)*. Besides starting material, the diols were present in minor amounts even after reaction at room temperature. Lithium tri (*sec*-butyl)borohydride *(Entry 10)* did react; however, after oxidative workup [18], the complex reaction mixture contained only small amounts of diols. Equally unsuccessful was an aluminum-alkoxide-catalyzed reduction *(Entry 13)* which led to extensive decomposition of **6**. Two experiments with phenyldimethylsilane [13] *(Entries 14* and *15)* failed as the starting material **6** reacted too sluggishly. No reaction was observed when triisobutylaluminum *(Entry 11)* was employed. Gratifyingly, the use of an excess of diisobutylaluminum hydride (DIBAH) *(Entry 9)* in THF/toluene proved to be an exception. Not only did we obtain the highest yield of diols, but also the best *trans* to *cis* diol ratio. Scaling up of this procedure then allowed the preparation of the desired *trans*-diol **3** (CGP 10000) in 55% yield from **6** (see *Exper. Part*).

Table 2. *Reduction of Acetoxy Ketone* **6**. *Reaction Conditions, Yields, and Diastereoisomeric Ratios of Diols* **3** *and* **9**

Entry	Reagent (mol-equiv.)	Conditions	Yield[a]) of diols **3** + **9**	Ratio[b]) *cis*/*trans* (**9**/**3**)
1	$LiAlH_4$ (1.5)	THF/Et_2O 1:1, 5–10°, 30 min	70%	47:53
2	$NaBH_4$ (0.6)	THF, 10°, 2 h[c])	65%	60:40
3	$NaBH_4$ (8.0)	CH_3OH, 40°, 45 min	55%	58:42
4	$NaBH_4$ (8.0)	CH_3OH/THF 1:1, 30–40°, 1 h	77%	61:39
5	Bu_4NBH_4 (1.0)	CH_2Cl_2, 20°, 1 h[c])	60%	57:43
6	$Zn(BH_4)_2$ (5.0)	THF/Et_2O 1:1.5, 20°, 2 h[c])	63%	50:50
7	$NaBH_4$(8.0), $CoCl_2$(4.0)	THF, 20°, 1 h[c])	< 15%[e])	1:1[d])
8	DIBAH (6.0)	toluene, 0°, 4 h	78%	33:67
9	DIBAH (6.0)	THF/toluene 3:1, 2°, 90 min	87%	18:82
10	Li(*s*-Bu)$_3$BH (4.0)	THF, 0–5°, 2 h[f])	< 15%[e])	> 9: < 1[d])
11	(i-Bu)$_3$Al (4.0)	THF, 20°, 2 h	0% (no reaction)	
12	AlH_3 (2.0)	THF, 20°, 2 h	< 10%[e])	not determined
13	Al[OCH(CH$_3$)$_2$]$_3$ (3.0)	$(CH_3)_2CHOH$, reflux, 3 h[c])	< 5%[e])	not determined
14	$C_6H_5Si(CH_3)_2H$ (1.2)	THF/DMF 1:9, Bu_4NF, 20°, 6 h[c])	< 5%[e])	not determined
15	$C_6H_5Si(CH_3)_2H$ (1.2)	CF_3COOH, 20°, 16 h[c])	< 5%[e])	not determined

[a]) Yield of mixture of diols purified by chromatography on silica gel (single spot on silica-gel-coated TLC plates).

[b]) Determined by ^{1}H-NMR analysis of the acetylated diol mixtures (see *Exper. Part*).

[c]) In these experiments, only the keto function of **6** was reduced. The diols were obtained after hydrolysis of the crude products with K_2CO_3 in CH_3OH.

[d]) Estimated by TLC analysis (Al_2O_3-coated plates) of the crude diol mixture.

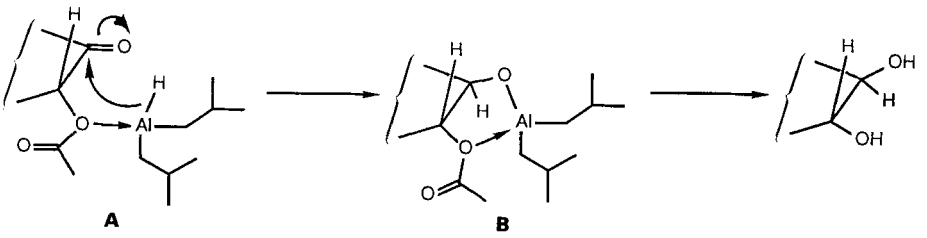
[e]) Estimated by TLC analysis (silica-gel-coated plates) of the crude reaction product.

[f]) Worked up after treatment with 2N NaOH/30% H_2O_2.

3. Discussion. – While quite some work – in connection with the establishment of *Cram*'s rule – has focussed on the stereoselective reduction of acyclic α-hydroxy ketones [19], reduction experiments with acyclic α-acetoxy ketones are scarce [13], and besides two isolated reports [20], no systematic work dealing with the reduction of cyclic α-acetoxy ketones has been published. In our case, the interpretation of the experimental results is complicated by the presence of a somewhat labile *N*-carbamoyl function capable of complexing with reducing agents. Regarding the stereochemical findings, one has to take into account the conformational flexibility of the 10,11-dihydrodibenz[*b*,*f*]azepine ring system [21] which, in part, might be responsible for the low stereoselectivity generally observed.

The about equal *cis* to *trans* diol ratios of 6:4 obtained with borohydride reagents in different solvents *(Entries 2–5)* show the lack of importance of polar effects on the stereochemical outcome. On the other hand, the roughly 1:1 ratio observed with $LiAlH_4$ *(Entry 1)* and $Zn(BH_4)_2$ *(Entry 6)* – a reagent known to greatly affect diastereoisomeric ratios due to its capacity for chelation [22] – argues against a major influence of metal ions in the reduction of **6** with anionic tetravalent hydride complexes. Thus, the pronounced change in stereoselectivity observed when a THF solution of **6** was reduced with the DIBAH/toluene reagent *(Entry 9)* must be explained in another way. Presumably, complexation of DIBAH with the acetoxy substituent leads to an intermediate of type **A** (see *Scheme 2*). Intramolecular delivery of the hydride ion *via* a 5-membered transition state affords a complex of type **B**, which is further reduced and hydrolyzed to give the *trans*-configurated diol. The superior stereoselectivity displayed by DIBAH in THF/toluene *(Entry 9)* as compared to the reaction in toluene *(Entry 8)* is remarkable. It might be ascribed to increased steric hindrance for intermolecular hydride attack in the THF-solvated substrate **6**.

Scheme 2



Our results underline the importance of DIBAH as exceptional reducing agent – a feature that has already been pointed out by *Winterfeldt* [23].

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Experimental Part

General. Unless noted otherwise, reagents and solvents were obtained from commercial sources and used without further purification. TLC: *Merck* precoated plates, silica gel $60F_{254}$ and aluminium oxide $60F_{254}$ (type *E*); visualization with UV light and/or I_2. Column chromatography (CC): at atmospheric pressure on *Merck* silica gel *60* (70–230 mesh). M.p.: in open capillary tubes; *Tottoli* apparatus *(Büchi)*; uncorrected. UV spectra: *Perkin-Elmer-Lambda-9* spectrometer; $\lambda_{max}(\varepsilon)$ in nm. IR spectra: *Perkin-Elmer-298* spectrometer; in cm^{-1}. ^{1}H-NMR spectra: *Varian-HA-100* (100 MHz) spectrometer; δ (ppm) relative to internal TMS, coupling constants (*J*) in Hz.

*10-Bromo-10,11-dihydro-11-oxo-5*H*-dibenz[*b,f*]azepine-5-carboxamide* (**5**). To a well stirred soln. of 20.0 g (79.2 mmol) of oxcarbazepine (**4**) [11] in 390 ml of AcOH (dissolved at 50° then slowly cooled to 15°) was added dropwise a mixture of 4.22 ml (13.14 g, 82.0 mmol) of Br_2 in 40 ml of AcOH at 15° within 45 min. The mixture was stirred for another 15 min at 15° and then poured into a cold (2°) soln. of 10.8 g (79.4 mmol) of $AcONa \cdot 3H_2O$ in 600 ml of H_2O. Stirring was continued in an ice/H_2O bath for 3 h and the crystals were collected and washed copiously with H_2O. The dried ($CaCl_2$) crude product (23.97 g) was stirred in 100 ml of CH_2Cl_2 for 6 h at r.t. The pale yellow solid was filtered, washed with 20 ml of CH_2Cl_2 and 100 ml of hexane and then dried at 30°/0.05 Torr for 18 h to give 19.26 g (73.4%) of **5**. M.p. 185° (slow dec.). TLC (silica gel) R_f 0.43 (CH_2Cl_2/MeOH 95:5). UV (EtOH): 266 (7600). IR (KBr): 3410*s* and 3250*m* (NH_2), 3110*m*, 1670–1650*s* (C=O, ketone and amide), 1585*s*, 1460*s*, 1430*m*, 1355*s*, 1280*m*, 1250*m*, 1210*m*, 755*s*, 660*m*, (C–Br). ^{1}H-NMR ((D_6)DMSO): 6.10 (*s*, H–C(10)); 5.60–6.50 (very br., $CONH_2$); 7.25–7.80 (*m*, 7 arom. H); 7.98 (*d*, *J* = 7, H–C(1)). Anal. calc. for $C_{15}H_{11}BrN_2O_2$ (331.17): C 54.40, H 3.35, Br 24.13, N 8.46; found: C 54.38, H 3.44, Br 24.14, N 8.40.

*5-Carbamoyl-10,11-dihydro-11-oxo-5*H*-dibenz[*b,f*]azepine-10-yl Acetate* (**6**) *and 5*H*-Dibenz[*b,f*]azepine-10(11*H*),11-dione* (**8**). A mixture of 119.1 g (0.36 mol) of **5** and 99.0 g (1.01 mol) of AcOK (freshly molten and then powdered) in 500 ml of AcOH was stirred at reflux for 45 min. The soln. was cooled to 70° and poured into 1.5 l of ice/H_2O. To the resulting well stirred orange suspension was added cautiously $KHCO_3$ in small portions until the pH of the mixture reached 5. Stirring was continued in an ice/H_2O bath for 1 h. The precipitate was filtered and washed copiously with H_2O. The solid was suspended in a mixture of 1000 ml of MeOH and 700 ml of CH_2Cl_2 and warmed at reflux for 5 min. The orange-red insoluble material was filtered off from the still warm soln. and washed with 100 ml of CH_2Cl_2. The filtrate was concentrated *in vacuo* until the volume was 800 ml and then kept at 2° for 17 h. The product was collected and washed with Et_2O/hexane 1:1. A final recrystallization from CH_2Cl_2/i-PrOH gave 71.6 g (64.1%) of pure **6** as colourless crystals. M.p. 215° (sintering), 222–227° (slow dec.). TLC (silica gel) R_f 0.61 (CH_2Cl_2/MeOH 9:1). UV (EtOH): 220 (sh), 256 (7600), 312 (2900). IR (CH_2Cl_2): 3510*m*, and 3400*m* (NH_2), 1750*s* (C=O, ester), 1700–1680*s* (C=O, ketone and amide), 1600*m*, 1580*s*, 1475*m*, 1370*s*, 1230*s* (O–C, ester), 1120*m*, 1075*m*, 980*w*. ^{1}H-NMR ((D_6)DMSO): 2.30 (*s*, $COCH_3$); 6.20–6.50 (br. *s*, NH_2); 6.68 (*s*, H–C(11)); 7.28–7.80 (*m*, H arom.); 7.97 (*d*, *J* = 7, H–C(9)). Anal. calc. for $C_{17}H_{14}N_2O_4$ (310.31): C 65.80, H 4.55, N 9.03; found: C 65.67, H 4.74, N 8.87.

The orange-red insoluble substance that had been removed during the recrystallization of **6** was further purified by refluxing it in CH_2Cl_2/MeOH 9:1 for 10 min. The insoluble crystals were collected, washed with CH_2Cl_2, and dried at 120° to give 1.95 g (2.4%) of **8**. M.p. > 330° (slow dec.). TLC (silica gel) R_f 0.79 (CH_2Cl_2/MeOH 9:1, tailing spot due to the low solubility). IR (KBr): 3290*m*, 3150*m*, 3080*m*, 1630*m*, 1615*m*, 1580*s*, 1560*s*, 1505*s*, 1460*s*, 1290*s*, 1200*m*, 915*m*, 822*m*, 742*s*. ^{1}H-NMR ((D_6)DMSO): 7.10–7.90 (*m*, 8 arom. H); 10.85 (br. *s*, NH). Literature data [12] for **8**: M.p. > 360° (dec.). IR (KBr): 3322, 1648, 1632, 1600, 1580. ^{1}H-NMR ((D_6)DMSO): 7.10–7.70 (*m*, 8 H); 10.92 (br., 1 H).

Reduction of **6** *with* $NABH_4$: cis-*10,11-Dihydro-10,11-dihydroxy-5*H*-dibenz[*b,f*]azepine-5-carboxamide* (**9**) *and* trans-*10,11-Dihydro-10,11-dihydroxy-5*H*-dibenz[*b,f*]azepine-5-carboxamide* (**3**). To a well stirred soln. of 30.0 g (96.7 mmol) of **6** in 1400 ml of THF/MeOH 1:1 was added under N_2 in portions of *ca.* 1 g a total of 30.0 g (793.0 mmol) of $NaBH_4$. Throughout the addition, the exothermic reaction was controlled by keeping the temp. between 35 and 38°. Stirring was continued for 90 min at r.t. and after cooling, a mixture of 50 ml of AcOH and 550 ml of H_2O was slowly added at 10°. The resulting soln. was concentrated *in vacuo* until pure H_2O distilled off (final volume *ca.* 500 ml). After 2 h at r.t., the precipitate was filtered and washed with 100 ml of H_2O. The dried ($CaCl_2$) crude product *A* was recrystallized from MeOH to give 13.98 g (53.5%) of **9**. M.p. 244–246° (dec.). TLC (silica gel) R_f 0.42 (CH_2Cl_2/MeOH 9:1). TLC (Al_2O_3) R_f 0.47 (CH_2Cl_2/MeOH 6:4). IR (KBr): 3500–3200*s* (OH, NH_2), 1665*s* (C=O), 1570*s*, 1490*s*, 1410–1390*s*, 1280*m*, 1255*m*, 1235*m*, 1200*m*, 1120*m*, 1070*s*, 1040*s*, 965*m*, 954*m*, 940*w*, 890*w*, 853*w*, 818*w*, 775*s*, 760*s*, 724*s*. ^{1}H-NMR: see *Table 1*. Literature data [6] for **9**: M.p. 242–245° (dec.). IR (nujol): 3500–3300, 1660, 770, 755. ^{1}H-NMR ((D_6)DMSO): 4.98, 5.07 (2 H); 5.34, 5.43 (2 OH); 5.70 (br., NH_2); 7.32 (*m*, 8 arom. H).

To the aq. mother liquor of the crude product *A*, 70 ml of AcOEt were added, and the vigorously stirred mixture was saturated completely with finely ground NaCl. This caused a crystalline product to settle between the two layers. After 17 h at r.t., the mixture was filtered and the crystals were washed with 50 ml of H_2O and then 100 ml of AcOEt. The air-dried crude product was heated at reflux in 140 ml of MeOH, and a small amount of insoluble material was removed by filtration through a plug of cotton wool. To the filtrate were added 180 ml of i-PrOH, and the soln. was evaporated at 0.5 Torr (bath temp. 60°) until the final volume was 100 ml. After cooling to r.t., the crystals were filtered, washed with 30 ml of i-PrOH and 100 ml of hexane, and dried at 110° for 6 h to give 4.97 g (19.0%) of **3**. M.p. 228–231° (dec.)[1]). TLC (silica gel) R_f 0.42 (CH_2Cl_2/MeOH 9:1). TLC (Al_2O_3) R_f 0.27 (CH_2Cl_2/MeOH 6:4). UV (EtOH): only end absorption. IR (KBr): 3150–3550*s* (OH, NH_2), 1665*s* (C=O), 1580*s*, 1490*s*, 1410–1395*s*, 1305*m*, 1235*m*, 1195*m*, 1120*m*, 1070*s*, 1045*m*, 1010*m*, 953*w*, 940*w*, 842*w*, 775*m*, 755*m*. ^{1}H-NMR: see *Table 1*. Anal. calc. for $C_{15}H_{14}N_2O_3$ (270.29): C 66.66, H 5.22, N 10.37; found: C 66.55, H 5.38, N 10.31.

Literature data [5] for **3**: M.p. 198–200° (crystallized from $CHCl_3$). UV (MeOH): 206 (31400, end absorption (?)). IR (nujol): 3500–3150, 1650. ^{1}H-NMR: no data.

cis-*5-Carbamoyl-10,11-dihydro-5*H-*dibenz[b,f]azepine-10,11-diyl Diacetate* (**10**). A mixture of 1.081 g (4.0 mmol) of **9** in 3.78 ml (4.08 g, 40 mmol) of Ac_2O and 6.5 ml of pyridine was stirred at r.t. for 17 h. The soln. was poured into a mixture of 7.0 ml of conc. HCl and 100 g of ice and extracted with 2 × 50 ml of AcOEt. The org. extracts were washed with 1N HCl, sat. $KHCO_3$ soln. and brine, dried (Na_2SO_4), and evaporated. In order to remove traces of Ac_2O, the residue was evaporated twice with toluene. Recrystallization from Et_2O/hexane gave 1.03 g (72.7%) of **10**. M.p. 143–145°. TLC (silica gel) R_f 0.42 (AcOEt). IR (CH_2Cl_2): 3510*m* and 3410*m* (NH_2), 1745*s* (C=O, ester), 1685*s* (C=O, amide), 1580*s*, 1490*m*, 1375*s*, 1230*s*, 1065*m*, 1030–1020*m*, 955*w*, ^{1}H-NMR: see *Table 1*. Anal. calc. for $C_{19}H_{18}N_2O_5$ (354.36): C 64.40, H 5.12, N 7.91; found: C 64.18, H 5.19, N 7.96.

trans-*5-Carbamoyl-10,11-dihydro-5*H-*dibenz[*b,f*]azepine-10,11-diyl Diacetate* (**11**). In the same manner as described above, 0.541 g of **3** were acetylated with 1.89 ml of Ac_2O and 3.25 ml of pyridine. The crude product was recrystallized from i-PrOH to give 0.578 g (81.6%) of **11**. M.p. 191–192°. TLC (silica gel). R_f 0.42 (AcOEt). IR (CH_2Cl_2): 3510*m* and 3410*m* (NH_2), 1760*s* and 1745*s* (C=O, ester), 1685*s* (C=O, amide), 1580*s*, 1490*m*, 1375*s*, 1225*s*, 1040–1020*m*, 970*w*. ^{1}H-NMR: see *Table 1*. Anal. calc. for $C_{19}H_{18}N_2O_5$ (354.36): C 64.40, H 5.12, N 7.91; found: C 64.28, H 5.10, N 7.85.

Small-Scale Reductions of Acetoxy Ketone **6**. *General.* The experiments were carried out with 1 mmol of **6** under N_2. The reducing agents and the reaction conditions are given in *Table 2*. After acid hydrolysis (pH ≈ 3) at 0–5°, workup consisted in evaporating the org. solvents. The aq. phase was saturated with NaCl and extracted thoroughly with AcOEt. The org. extracts were washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on 30 g of silica gel with CH_2Cl_2/MeOH 9:1. The fractions showing a single spot on TLC (R_f 0.42, CH_2Cl_2/MeOH 9:1) were combined, evaporated, and dried to represent the chemical yield of the diols **3** and **9**. These diol mixtures were then acetylated as described for **9** and the acetates **10** and **11** were directly analyzed by ^{1}H-NMR spectroscopy. The integrals for H–C(10) and H–C(11) (6.32 ppm for **10** and 6.24 ppm for **11**) were measured to allow for the calculation of the *cis/trans* ratios as given in *Table 2*.

Reduction of **6** *with DIBAH*: trans-*10,11-Dihydro-10,11-dihydroxy-5*H-*dibenz[*b,f*]azepine-5-carboxamide* (**3**). To a soln. of 24.83 g (80.0 mmol) of **6** in 1200 ml of THF under Ar were added dropwise at 0° 400 ml (480 mmol) of 1.2M DIBAH/toluene within 3 h. After strirring for another 90 min at 0°, 500 ml of H_2O were added slowly and then 250 ml of 5N HCl. The resulting mixture (pH ≈ 4) was evaporated until pure H_2O distilled (final volume *ca.* 400 ml). A small amount of insoluble material was filtered off. To the well stirred filtrate were added 80 ml of AcOEt and finely ground NaCl until the aq. phase was completely saturated. After 90 min, the crystalline product that had separated between the two layers, was collected and washed with 30 ml of cold H_2O. Recrystallization from 640 ml of hot H_2O gave a first crop (10.39 g) of almost pure **3**. In order to recover the remainder of **3**, the aq. mother liquor was evaporated to dryness, and the residue (7.80 g) was acetylated with 27.30 ml (29.50 g, 289 mmol) of Ac_2O and 45 ml of pyridine. Workup as decribed for **10** and recrystallization from i-PrOH gave 4.47 g (12.61 mmol) of **11** (m.p. 187–191°) that was cleaved in 260 ml of MeOH with 3.49 g (25.22 mmol) of anh. K_2CO_3 at r.t. for 1 h. The pH of the mixture was adjusted to 4 with 0.5N HCl, and the soln. was concentrated *in vacuo* until pure H_2O distilled off (final volume *ca.* 60 ml). Then, 10 ml of AcOEt were added, and the aq. phase was completely saturated with NaCl. The crystals were collected and washed with 20 ml of cold H_2O to give a second crop (2.96 g) of almost pure **3**. The combined crops were recrystallized from i-PrOH/CH_3OH to give 11.94 g (55.2%) of anal. pure **3**. M.p. 228–231° (dec.).

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[1]) A different crystal modification was obtained upon crystallization from CH_2Cl_2/MeOH 9:1. M.p. 201–203°.

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