66. Synthesis of Chiral Bicyclic Bis-lactam Components for the Controlled Self-Assembly of Hydrogen-Bonded Arrays

by **Marie-Josèphe Brienne, Jacqueline Gabard, Martine Leclercq**, and **Jean-Marie Lehn***

Chimie des Interactions Moléculaires, Collège de France, 11 place Marcelin Berthelot, F-75005 Paris

and **Michel Chevé**

Département de Chimie Pharmaceutique, Centre de Recherche *Rhône-Poulenc Rorer*, F-94403 Vitry sur Seine

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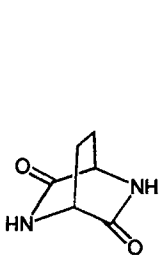
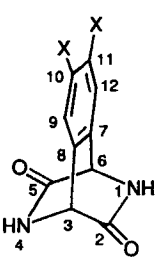
The chiral biyclic bis-lactams of structures **3** and **4** were synthesized from the key intermediate **2'b**, the *N,N'*-bis(4-methoxybenzyl) derivative of **2** (X = MeO) (*Scheme 6*). The synthesis of this intermediate involved two key steps: *1*) a double condensation of glyoxylic acid/anisamide (= oxoacetic acid/4-methoxybenzamide) adduct **11c** with veratrole (1,2-dimethoxybenzene; **10**) allowed the introduction of two glycine units at the 4,5-positions of the veratrole ring to give **18c** (*Schemes 3* and *4*); *2*) in order to circumvent the hydrolysis of 4-methoxybenzoyl protective groups which proved to be unfeasible, these groups were transformed into 4-methoxybenzyl groups through a sequence involving thiocarbonylation followed by reduction (*Scheme 5*). Thereafter, the double intramolecular cyclization of the resulting diamino diester **22c** proceeded easily to afford **2'b**. This intermediate may be transformed *via* the tetrol **2'g** or the diol **2'h** into the *N*-protected derivatives of **2** (X = OR) and of **3** (X = OCOR). Cleavage of the 4-alkoxybenzyl groups was achieved by ceric ammonium nitrate. However, when the aromatic ring bore ether functions (*N*-protected **2**), this normal reaction was accompanied by the oxidative ring cleavage to give the diene-diester structure **4** (*Schemes 5* and *6*).

Introduction. – In order to investigate the effect of molecular chirality on self-assembly, we previously studied the crystal structures of the H-bonded arrays formed by the racemate and by the enantiomerically pure (–)-form of the bicyclic bis-lactam **1** [1]. In the racemate structure, the molecules are, as anticipated, assembled into an infinite undulating chain of alternating (+)- and (–)-units (see *Fig., a*). In the enantiomer structure, the molecules are assembled into cyclic tetrameric arrays different from the superstructure of racemic (±)-**1**. It was different from the hexameric assembly (see *Fig. b*)

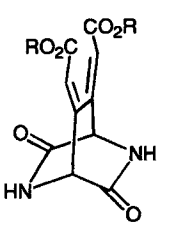


1



2 X = OR

3 X = OCOR



4

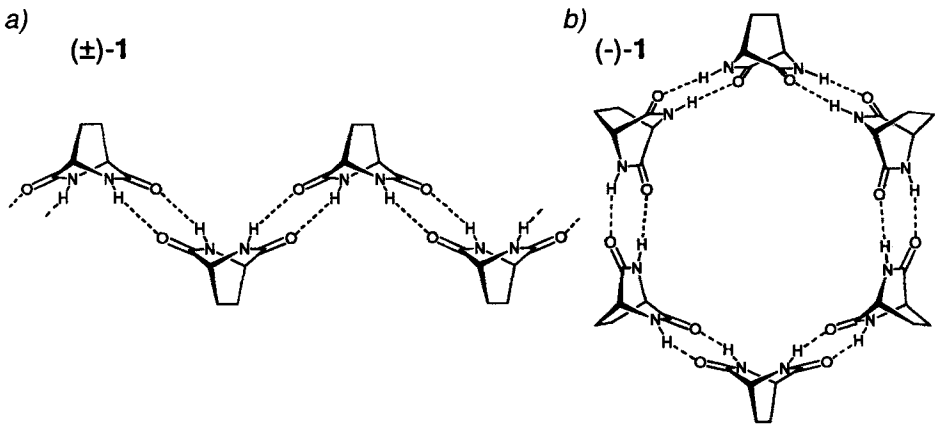


Figure. *Possible H-bonding patterns for* a) (±)-**1** *and* b) (−)-**1**

expected on the basis of internal H-bonding through the formation of cyclic bidentate interaction units as found in (±)-**1**. This structure is clearly not favorable from the point of view of the crystal packing, and we have not yet been able to find a guest molecule having the appropriate size and shape to fill up the cavity and enforce the crystallization in the expected way.

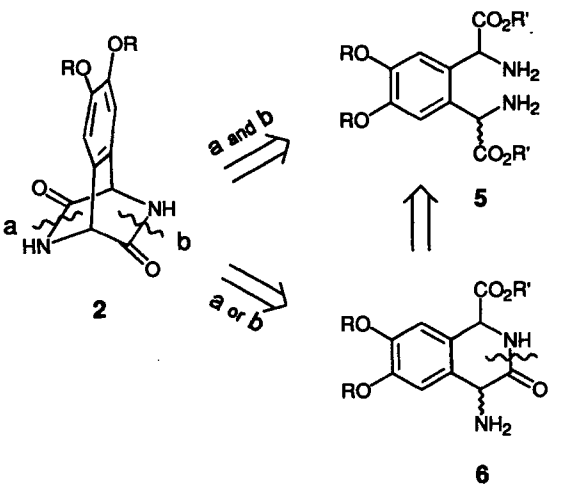
In the present paper, we describe another approach based on structural modifications of **1**. The structures **2** or **3** seemed to us a good choice since they retained the unique H-bonding pattern of 2,5-diazabicyclo[2.2.2]octane-3,6-dione (**1**) while allowing introduction of various substituents. Moreover, these modifications do not cause any stereochemical complications that would be encountered with the introduction of one or two substituents directly on the ethylene bridge. After several attempts to synthesize compounds **2**, we succeeded in setting up a route which gave us access to *N*-protected compounds of type **2** (series **2′**[1])) and eventually to *N*-protected compounds of type **3** (series **3′**). Unfortunately, for series **2′** the removal of the protective group could not be achieved without the cleavage of the aromatic ring to give compounds of structure **4**. In series **3′**, however, the same deprotection easily gave the expected compounds **3**. These sets of synthetic investigations gave also rise to some novel reactions.

Synthetic Attempts towards Structures of Type 2. – Our initial efforts were concentrated on the synthesis of compounds **5** or **6**, the direct precursors of structures **2** (*Scheme 1*).

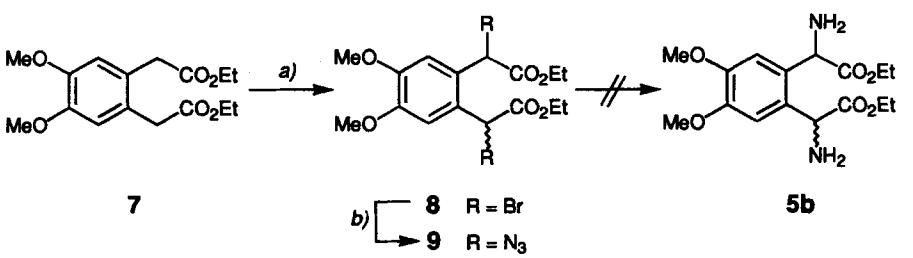
Our first approach was similar to that used to synthesize **1** [1] (*Scheme 2*). The synthesis started with diester **7** obtained in five steps from 3,4-dimethoxybenzoic acid as described in [2]. Benzylic bromination of **7** was achieved by *N*-bromosuccinimide in CCl_4 according to a described procedure [3] followed by treatment of the resulting mixture of diastereoisomers **8** by NaN_3 in DMF to give **9** as a mixture of diastereoisomers. Attempts to transform **9** into the expected amino ester **5b** were unsuccessful (catalytic hydrogena-

[1]) Primes added to compound numbers **1**–**4** denotes the corresponding *N*-protected compounds.

Scheme 1



Scheme 2

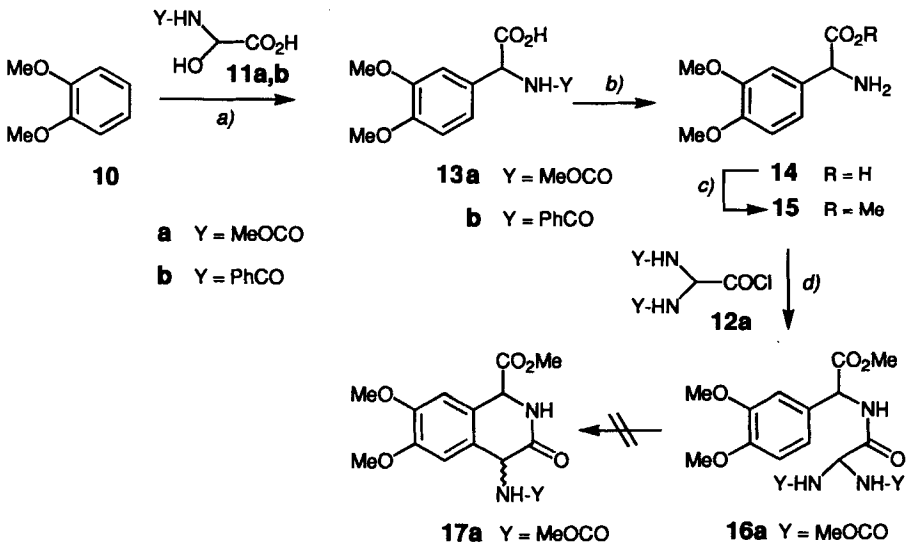


a) *N*-Bromosuccinimide, CCl_4, *hv*, r.t., 16 h. *b*) NaN_3, DMF, r.t., 4 h.

tion in the presence of Pd/C or PtO_2, *Staudinger* reaction [4]). Other efforts to obtain derivatives of amino ester **5b** by substituting the Br-atoms of **8** by several nucleophiles (sodium phthalimide/DMF [5], $NaHNCOCF_3$/DMF [6]) also failed.

Our next synthetic plan (*Scheme 3*) was centered around an intramolecular amidoalkylation (**16a** → **17a**) using a methodology described in [7] [8]. Under acidic conditions [7], veratrole (= 1,2-dimethoxybenzene; **10**) and glyoxylic acid/amide adducts **11** condensed easily to give the 3,4-dimethoxyphenylglycine derivatives **13**. Hydrolysis of **13b** (5N HCl at reflux) followed by esterification of the resulting amino acid **14** (HCl/MeOH) afforded the amino ester **15**, which was then condensed with the acid chloride **12a** [8] to yield **16a**. Surprisingly, while smooth intramolecular cyclization was reported [8] with the parent compound devoid of the MeO substituents in methanesulfonic acid, **16a** only afforded complex reaction mixtures under the same acidic conditions. The failure of this *intramolecular* reaction is rather surprising since, as will be seen below, a similar *intermolecular* condensation (**13** → **18**, *Scheme 4*), is possible.

Scheme 3



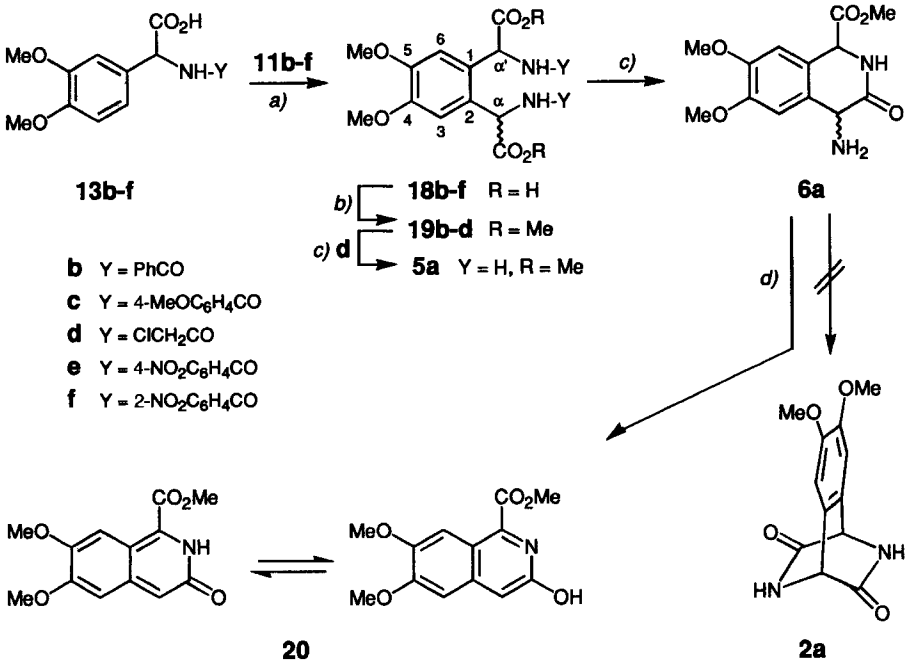
a) **11** (1 equiv.), H_2SO_4/AcOH 1:9, r.t., 1–2 days. *b*) 5N HCl, reflux, 18 h. *c*) $MeSO_3H$, MeOH, reflux, 18 h. *d*) **12a** (1.1 equiv.), Et_3N, CH_2Cl_2, r.t., 15 h.

An alternative route (*Scheme 4*) to compounds of type **5** was considered based on our discovery that, in methanesulfonic acid, **11b** condensed with the acid **13b** to give the *N,N'*-dibenzoyl derivative **18b** of **5** (R = Me, R' = H) as mixture of diastereoisomers **A**[2]) and **B** in 80% yield, while **11a** and **13a** gave only trace amounts of the corresponding *N,N'*-bis(methoxycarbonyl) derivative. Other *N,N'*-diacyl derivatives, **18c–f**, were synthesized by the same procedure although in lower yields (45–55%). In the two most favorable cases **18b, c**, a one-pot synthesis was achieved from veratrole (**10**) and **11b, c** (2 equiv.). The success of this reaction yet unreported may be attributed to the presence of the MeO groups in 3 and 4 positions which are known to facilitate *Friedel-Crafts*-type reactions. The acylamino acids **18b, c** were transformed into their dimethyl esters **19b, c** by usual acidic procedures (H_2SO_4 in MeOH, H_2SO_4 in MeOH/$ClCH_2CH_2Cl$ [9]). Esterification of **18d** required neutral conditions such as diazomethane in MeOH/Et_2O (quant. yield).

Several attempts to determine the relative configuration *meso* or *rac* (±) of these compounds by resolution of acids **18b, c** using chiral amines were unsuccessful. Finally, esters **19cA**[2]) and **19cB** were examined by HPLC on a chiral phase. While ester **19cA** gave a single peak, ester **19cB** was resolved into enantiomers thus establishing the relative configuration for **18cA** and **19cA** as *meso* and for **18cB** and **19cB** as *rac*. Comparison of NMR spectra of the series **18** and **19** (*Table 4* in *Exper. Part*) suggests, in particular, the same relative configurations (**A** = *meso* and **B** = *rac*) for diastereoisomers **18b** and **19b**. For all other compounds, however, no conclusion can be drawn. It should be noted that

[2]) We denote **A** the isomer which is the most easily isolated by crystallization from the reaction mixture.

Scheme 4



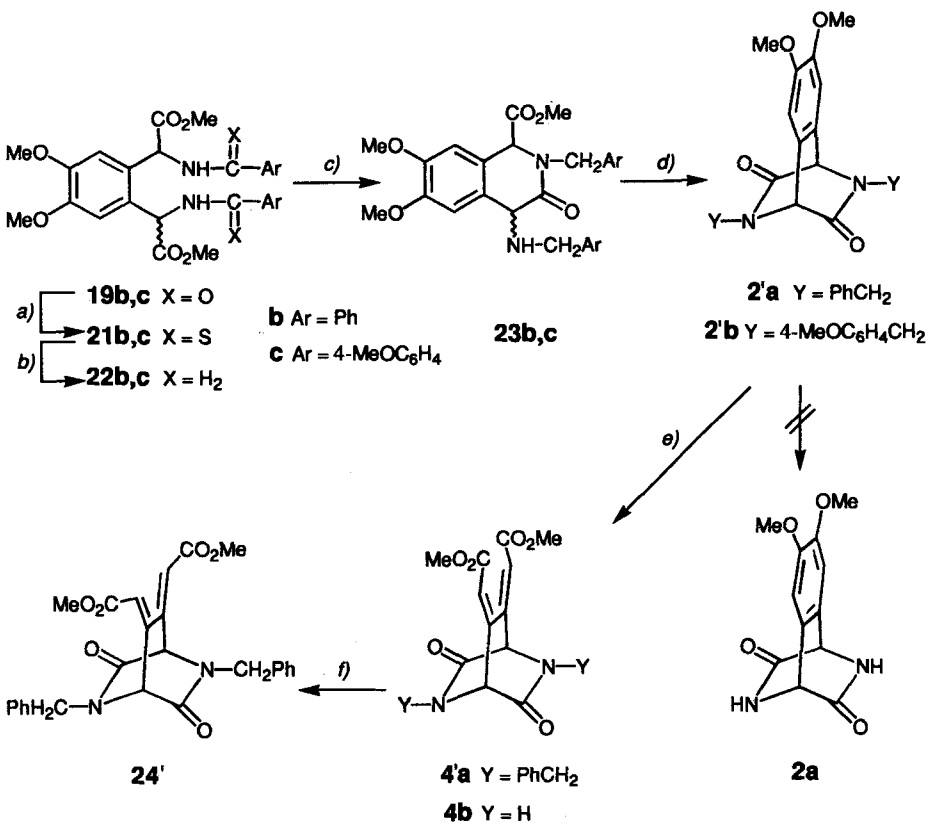
a) **11** (1 equiv.), $MeSO_3H$, r.t., 2 days. *b*) *Method A*: H_2SO_4, MeOH, reflux, 17 h; *Method B*: H_2SO_4, MeOH, 1,2-dichloroethane, reflux, 24 h; *Method C*: CH_2N_2, Et_2O/MeOH, r.t. *c*) **19d**, *N*-piperidinothiourea, AcOH, abs. EtOH, reflux, 4 h. *d*) MeOH, reflux, 1.5 h.

in most of the cases, in the reaction giving rise to compounds **18**, isomer **A** (proved to be *meso* in series **b** and **c**) was always the major compound.

All attempts to hydrolyze the *N*-acyl groups of **18b–d** or **19b–d** under either acidic or basic standard procedures were unsuccessful. However, we were able to cleave the *N*-(chloroacetyl) groups of **19d** by means of *N*-piperidinothiourea [10] producing in fair yields (40–45%) the amino-tetrahydro-oxoisoquinolinecarboxylate **6a** resulting from the intramolecular cyclization of the intermediate amino ester **5a** (not isolated). Attempts to achieve the second intramolecular cyclization to give **2a** were unsuccessful (MeONa in MeOH, NaCN in MeOH) due to formation of complex product mixtures. Even in the absence of an alkaline catalyst, the tetrahydroisoquinolinecarboxylate **6a** in refluxing MeOH gave very rapidly a nearly quantitative formation of a yellow compound. Based on NMR data and elemental analysis, the dihydroisoquinolininecarboxylate structure **20**, resulting of the loss of NH_3, was attributed to this compound. By action of a base, **20** was further decomposed to give complex mixtures.

Synthesis of *N*-Protected 2 (Series 2') and Formation of Cleavage Compounds of Type 4. – The easy accessibility of the bis(acylamino) derivatives **19b, c** encouraged us to use these compounds to reach our target structure **2**. Since the cleavage of amide groups proved to be unfeasible, we considered that the transformation of the benzoylamino into benzylamino groups would be a good alternative.

Scheme 5



a) *Lawesson*'s reagent, THF, 60°, 18–24 h. *b*) *Raney*-Ni, MeOH/THF, r.t., 8 min. *c*) $CHCl_3$, r.t., 2 days. *d*) NaOMe, MeOH, r.t., 24 h. *e*) CAN, $MeCN/H_2O$, r.t., 1.5 h. *f*) I_2, toluene, *hv*, reflux, 2.5 h.

Among the methods available for the reduction of amides to amines we chose a procedure already described [11] *via* the corresponding thioamides, compatible with the presence of ester groups (*Scheme 5*). Amides **19b, c** were readily transformed to bis(thiobenzoyl) derivatives **21b, c** by using *Lawesson*'s reagent in THF [12] (70% yield). Subsequent treatment with *Raney*-Ni (in THF/MeOH) afforded the corresponding dibenzyl derivatives **22b, c**. The reduction was very fast (in *ca.* 8 min). The reaction was stopped when the initial yellow color of the solution disappeared. Longer reaction times led to recoloration of the reaction mixture and formation of undesired products. These amino esters **22b, c** cyclized spontaneously to give amino-tetrahydro-oxoisoquinolinecarboxylates **23b, c**. Since no epimerization seemed to occur during cyclization, the *meso*-isomer of **21b, c** gave *cis*-**23b, c** while the *rac*-isomer of **21b, c** gave *trans*-**23b, c**. In contrast to the results observed for **6a** (see above), intramolecular lactamization of **23b** and **23c** took place readily under the same conditions (NaOMe/MeOH) to give **2'a** and **2'b** [1]), respectively, in 50–60% overall yield from **21b** and **21c**. Moreover, lactamization proceeded on both diastereoisomers as well, meaning that epimerization of *trans*- into *cis*-**23** took place before lactamization.

Debenzylation of **2'a** using several known methods [13] was unsuccessful. Among the methods examined were: H_2, Pd/C, AcOH; Pd/C, HCO_2NH_4, MeOH, reflux [14]; *t*-BuLi, THF then O_2 [15]; *t*-BuOK, DMSO then O_2 [16]; Li, NH_3 [17]; BBr_3, xylene or mesitylene, reflux [18]. Under these last conditions, demethylation was the unique reaction observed. In all other cases, either starting material was recovered or complex reaction mixtures due to degradation of the bicyclic system were obtained.

Cerium ammonium nitrate ($Ce(NH_4)_2(NO_3)_6$; CAN) is an effective reagent for the removal of a 4-methoxybenzyl group on a N-atom [19]. Under these conditions the *N*-benzyl groups are not cleaved. We previously used this method with success (85% yield) for deblocking the *N,N'*-bis(4-methoxybenzyl) derivative of **1** (**1'**) [1]. Treatment of **2'b** under the same conditions also cleaved the protective groups but the only isolated product (30–40% yield) was not the desired product **2a**. From elemental analysis, the empirical formula of that new compound was $C_{12}H_{12}N_2O_6$ (280.24) instead of $C_{12}H_{12}N_2O_4$ (248.24) for the expected compound **2a**. Mass spectrometry was at first a bit confusing since besides a large signal $[M + 1]^+$ at 281.3, a signal at 249.3, almost as intense, was also present. Moreover, the presence in the IR spectrum of a C=O band at 1730 cm^{-1} clearly indicated the presence of an ester group. All these data are consistent with the structure of (*E,E*)-diene-diester **4b**. This means that besides the normal cleavage of the *N*-(4-methoxybenzyl) group of **2'b** under the action of CAN, the aromatic ring was oxidized simultaneously. Since CAN does not affect the benzyl groups, the same treatment converted **2'a** to the dibenzyl derivative **4'a**. The (*E,E*) configuration of the diene-diester **4'a** was confirmed by its isomerization into the (*Z,Z*)-derivative **24'** in the presence of I_2. Moreover, **4'a** was easily hydrogenated to give a mixture of isomers which were not studied further. NMR Data of these compounds discussed below confirmed their structures.

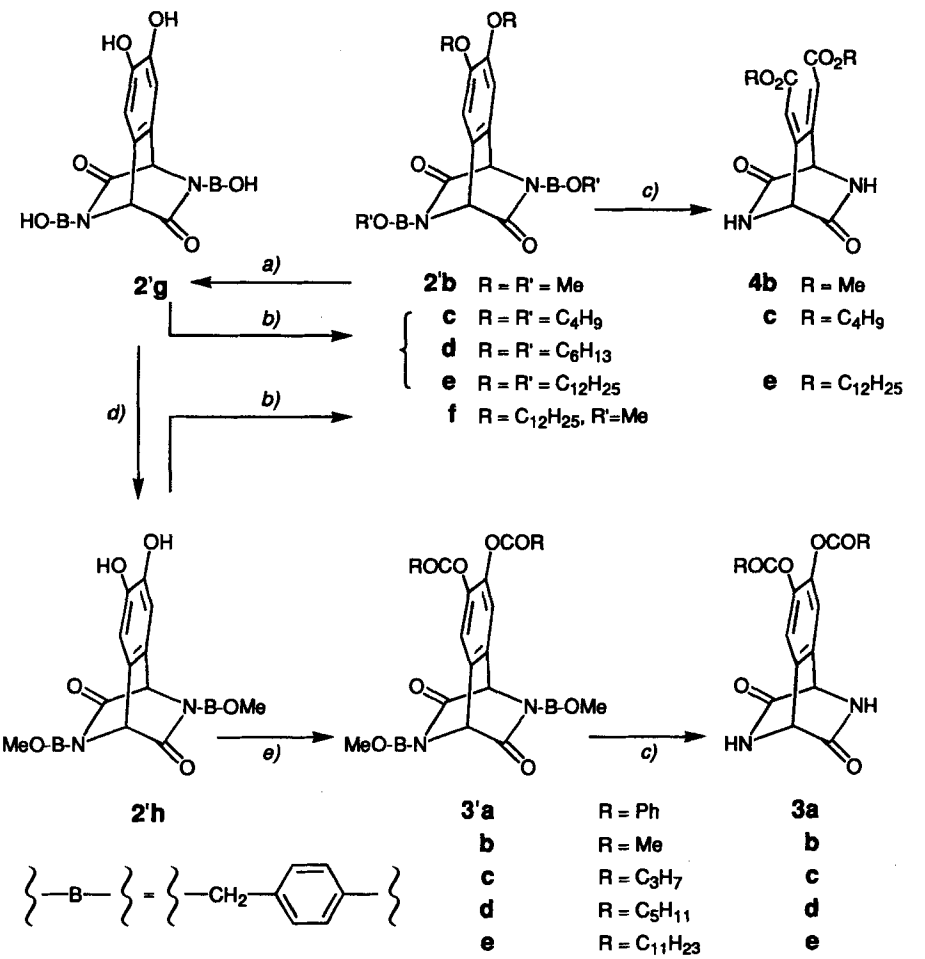
To our knowledge, such an oxidative cleavage of an *o*-dimethoxyaryl ring by CAN has not yet been reported and would deserve a more thorough study.

Synthesis of Compounds of Types 3 and 4. – The *N*-(4-methoxybenzyl) derivative **2'b** turned out to be a good intermediate to the synthesis of various diesters of type **4** and eventually of type **3** (*Scheme 6*).

Treatment of **2'b** with BBr_3 in CH_2Cl_2 afforded tetrol **2'g** in good yield. Realkylation by various alkyl bromides to give compounds **2'b–e**, followed by treatment with CAN yielded diene-diesters **4b, c, e**. The reaction with CAN proceeded in the same manner as for the parent compound **2'b** (see above), although a significant decrease of the reaction yield was observed with the lengthening of the ether chains (only 10% for **4e**) due, in particular, to a decreasing solubility.

The *N*-(4-hydroxybenzyl) groups of tetrol **2'g** could be selectively methylated in the presence of borax known to protect the *ortho*-dihydroxy functions [20] to give **2'h** in good yield (> 80%). This diol was realkylated by dodecyl bromide to give **2'f** or esterified with various acyl chlorides to yield compounds **3'a–e**. Treatment of the latter with CAN afforded esters **3a–e**. It is noteworthy that the aromatic ring bearing ester functions (series **3'**) remains unaffected by the oxidative treatment with CAN, in contrast to the cleavage observed when the aromatic ring bears ether groups (series **2'**).

Scheme 6



a) BBr_3, CH_2Cl_2, r.t., 5 h. *b*) K_2CO_3, alkyl bromide, DMF, 80°, 15 h. *c*) CAN, MeCN/H_2O, r.t., 1.5–3 h. *d*) 1) NaOH, borax, H_2O, 1 h; 2) Me_2SO_4, NaOH, 3 h; 3) 3.6N H_2SO_4, reflux, 15 min.

Resolution of 3c. – We previously described the easy resolution of the *N,N'*-bis(4-methoxybenzyl) derivative of **1** (**1'**) [1] on the gram scale by HPLC on tris(3,5-dimethylphenylcarbamoyl)cellulose (*Chiralcel OD*). The same type of phases, *Chiralcel OD* and *OC* (tris(phenylcarbamoyl)cellulose), was less efficient for compounds **2'a** and **3'c** and gave satisfactory results only on the analytical scale. In contrast, compound **3c** was nicely resolved on *Chiralcel OC*. In view of this result, we considered the possibility of transforming **3c** into the diol **2** (X = OH) which eventually would give access to a variety of compounds **2** or **3** in racemic or enantiomeric forms. Unfortunately, all attempts to hydrolyze the ester functions of **3c** under either acidic or basic standard procedures were unsuccessful.

NMR Spectral Features of Compounds of Types 2–4. – All assignments of ^{1}H-NMR-resonances (*Tables 1* and *2*), and ^{13}C-NMR resonances (*Table 3*) were obtained by conventional decoupling irradiations, NOESY, DEPT, or INEPT techniques. All spectra were perfectly consistent with the C_2 symmetry of the molecules.

Table 1. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *for Compounds* **2'–4', 3, 4,** *and* **24'** *in* $CDCl_3$[a]). For convenience, all atoms are numbered as for **2** (arbitrary numbering).

	2'a	**2'b**	**2'c**	**2'd**	**2'e**[b])	**2'f**	
H–C(3)[c])	4.68	4.66	4.63	4.63	4.78	4.64	
H–C(9)[c])	6.50	6.49	6.52	6.52	6.84	6.52	
CH_AH_B–N[d])	4.79–4.36	4.75–4.30	4.71–4.30	4.70–4.30	4.62–4.46	4.70–4.32	
	3'a	**3'b**	**3'c**	**3'd**	**3'e**	**4'a**	**24'**
H–C(3)[c])	4.79	4.72	4.72	4.71	4.71	4.37	6.14
H–C(9)[c])	7.07	6.88	6.86	6.86	6.86	6.05	6.18
CH_AH_B–N[d])	4.70–4.42	4.61–4.40	4.63–4.39	4.62–4.47	4.61–4.40	4.73–4.48	4.76–4.40
	3d	**3e**	**4c**	**4e**			
H–C(3)[e])	4.79	4.79	4.45	4.44			
H–C(9)[c])	7.28	7.24	6.34	6.33			
NH[e])	7.28	7.11[f])	7.29	6.98			

[a]) Resonances for other protons, see *Exper. Part.*
[b]) In (D_8)THF.
[c]) *s.*
[d]) *J*(*A*,*B*) [Hz]: 14.6 (**24'**); 14.7 (**2'b, e, 3'a–e**); 14.8 (**2'c, d, f**); 14.9 (**2'a**); 15.1 (**4'a**).
[e]) *m*, *AA'XX'* spin system.
[f]) Broad *s.*

Table 2. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *for Compounds* **2', 4', 3,** *and* **4**, *in* $(D_6)DMSO$[a]). For convenience, all atoms are numbered as for **2** (arbitrary numbering).

	2'a	**2'b**	**2'g**	**2'h**	**4'a**	
H–C(3)[b])	5.09	5.02	4.88	4.94	5.04	
H–C(9)[b])	7.09	7.03	6.82	6.83	6.46	
CH_AH_B–N[c])	4.58–4.32	4.48–4.25	4.42–4.09	4.47–4.17	4.64–4.36	
	3a	**3b**	**3c**	**3d**	**3e**	**4b**
H–C(3)[d])	4.94	4.88	4.87	4.88	4.86	4.59
H–C(9)[b])	7.80	7.53	7.53	7.53	7.52	6.52
NH[d])	9.34	9.27	9.26	9.26	9.26	9.13

[a]) Resonances for other protons, see *Exper. Part.*
[b]) *s.*
[c]) *J*(*A*,*B*) [Hz]: 14.7 (**2'b**); 14.8 (**2'g, 2'h**); 15.1 (**2'a**); 15.3 (**4'a**).
[d]) *m*, *AA'XX'* spin system.

Table 3. *Selected ^{13}C-NMR Chemical Shifts* [ppm] *for Compounds* **2'a, 2'b, 4'a, 3a, 4b**; *and* **24'**, *in $CDCl_3$ and (D_6)DMSO*[a]). For convenience, all atoms are numbered as for **2** (arbitrary numbering).

	$CDCl_3$			(D_6)DMSO				
	2'a	**4'a**	**24'**	**2'a**	**2'b**	**3a**	**4'a**	**4b**
C(2)	168.8	166.0	165.6	168.7	168.6	171.3	166.1	169.2
C(3)	64.2	66.9	59.4	63.9	63.8	58.9	66.0	61.3
C(8)	129.9	138.5	144.1	130.4	130.4	137.9	138.9	140.5
C(9)	108.0	123.8	115.3	109.3	109.2	120.1	123.6	123.1
C(10)	148.2	164.5	164.3	147.9	147.9	140.9	164.6	165.0

[a]) Resonances for other C-atoms, see *Exper. Part.*

For all *N*-protected compounds (prime series), H–C(3) appeared as a *s* in the ^{1}H-NMR while for deprotected compounds, H–C(3) formed with NH a *AA'XX'* spin system and appeared as a *m*. For all compounds of the series **2'**, **3**, and **3'**, the H–C(3) signal was found within the range 4.6–4.8 ppm in $CDCl_3$ (*Table 1*) and 4.9–5.1 ppm in (D_6)DMSO (*Table 2*). Considering that the bridgehead proton of **1** resonated at 3.68 ppm in (D_6)DMSO and that of its *N,N'*-bis(4-methoxybenzyl) derivative **1'** at 3.99 in $CDCl_3$ and 4.03 in (D_6)DMSO, the deshielding effect $\Delta\delta$ of the aromatic fused ring on H–C(3) was 0.6–0.8 in $CDCl_3$ and 0.9–1.2 in (D_6)DMSO, values only slightly lower than those observed ($\Delta\delta$ 1.4) in the bicyclo[2.2.2]octane series [21]. In the exocyclic diene structures such as **4'a** and **4b, c, e**, the H–C(3) signal was shifted to low fields by 0.4 ppm in $CDCl_3$ and by *ca.* 1 ppm in (D_6)DMSO. This effect may be compared to the effect observed for some vicinal dimethylidene derivatives of bicyclo[2.2.2]octane [22] ($\Delta\delta$ 0.4–0.7), although in series **4** and **4'** the C=C bonds are certainly not coplanar due to a severe steric hindrance between the CO_2Me groups. By contrast, for **24'** with the (*Z,Z*)-configuration, the H–C(3) signal was shifted downfield by 1.8 ppm (δ 6.14) as compared with its (*E,E*)-isomer **4'a**. Obviously, this shift was caused by the anisotropic effect of the ester carbonyl group and confirmed the configurational assignments. Another evidence for these assignments was the observation of a NOE at H–C(9) on irradiation of H–C(3) in **4'a** and **2'a** indicating the proximity of these protons.

For all compounds of the series **2'** and **3'**, δ values in $CDCl_3$ for H–C(9) (*s* at *ca.* 6.5 for **2'** and 6.9 for **3'**, *Table 1*) were in good agreement with the predicted values based on empirical increments for aromatic substituents [23]. As expected, this proton in the diene series **4** and **4'** appeared at higher field. On the other hand, the inside proton of **24'** was slightly deshielded (δ 6.18) as compared to the outside proton of its isomer **4'a** (δ 6.05). This deshielding may result from the anisotropic effect of the C=C bond as it was observed in dimethylidene derivatives of bicyclo[2.2.2]octane [22].

Conclusion. – The present synthetic work gives access to the highly functionalized bicyclo[2.2.2]octane structures **3** and **4**. It revealed novel reactions that could possess further synthetic potential. Furthermore, in view of the H-bonding features of the parent compound **1** [1], the derivatives of types **3** and **4** may also form superstructures displaying the effect of molecular chirality on self-assembly [24]. In addition, such arrays may present novel physicochemical properties, as was the case in the generation of liquid crystalline phases through the self-assembly of complementary H-bonded components [25] [26].

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Experimental Part

General. The following reagents were commercially available: α-hydroxyhippuric acid (= (benzoylamino)-hydroxyacetic acid; **11b**, *Aldrich*), glyoxylic acid monohydrate (= oxoacetic acid; *Aldrich* or *Janssen Chimica*),

Lawesson's reagent (*Aldrich*), methanesulfonic acid (*puriss.*; *Fluka*). *Raney*-Ni (*Aldrich* or *Prolabo*), ceric ammonium nitrate (CAN; *Aldrich*), substituted benzamides and chloroacetamide (*Aldrich*). TLC: *Merck* silica gel *60 F254*, 0.25 mm (anal. TLC), 1 or 2 mm (prep. TLC), UV detection. Prep. column chromatography (CC): *Merck* silica gel *60* (0.040–0.063 mm) or Al_2O_3 *90* activity II–III. M.p. and enthalpies of fusion (ΔH): *Perkin-Elmer-DSC7* differential scanning calorimeter, heating rate 5°/min unless otherwise state, temperatures in °, ΔH in kJ/mol. IR: *Perkin-Elmer* 297, KBr pellets. NMR: *Bruker AM200SY* equipped with a data system *Aspect 3000*, δ in ppm downfield from $SiMe_4$, *J* in Hz. MS: FAB (positive). Elemental analyses: 'Service Central d'Analyse du CNRS'.

Diethyl α,α'-Dibromo-4,5-dimethoxybenzene-1,2-diacetate (**8**). A stirred mixture of **7** (2.4 g, 7.74 mmol), prepared according to [2], *N*-bromosuccinimide (NBS; 2.76 g, 15.86 mmol) and CCl_4 (30 ml) was irradiated with two 100-W lamps for 16 h. The insoluble *N*-succinimide was filtered off and the filtrate evaporated to give **8** (3.6 g) as a mixture of 2 diastereoisomers which was used without further purification.

Diethyl α,α'-Diazido-4,5-dimethoxybenzene-1,2-diacetate (**9**). A mixture of crude **8** (1.9 g, 4 mmol), NaN_3 (0.57 g, 8.8 mmol), and DMF (5 ml) was stirred at r.t. for 4 h, then diluted with H_2O, and extracted with Et_2O. After evaporation, the residue was purified by CC (SiO_2, 50 g, CH_2Cl_2) to give **9** as a 1:1 mixture of 2 diastereoisomers. IR (film): 2100*s*, 1740*s*, 1610*m*. ^{1}H-NMR ($CDCl_3$): 6.91, 6.88 (2*s*, arom. H); 5.42, 5.38 (2*s*, CH); 4.25, 4.30 (2*q*, CH_2); 3.9 (*s*, MeO); 1.26, 1.25 (2*t*, Me).

Hydroxy[(methoxycarbonyl)amino]acetic Acid (**11a**). Prepared according to [8].

Hydroxy[(4-methoxybenzoyl)amino]acetic Acid (**11c**). A mixture of glyoxylic acid monohydrate (18.4 g, 0.2 mol) and anisamide (30.25 g, 0.2 mol) in acetone (200 ml) was refluxed with stirring. Dissolution occurred after a few minutes followed by the progressive apparition of a precipitate. After 1 h, more glyoxylic acid monohydrate (9.2 g, 0.1 mol) and acetone (200 ml) were added, and reflux was continued for 23 h. The mixture was cooled to r.t. and left overnight. The solid **11c** was collected by filtration (33 g, 73%). M.p. 148.5° (dec.; 10°/min). ^{1}H-NMR ((D$_6$)DMSO): 9.09 (*d*, *J* = 8, NH); 7.87, 6.98 (arom. H); 5.57 (*d*, *J* = 8, CH); 3.80 (*s*, MeO). Anal. calc. for $C_{10}H_{11}NO_5$ (225.20): C 53.33, H 4.92, N 6.22; found: C 53.4, H 4.9, N 6.2.

[(Chloroacetyl)amino]hydroxyacetic Acid (**11d**). A mixture of glyoxylic acid monohydrate (9.2 g, 0.1 mol) and chloroacetamide (9.4 g, 0.1 mol) was heated on a rotatory evaporator at 60° for 30 min under 1 atm pressure and then for 1 h *in vacuo*. The gummy residue was dissolved in AcOEt (50 ml) at 60° and the soln. cooled to r.t. and allowed to crystallize overnight. The crystalline precipitate was collected by filtration (7.85 g, 47%). M.p. *ca.* 120°. ^{1}H-NMR ((D$_6$)DMSO): 8.97 (*d*, *J* = 8, NH); 5.38 (*d*, *J* = 8, CH); 4.10 (*s*, CH_2). ([27]: M.p. 105°. ^{1}H-NMR: same δ except for NH, δ 8.8). Anal. calc. for $C_4H_6ClNO_4$ (167.55): C 28.67, H 3.61, Cl 21.16, N 8.36; found: C 28.75, H 3.7, Cl 20.9, N 8.4.

Hydroxy[(4-nitrobenzoyl)amino]acetic Acid (**11e**). An intimate mixture of solid glyoxylic acid monohydrate (5.55 g, 60 mmol) and 4-nitrobenzamide (10.05 g, 60 mmol) was heated on a rotatory evaporator at 60°, for 20 min at 1 atm and then for 20 min *in vacuo*. Acetone (500 ml) was added, and the suspension refluxed for 3 h with stirring and then evaporated. The glassy residue containing *ca.* 70% of **11e** and 30% of 4-nitrobenzamide was used without further purification. ^{1}H-NMR ((D$_6$)DMSO): 9.63 (*d*, *J* = 8, NH); 8.30, 8.10 (4 arom. H); 5.60 (*d*, *J* = 8, CH).

Hydroxy[(2-nitrobenzoyl)amino]acetic Acid (**11f**). As described for **11e**, from glyoxylic acid monohydrate (2.76 g, 30 mmol) and 2-nitrobenzamide (5 g, 30 mmol). The residue containing *ca.* 70% **11f** and 30% of 2-nitrobenzamide was used without further purification. ^{1}H-NMR ((D$_6$)DMSO): 9.52 (*d*, *J* = 8.3, NH); 8.00, 7.7 (4 arom. H); 5.55 (*d*, *J* = 8.3, CH).

Acids **13a–f**: *General Procedure*. The procedure described in [7] was slightly modified as following. To a cooled and stirred soln. (*ca.* 10°) of veratrole (**10**; 0.2 mol) in conc. H_2SO_4 (10 ml) and AcOH (90 ml) was added the appropriate reagent **11a–f** (0.1 mol). Stirring was continued for 24–48 h at r.t. The mixture was poured into ice and H_2O and the resulting precipitate collected by filtration, washed successively with H_2O and pentane, and then recrystallized.

3,4-Dimethoxy-α-[(methoxycarbonyl)amino]benzeneacetic Acid (**13a**): Recrystallized from AcOEt/hexane. Yield 81%. M.p. 138°. ΔH = 30.7. ^{1}H-NMR ((D$_6$)DMSO): 7.87 (*d*, *J* = 8, NH); 6.98 (*s*, 1 arom. H); 6.89 (*d*, 2 arom. H); 5.02 (*d*, *J* = 8, CH); 3.72, 3.71 (2*s*, 2 MeO); 3.54 (*s*, MeO). Anal. calc. for $C_{12}H_{15}NO_6$ (269.25): C 53.53, H 5.62, N 5.20; found: C 53.6, H 5.5, N 5.0.

α-(Benzoylamino)-3,4-dimethoxybenzeneacetic Acid (**13b**): Recrystallized from methoxyethanol/H_2O. Yield 88%. M.p. 211°. ΔH = 53.4. ^{1}H-NMR ((D$_6$)DMSO): 8.93 (*d*, *J* = 7, NH); 7.88, 7.48 (2*m*, PhCO); 7.11 (*d*, 1 arom. H); 6.97 (*m*, 2 arom. H); 5.49 (*d*, *J* = 7, CH); 3.75, 3.74 (2*s*, 2 MeO). Anal. calc. for $C_{17}H_{17}NO_5$ (315.33): C 64.75, H 5.43, N 4.44; found: C 64.7, H 5.4, N 4.3.

3,4-Dimethoxy-α-[(4-methoxybenzoyl)amino]benzeneacetic Acid (**13c**): Recrystallized from methoxyethanol/H_2O. Yield 73%. M.p. 179 and 198°. ^{1}H-NMR ((D$_6$)DMSO): 8.74 (*d*, *J* = 7, NH); 7.88, 6.97 (2*d*, MeOC$_6H_4$CO); 7.09 (*d*, 1 arom. H); 6.97 (*m*, 2 arom. H); 5.47 (*d*, *J* = 7, CH); 3.79, 3.74, 3.72 (3*s*, 3 MeO). Anal. calc. for $C_{18}H_{19}NO_6$ (345.36): C 62.60, H 5.55, N 4.06; found: C 62.5, H 5.6, N 4.0.

α-[(Chloroacetyl)amino]-3,4-dimethoxybenzeneacetic Acid (**13d**): Recrystallized from EtOH. Yield 84%. M.p. 168 and 172°. ^{1}H-NMR ((D$_6$)DMSO): 8.88 (*d*, *J* = 7.2, NH); 6.94 (*m*, 3 arom. H); 5.22 (*d*, *J* = 7.2, CH); 4.15 (*s*, CH_2Cl); 3.73 (*s*, 2 MeO). Anal. calc. for $C_{12}H_{14}ClNO_5$ (287.70): C 50.10, H 4.91, N 4.87; found: C 50.4, H 4.9, N 4.65.

3,4-Dimethoxy-α-[(4-nitrobenzoyl)amino]benzeneacetic Acid (**13e**): Recrystallized from EtOH. Yield 64%. M.p. 187°. ΔH = 39.5. ^{1}H-NMR ((D$_6$)DMSO): 9.32 (*d*, *J* = 7, NH); 8.30, 8.11 (2*d*, $NO_2C_6H_4$); 7.11 (*d*, 1 arom. H); 6.99 (*m*, 2 arom. H); 5.49 (*d*, *J* = 7, CH); 3.75, 3.74 (2*s*, 2 MeO). Anal. calc. for $C_{17}H_{16}N_2O_7$ (360.33): C 56.67, H 4.48, N 7.77; found: C 56.1, H 4.7, N 7.8.

3,4-Dimethoxy-α-[(2-nitrobenzoyl)amino]benzeneacetic Acid (**13f**): Recrystallized from AcOH/H_2O. Yield 66%. M.p. 204.5°. ΔH = 49.8. ^{1}H-NMR ((D$_6$)DMSO): 9.40 (*d*, *J* = 8, NH); 8.04, 8.11 (2*m*, $NO_2C_6H_4$); 7.04 (*s*, 1 arom. H); 6.96 (*m*, 2 arom. H); 5.45 (*d*, *J* = 8, CH); 3.75, 3.74 (2*s*, 2 MeO). Anal. calc. for $C_{17}H_{16}N_2O_7$ (360.33): C 56.67, H 4.48, N 7.77; found: C 56.6, H 4.5, N 7.6.

α-Amino-3,4-dimethoxybenzeneacetic Acid Hydrochloride (**14** · HCl). A mixture of **13b** (3.15 g, 10 mmol), conc. HCl soln. (50 ml), and H_2O (50 ml) was refluxed for 18 h. After cooling to r.t., the precipitated benzoic acid was filtered off. The filtrate was discolored with activated carbon (*Norit*) and evaporated. The residue was recrystal-
lized from MeOH/AcOEt: **14** · HCl (845 mg, 34%).

Methyl α-Amino-3,4-dimethoxybenzeneacetate (**15**). A mixture of **14** · HCl (1.05 g, 4.24 mmol), methanesulfonic acid (0.55 ml), and MeOH (20 ml) was refluxed for 18 h. After evaporation, the residue was dissolved in H_2O, conc. NaOH soln. was added, the mixture extracted with CH_2Cl_2, and the org. phase washed with H_2O, dried (Na_2SO_4), and evaporated: 760 mg (80%) of **15**. This product was used in the next step without further purification.

Methyl α-{{Bis[(methoxycarbonyl)amino]acetyl}amino}-3,4-dimethoxybenzeneacetic Acid (**16a**). A mixture of **15** (735 mg, 3.27 mmol), bis[(methoxycarbonyl)amino]acetyl chloride (**12a**; 808 mg, 3.6 mmol; prepared according to [8]), Et_3N (485 mg, 4.8 mmol), and CH_2Cl_2 (6 ml) was stirred overnight at r.t. The org. phase was washed successively with dil. HCl soln., aq. $NaHCO_3$ soln., and H_2O, dried (Na_2SO_4), and evaporated; pure **16a** (900 mg, 67%). An anal. sample was obtained by recrystallization from CH_2Cl_2/hexane. M.p. 202° (10°/min). ^{1}H-NMR ($CDCl_3$): 7.54 (br. *d*, NH); 6.92–6.80 (3 arom. H); 5.94 (br. *d*, 2 NH); 5.53 (*t*, *J* = 7, H–C(α)); 5.44 (*d*, *J* = 7, NHC*H*NH); 3.88, 3.86, 3.73, 3.72, 3.67 (5*s*, 5 MeO). Anal. calc. for $C_{17}H_{23}N_3O_9$ (413.39): C 49.39, H 5.61, N 10.16; found: C 49.4, H 5.6, N 10.3.

α,α'-Bis(benzoylamino)-4,5-dimethoxybenzene-1,2-diacetic Acid (**18b**). *Method A* (from **13b**): To a cooled (10–15°) suspension of **11b** (16.8 g, 84 mmol) in methanesulfonic acid (80 ml) was added **13b** (25.82 g, 80 mmol). *Method B* (from veratrole (**10**): To a cooled (10–15°) mixture of **10** (11 g, 80 mmol) in methanesulfonic acid (160 ml) was added **11b** (31.36 g, 160.8 mmol). *Methods A* and *B*: the reaction was carried alike as following and gave about the same yields. The mixture was stirred at 10–15° for 15 min, at r.t. until the solids were dissolved (a few hours), and then left for 48 h. The mixture was poured into a mixture of ice/H_2O (*ca.* 600 ml) and AcOEt (1200 ml) with stirring. The org. phase was decanted, washed twice with H_2O, dried (Na_2SO_4) and then evaporated. The crude product (*ca.* 40 g) was recrystallized from AcOEt (160 ml) to give **18b** as a diastereoisomer mixture **18bA**/**18bB** *ca* 2:1 (32 g, 81%) which can be used in the next step without further purification.

Separation of **18bA**/**18bB**: Crude product obtained as above (*ca.* 40 g, 80 mmol) was treated with cyclohexanamine (15.8 g, 160 mmol) in EtOH (250 ml) to give a crystalline precipitate (30 g) which was collected by filtration. This salt was suspended in EtOH (500 ml) and the suspension refluxed for 15 min with stirring. After several hours at r.t., the precipitate was collected by filtration, washed with EtOH, and dried to give a 1st crop (26.4 g). The combined mother liquors were concentrated to give a 2nd crop (10.92 g). The last mother liquors were concentrated nearly to dryness, AcOEt was added to give a 3rd crop (4.43 g). The 1st and 2nd crop was stirred in 1N HCl (5 ml/mmol of salt) for 2 h to give **18bA**/**18bB** *ca.* 8:2 (26.34 g). Acid **18bA** (15 g, 38%) was obtained by treating this crop with default cyclohexanamine followed by decomposition of the resulting pure salt of **18bA** Acid **18bB** (2.18 g, 5%) was obtained by decomposition of the 3rd crop.

meso-*Acid* **18bA**: M.p. 233° (dec.). ^{1}H-NMR ((D$_6$)DMSO): *Table 4*; additionally: 12.98 (br. *s*, 2 CO_2H); 7.78, 7.43 (2*m* 2PhCO). Anal. calc. for $C_{26}H_{24}N_2O_8$ (492.49): C 63.41, H 4.91, N 5.69; found: C 63.3, H 5.0, N 5.6.

rac-*Acid* **18bB**: M.p. 242° (dec.). ^{1}H-NMR ((D$_6$)DMSO): *Table 4*; additionally: 12.8 (br. *s*, 2 CO_2H); 7.92, 7.50 (2*m*, 2PhCO). Anal. calc. for $C_{26}H_{24}N_2O_8$ (492.49): C 63.41, H 4.91, N 5.69; found: C 63.3, H 5.0, N 5.75.

Table 4. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *for the Diastereoisomers* **A** *and* **B** *of Diacids* **18b–f** *in (D$_6$)DMSO and of Diesters* **19b–d** *in CDCl$_3$*[a])[b])

	18bA *meso*	**18bB** *rac*	**18cA** *meso*	**18cB** *rac*	**18dA**	**18dB**	**18eA**	**18eB**
H–C(α)[c])	5.83	5.89	5.77	5.84	5.56	5.61	5.83	5.92
H–C(3)[d])	7.09	7.08	7.08	7.06	6.89	6.87	7.02	7.06
MeO–C(4)[d])	3.76	3.75	3.77[e])	3.74[f])	3.73	3.73	3.76	3.76
NH[c])	8.78	9.23	8.57	9.11	9.04	8.84	9.10	9.51
J(α,NH)	6.8	7.2	6.5	7.5	7.3	7.5	6.9	7.4
	18fA	**18fB**	**19bA** *meso*	**19bB** *rac*	**19cA** *meso*	**19cB** *rac*	**19dA**	**19dB**
H–C(α)[c])	5.95	5.82	5.90	5.92	5.80	5.89	5.68	5.85
H–C(3)[d])	7.00	7.00	6.87	6.84	6.86	6.83	6.73	6.75
MeO–C(4)[d])[g])	3.76	3.75	3.81	3.86	3.84[e])	3.85[f])	3.87	3.86
MeOOC[d])[g])	–	–	3.78	3.77	3.81	3.76	3.74	3.80
NH[c])	9.40	9.57	7.72	8.9[h])	7.63	8.8[h])	8.68	7.57
J(α,NH)	7.3	7.5	4.8	5.5	4.5	5.9	6.0	6.3

[a]) **A** and **B** designate the two diastereoisomeric forms of **18** and **19**.
[b]) Resonances for other protons, see *Exper. Part.*
[c]) *d.*
[d]) *s.*
[e]) Superimposed by the 4-*Me*OC$_6$H$_4$ signal.
[f]) Additional *s* for 4-*Me*OC$_6$H$_4$ at 3.80 ppm. Assignments may be interchanged.
[g]) Assignments may be interchanged.
[h]) The *d* appears as br. *s*.

4,5-*Dimethoxy-α,α'-bis[(4-methoxybenzoyl)amino]benzene-1,2-diacetic Acid* (**18c**). *Method A* (from **13c**): As described for **18b** from **11c** (23.63 g, 0.105 mol), **13c** (34.5 g, 0.1 mol), and methanesulfonic acid (200 ml). The mixture was stirred at r.t. until the solids were dissolved and then left for 2 days. *Method B* (from **10**). To a cooled (10–15°) mixture of **10** (13.8 g, 0.1 mol) and methanesulfonic acid (160 ml) was added **11c** (23 g, 0.102 mol) with stirring. The mixture was stirred at r.t. until the solids were dissolved and then left. After 2 days, **11c** (23 g, 0.102 mol) and methanesulfonic acid (90 ml) were added. The mixture was stirred at r.t. until the solids were dissolved and then left again for 2 days. *Methods A* and *B*: the reaction was carried alike as following. The mixture was poured into a mixture of ice/H_2O (*ca.* 1:1) and AcOEt (750 ml) with stirring. The org. phase was decanted, the aq. phase extracted again with AcOEt (250 ml), the combined org. phase washed twice with H_2O, dried (Na_2SO_4), and evaporated, and the residue recrystallized from AcOEt (100 ml): 28–31 g of **18c** (diastereoisomers **A** and **B** *ca.* 2:1) containing a small amount of **13c**. This product can be used in the next step without further purification.

Separation of **18cA/18cB**: Crude product (30.3 g, 55 mmol) obtained as above was treated by cyclohexanamine (11 g, 110 mmol) in EtOH (110 ml). The resulting salt was collected by filtration and suspended in EtOH (10 ml per g of salt) and the suspension refluxed for 15 min with stirring. After several hours at r.t., the precipitate was collected by filtration, washed with EtOH, and dried. The operation was repeated again to give pure salt of **18cA** (24 g). The combined mother liquors were concentrated to give a 2nd crop (2.33 g) which was recrystallized from EtOH (23 ml) to give pure salt of **18cB** (1.9 g). Treatment of these salts with 1N HCl (5 ml/mmol of salt) for 2 h with stirring gave acid **18cA** or **18cB**, resp.

meso-*Acid* **18cA**: M.p. 217° (dec.; 10°/min). ^{1}H-NMR ((D$_6$)DMSO): *Table 4*; additionally: 13.0 (br. *s*, 2 CO_2H); 7.76, 6.88 (2 MeOC_6H_4). Anal. calc. for $C_{28}H_{28}N_2O_{10}$ (552.55): C 60.87, H 5.11, N 5.07; found: C 60.8, H 5.15, N 5.0.

rac-*Acid* **18cB**: M.p. 199° (dec.). ^{1}H-NMR ((D$_6$)DMSO): *Table 4*; additionally: 12.8 (br. *s*, 2 CO_2H); 7.92, 6.08 (2 MeOC_6H_4). Anal. calc. for $C_{28}H_{28}N_2O_{10} \cdot 1.5\ H_2O$ (579.58): C 58.03, H 5.39, N 4.83; found: C 58.3, H 5.4, N 4.9.

α,α'-Bis[(chloroacetyl)amino]-4,5-dimethoxybenzene-1,2-diacetic Acid (**18d**). As described for **18b**, from **11d** (1.75 g, 10.5 mmol), **13d** (2.87 g, 10 mmol), and methanesulfonic acid (10 ml). After the reaction (48 h), the mixture was poured into a stirred mixture of ice/H_2O (*ca.* 100 ml), NaCl (15 g), and AcOEt (50 ml). The org. phase was decanted, the aq. phase extracted again with AcOEt (50 ml), and the combined org. phase washed with brine (50 ml) and then concentrated to *ca.* 50 ml while crystallization occurred. After several hours at r.t., the crystalline precipitate was collected by filtration and dried; **18dA/18dB** (3.45 g) contaminated with a small amount of unidentified impurities. This product was used in the next step without further purification.

Separation of **18dA/18dB**: To the crude product obtained as above (1 g, 2.29 mmol) MeOH (10 ml) was added, and the suspension refluxed for 10 min and then left a $-20°$ overnight to give crystals of pure diastereoisomer **18dA** (194 mg). The mother liquors were evaporated and treated with cyclohexanamine (0.25 g, 2.5 mmol) in EtOH (3 ml). The resulting salt was collected by filtration and recrystallized from EtOH (5 ml) to give pure salt of **18dB** (110 mg). Alternately, the same crude product (1 g, 2.29 mmol) was treated directly with cyclohexanamine (0.39 g, 3.9 mmol) in EtOH (5 ml). The resulting salt was collected by filtration (820 mg) and recrystallized from EtOH (20 ml) to give pure salt of **18dA** (410 mg). The salts were decomposed with 1N HCl (5 ml/mmol of salt) and acids **18dA** or **18dB** extracted with AcOEt.

Isomer **18dA**: M.p. 229° (dec.; 10°/min). ^{1}H-NMR ((D$_6$)DMSO): *Table 4*; additionally: 12.96 (br. *s*, 2 CO_2H); 4.15, 4.11 (*AB*, J = 13.1, 2 CH_2Cl). Anal. calc. for $C_{16}H_{18}Cl_2N_2O_8 \cdot 1.5\ H_2O$ (464.26): C 41.22, H 4.56, N 6.01; found: C 41.4, H 4.6, N 6.0. *Cyclohexanamine Salt*: Anal. calc. for $C_{16}H_{18}Cl_2N_2O_8 \cdot 2\ C_6H_{13}N$ (635.59): C 52.91, H 6.98, N 8.82; found: C 53.0, H 7.0, N 8.8.

Isomer **18dB**: M.p. 200° (dec.; 10°/min). ^{1}H-NMR ((D$_6$)DMSO): *Table 4*; additionally: 13.1 (br. *s*, 2 CO_2H); 4.11, (*AB*, J = 13.0, 2 CH_2Cl). Anal. calc. for $C_{16}H_{18}Cl_2N_2O_8$ (437.24): C 43.95, H 4.15, N 6.41; found: C 44.0, H 4.26, N 6.4. *Cyclohexanamine Salt*: Anal. calc. for $C_{16}H_{18}Cl_2N_2O_8 \cdot 2\ C_6H_{13}N$ (635.59): C 52.91, H 6.98, N 8.82; found: C 52.8, H 7.1, N 8.7.

4,5-Dimethoxy-α,α'-bis[(4-nitrobenzoyl)amino]benzene-1,2-diacetic Acid (**18e**). As described for **18c**, from crude **11e** (20.5 g), **13e** (18 g, 50 mmol), and methanesulfonic acid (150 ml). The crude **18e** (33.5 g) was purified *via* its cyclohexanamine salt as described for **18c** to give **18eA** (salt: 12 g; acid: 7.1 g after recrystallization from AcOEt, 24%) and **18eB** (salt: 5.68 g; acid: 3.9 g after recrystallization from AcOEt, 13%).

Isomer **18eA**: M.p. 202° (dec.). ^{1}H-NMR ((D$_6$)DMSO): *Table 4*; additionally: 8.13, 7.93 (2 $NO_2C_6H_4$). Anal. calc. for $C_{26}H_{22}N_4O_{12} \cdot 1\ H_2O$ (600.50): C 52.00, H 4.03, N 9.33; found: C 52.4, H 3.8, N 9.1. *Cyclohexanamine Salt*: Anal. calc. for $C_{26}H_{22}N_4O_{12} \cdot 2\ C_6H_{13}N \cdot 2\ H_2O$ (816.86): C 55.87, H 6.42, N 10.29; found: C 55.8, H 6.4, N 10.3.

Isomer **18eB**: M.p. 220° (dec.). ^{1}H-NMR ((D$_6$)DMSO): *Table 4*; additionally: 8.30, 8.12 (2 $NO_2C_6H_4$). Anal. calc. for $C_{26}H_{22}N_4O_{12} \cdot 1H_2O$ (600.50): C 52.00, H 4.03, N 9.33; found: C 52.1, H 4.0, N 9.1. *Cyclohexanamine Salt:* Anal. calc. for $C_{26}H_{22}N_4O_{12} \cdot 2C_6H_{13}N$ (780.23): C 58.45, H 6.20, N 10.76; found: C 58.5, H 6.3, N 10.7.

4,5-Dimethoxy-α,α'-bis[(2-nitrobenzoyl)amino]benzene-1,2-diacetic Acid (**18f**). As described for **18c**, from crude **11f** (5 g), **13f** (6.48 g, 18 mmol), and methanesulfonic acid (40 ml). The crude **18f** (9.17 g) was purified *via* its cyclohexanamine salt as described for **18c** to give the isomer **18fA** (salt: 3.55 g; acid: 2.42 g, 23%) and the isomer **18fB** (acid: 1.3 g after recrystallization from AcOH, 12%).

Isomer **18fA**: M.p. 223° (dec.; 10°/min). ^{1}H-NMR ((D$_6$)DMSO): *Table 4* additionally: 8.02, 7.70 (2 NO_2-C_6H_4). Anal. calc. for $C_{26}H_{22}N_4O_{12} \cdot 1\ H_2O$ (600.50): C 52.00, H 4.03, N 9.33; found: C 52.3, H 4.0, N 9.4.

Isomer **18fB**: M.p. 231° (dec.; 10°/min). ^{1}H-NMR ((D$_6$)DMSO): *Table 4* additionally: 8.00, 7.70 (2 $NO_2C_6H_4$). Anal. calc. for $C_{26}H_{22}N_4O_{12}$ (582.48): C 53.61, H 3.81, N 9.62; found: C 53.6, H 3.9, N 9.6.

Dimethyl α,α'-Bis(benzoylamino)-4,5-dimethoxybenzene-1,2-diacetate (**19b**). *Method A*: A mixture of **18b** (9 g, 18.3 mmol), H_2SO_4 (2.1 ml), and MeOH (600 ml) was refluxed for 17 h. The resulting soln. was concentrated and then diluted with H_2O. The crystalline precipitate was collected by filtration, washed successively with aq. $NaHCO_3$ soln. and H_2O, and then air-dried at 70°: **19b** (8.1 g, 85%). *Method B*: A mixture of **18b** (19 g, 38.6 mmol), H_2SO_4 (0.3 ml), MeOH (12 ml), and 1,2-dichloroethane (80 ml) was refluxed for 17–24 h. After cooling to r.t., the org. phase was washed with H_2O, dried (Na_2SO_4), and then filtered through a short column of Al_2O_3 (80 g, MeOH/CH_2Cl_2 1:99); **19b** (17.1 g, 85%).

meso-*Ester* **19bA**: Recrystallized from AcOEt. M.p. 185.5°. ΔH = 52.0. ^{1}H-NMR ($CDCl_3$): *Table 4*; additionally: 7.88, 7.44 (2*m*, 2 PhCO). ^{13}C-NMR ($CDCl_3$): 171.0 (*C*O_2Me); 166.6 (CONH); 149.4 (*C*-OMe); 133.12, 131.6 (quat. C); 128.25, 127.1, 110.9 (CH); 55.85 (MeO); 54.3, 52.8 (MeO). Anal. calc. for $C_{28}H_{28}N_2O_8$ (520.55): C 64.61, H 5.42, N 5.38; found: C 64.4, H 5.2, N 5.4.

rac-*Ester* **19bB**: Recrystallized from AcOEt. M.p. 219°. ΔH = 51.0. ^{1}H-NMR ($CDCl_3$): *Table 4*; additionally: 8.01, 7.50 (2*m*, 2 PhCO). Anal. calc. for $C_{28}H_{28}N_2O_8$ (520.55): C 64.61, H 5.42, N 5.38; found: C 64.6, H 5.3, N 5.3.

Dimethyl 4,5-Dimethoxy-α,α'-bis[(4-methoxybenzoyl)amino]benzene-1,2-diacetate (**19c**). As described for **19b**.

meso-*Ester* **19cA**: Recrystallized from CH_2Cl_2/MeOH. M.p. 222°. ΔH = 66.6. Chromatography on a chiral phase (*DNB PHGly 2.4.3*, 4.6 × 250 mm, heptane/EtOH/CH_2Cl_2 75:1:24, flow rate 1 ml/min, UV detection at 254 nm): 1 peak, t_R 34 min. ^{1}H-NMR ($CDCl_3$): *Table 4*; additionally: 7.87, 6.91 (2 MeOC_6H_4). Anal. calc. for $C_{30}H_{32}N_2O_{10}$ (580.60): C 62.06, H 5.56, N 4.83; found: C 62.3, H 5.6, N 4.8.

rac-*Ester* **19cB**: Recrystallized from MeOH. M.p. 191.5°. ΔH = 36.3. Chromatography on a chiral phase (see **19cA**): 2 peaks, t_R 26 and 30 min. ^{1}H-NMR ($CDCl_3$): *Table 4*; additionally: 7.98, 6.92 (2 MeOC_6H_4). Anal. calc. for $C_{30}H_{32}N_2O_{10}$ (580.60): C 62.06, H 5.56, N 4.83; found: C 62.1, H 5.5, N 4.65.

Dimethyl α,α'-Bis[(chloroacetyl)amino]-4,5-dimethoxybenzene-1,2-diacetate (**19d**). To a soln. of crude **18dA**/**18dB** (2.28 g; *ca.* 2:1) in MeOH (60 ml) was added portionwise a soln. of diazomethane in Et_2O (80 ml). After 1 h, the Et_2O was evaporated at r.t. The residue was purified by CC (SiO_2, 100 g, acetone/MeOH/CH_2Cl_2 2.5:2.5:95) to give successively pure **19dA** (400 mg), **19dA**/**19dB** (600 mg), and pure **19dB** (250 mg).

Isomer **19dA**: M.p. 172°. ΔH = 49.3. ^{1}H-NMR ($CDCl_3$): *Table 4*; additionally: 4.09, 4.06 (*AB*, *J* = 14.6, 2 CH_2Cl). Anal. calc. for $C_{18}H_{22}Cl_2N_2O_8$ (465.29): C 46.46, H 4.77, N 6.02; found: C 46.8, H 4.75, N 6.0.

Isomer **19dB**: M.p. 166 and 172°. ^{1}H-NMR ($CDCl_3$): *Table 4*; additionally: 4.08, 4.06 (*AB*, *J* = 15.0, 2 CH_2Cl). Anal. calc. for $C_{18}H_{22}Cl_2N_2O_8$ (465.29): C 46.46, H 4.77, N 6.02; found: C 46.5, H 4.8, N 5.9.

Methyl 4-Amino-1,2,3,4-tetrahydro-6,7-dimethoxy-3-oxoisoquinoline-1-carboxylate (**6a**). The procedure described in [10] was modified as follows: A mixture of **19d** (**A**/**B** *ca.* 1:1; 3.4 g, 7.31 mmol), *N*-piperidinothiourea [28] (3.9 g, 27.1 mmol), AcOH (0.35 ml), and abs. EtOH (150 ml) was refluxed for 4 h under N_2. After evaporation, the residue was dissolved in $CHCl_3$ (300 ml) and the org. phase washed with H_2O (2 × 50 ml). To the combined aq. phase was added conc. NH_4OH soln. The resulting cloudy mixture was extracted twice with CH_2Cl_2. The org. phase was dried (Na_2SO_4) and evaporated at r.t. and the residue recrystallized from AcOEt: **6a** (0.9 g, 44%) as a 8:2 diastereoisomer mixture. Anal. calc. for $C_{13}H_{16}N_2O_5$ (280.29): C 55.71, H 5.75, N 9.99; found: C 55.5, H 5.7, N 10.0.

Major Isomer: ^{1}H-NMR ($CDCl_3$): 7.31 (*s*, H–C(5) or H–C(8)); 6.86 (*s*, H–C(8) or H–C(5)); 6.72 (*d*, *J* = 5, NH); 5.03 (*d*, *J* = 5, H–C(1)); 4.54 (*s*, H–C(4)); 3.92, 3.90, 3.71 (3*s*, 3 MeO).

Minor Isomer: ^{1}H-NMR ($CDCl_3$): 7.01 (*s*, H–C(5) or H–C(8)); 6.83 (*s*, H–C(8) or H–C(5)); 6.6 (br. *d*, NH); 5.11 (*d*, *J* = 3, H–C(1)); 4.24 (*s*, H–C(4)); 3.91, 3.89, 3.80 (3*s*, 3MeO).

Methyl 3-Hydroxy-6,7-dimethoxyisoquinoline-1-carboxylate (**20**). A mixture of **6a** (145 mg, 0.52 mmol) and MeOH (100 ml) was refluxed under N_2 for 1.5 h to give a bright yellow soln. The solvent was evaporated, the residue taken in acetone, and the soln. filtrated through a short column of SiO_2 (7 g): pure **20** (125 mg, 91%) as yellow crystals. An anal. sample was obtained by recrystallization from $CHCl_2$/Et_2O. M.p. 222° (10°/min) ^{1}H-NMR ($CDCl_3$): 8.06 (*s*, H–C(8)); 7.09 (*s*, H–C(4)); 6.78 (*s*, H–C(5)); 3.99, 3.98, 3.95 (3*s*, 3 MeO). ^{13}C-NMR ($CDCl_3$): 164.3 (*C*O_2Me); 158.8 (C(3)); 154.1 (C(6)); 150.3 (C(7)); 140.5 (C(4a)); 136.4 (C(1)); 119.1 (C(8a)); 110.2 (C(4)); 103.1, 102.7 (C(8), C(5)); 55.9, 55.8 (MeO); 52.6 (CO$_2$*Me*). Anal. calc. for $C_{13}H_{13}NO_5$ (280.28): C 59.31, H 4.98, N 5.32; found: C 59.5, H 5.0, N 5.1.

Dimethyl 4,5-Dimethoxy-α,α'-bis[(phenylthioxomethyl)amino]benzene-1,2-diacetate (**21b**). To a soln. of **19bA** (3.1 g, 6 mmol) in dry THF (240 ml) was added *Lawesson*'s reagent (5 g, 12.4 mmol). The mixture was stirred at 60° for 18–24 h and then evaporated. The residue was purified by CC (SiO_2, 300 g, AcOEt/hexane 1:1) to give **21bA** (1.65 g) followed by a mixture of **21bA** and dimethyl α-(benzoylamino)-4,5-dimethoxy-α'-[(phenylthioxomethyl)amino]benzene-1,2-diacetate. A second CC (SiO_2, 100 g) gave an additional crop of **21bA** (0.6 g). Overall yield 68%. M.p. 208°. ^{1}H-NMR ($CDCl_3$): 8.53 (*d*, *J* = 5.5, 2 NH); 7.84, 7.44 (2*m*, 2 PhCS); 6.90 (*s*, 2 arom. H); 6.42 (*d*, *J* = 5.5, 2 CH); 3.86, 3.83 (*s*, 4 MeO). Anal. calc. for $C_{28}H_{28}N_2O_6S_2$ (552.67): C 60.85, H 5.11, N 5.07; found: C 60.8, H 5.2, N 5.0.

Dimethyl 4,5-Dimethoxy-α,α'-bis{[(4-methoxyphenyl)thioxomethyl]amino}benzene-1,2-diacetate (**21c**). Representative procedure for **21cA**: To a soln. of **19cA** (7 g, 12 mmol) in dry THF (400 ml) was added *Lawesson*'s reagent (14 g, 34.6 mmol). The mixture was stirred at 60° for 18–24 h and the solvent evaporated. The residue was purified by CC (SiO_2, 200 g, MeOH/CH_2Cl_2 0:100 to 3:97): **21cA** (5.7 g, 77%).

meso-*Ester* **21cA**: Recrystallized from CH_2Cl_2/Et_2O. M.p. 214° (dec.). ^{1}H-NMR ($CDCl_3$): 8.46 (*d*, *J* = 5, 2 NH); 7.86, 6.88 (2 MeOC_6H_4); 6.89 (*s*, 2 arom. H); 6.40 (*d*, *J* = 5, 2 CH); 3.85, 3.84, 3.82 (3*s*, 6 MeO). Anal. calc. for $C_{30}H_{32}N_2O_8S_2$ (612.57): C 58.81, H 5.26, N 4.57; found: C 58.9, H 5.2, N 4.3.

rac-*Ester* **21cB**: Recrystallized from CH_2Cl_2/Et_2O. ^{1}H-NMR ($CDCl_3$): 8.69 (br. *d*, NH); 7.71, 6.78 (2 MeOC_6H_4); 6.93 (*s*, 2 arom. H); 6.50 (*d*, *J* = 6.5, 2 CH); 3.88, 3.80, 3.77 (3*s*, 6 MeO). Anal. calc. for $C_{30}H_{32}N_2O_8S_2$ (612.57): C 58.81, H 5.26, N 4.57; found: C 58.7, H 5.35, N 4.4.

Preparation of **2'a** *and* **2'b**: *General Procedure. Raney*-Ni (125 g), washed with H_2O (3 ×) and then with MeOH (3 ×), was added to yellow soln. of **21b, c** (either diastereoisomer **A** or **B** or their mixtures, 8–10 mmol) in a mixture of THF (200 ml) and MeOH (200 ml). The mixture was vigorously stirred for 8 min, the Ni filtered off and rinsed with MeOH, and the colorless filtrate evaporated at r.t. The resulting crude **22b, c** was dissolved in $CHCl_3$ (400 ml) and the soln. left at r.t. for 48 h. After evaporation, the residue (crude **23b, c**) was dissolved in MeOH (300 ml) and treated with 1M NaOMe (22 ml). After 24 h at r.t., aq. 1M AcOH (22 ml) was added and the mixture evaporated at r.t. The residue was purified by CC (SiO_2, 25 g, CH_2Cl_2) followed by recrystallization from CH_2Cl_2/Et_2O. Overall yield from **21b, c**: 50–60% of **2'a, b**.

Dimethyl meso-α,α'-*Bis(benzylamino)-4,5-dimethoxybenzene-1,2-diacetate* (**22bA**): crude product obtained from **21bA** (*meso*). ^{1}H-NMR ($CDCl_3$): 7.29 (*m*, 2 Ph); 6.91 (*s*, 2 arom. H); 4.80 (*s*, H–C(α), H–C(α')); 3.86 (*s*, 2 MeO); 3.67 (*s*, 2 CO_2Me); 3.73, 3.63 (*AB*, *J* = 9.5, 2 PhCH_2).

Methyl trans-*2-Benzyl-4-(benzylamino)-1,2,3,4-tetrahydro-6,7-dimethoxy-3-oxoisoquinoline-1-carboxylate* (**23bA**): crude product obtained **22bA** (*meso*). ^{1}H-NMR ($CDCl_3$): 7.25–7.48 (12 H, NH, H–C(5) or H–C(8), Ph); 6.72 (*s*, H–C(8) or H–C(5)); 5.25, 4.32 (*AB*, *J* = 15.0, CH_2–N(2)); 4.90 (*s*, H–C(1)); 4.59 (*s*, H–C(4)); 3.86 (*s*, CH_2NH–C(4), MeO–C(6) or MeO–C(7)); 3.84 (*s*, MeO–C(7) or MeO–C(6)); 3.56 (*s*, CO_2Me).

Methyl trans-*1,2,3,4-Tetrahydro-6,7-dimethoxy-2-(4-methoxybenzyl)-4-[(4-methoxybenzyl)amino]-3-oxoisoquinoline-1-carboxylate* (**23cA**): crude product obtained from **21cA** (*meso*). ^{1}H-NMR ($CDCl_3$): 7.37, 7.17, 6.90, 6.86 (2 MeOC_6H_4); 7.35 (*s*, H–C(5) or H–C(8)); 6.71 (*s*, H–C(8) or H–C(5)); 5.14, 4.29 (*AB*, *J* = 14.8, CH_2–N(2)); 4.88 (*s*, H–C(1)); 4.55 (*s*, H–C(4)); 3.80 (CH_2NH–C(4)); 3.88, 3.84, 3.78 (3*s*, 4 MeO); 3.56 (*s*, CO_2Me).

Methyl cis-*1,2,3,4-Tetrahydro-6,7-dimethoxy-2-(4-methoxybenzyl)-4-[(4-methoxybenzyl)amino]-3-oxoisoquinoline-1-carboxylate* (**23cB**): crude product obtained from **21cB** (*rac*). ^{1}H-NMR ($CDCl_3$): 7.35, 7.19, 6.87 (2 MeOC_6H_4); 6.73 (*s*, H–C(5)); 6.68 (*s*, H–C(8)); 5.30, 4.10 (*AB*, *J* = 14.8, CH_2–N(2)); 4.88 (*s*, H–C(1)); 4.24 (*s*, H–C(4)); 3.96, 3.90 (*AB*, *J* = 12.7, 2H, CH_2NH–C(4)); 3.86, 3.82, 3.79 (3*s*, 4 MeO); 3.60 (*s*, CO_2Me).

*2,9-Dibenzyl-1,2-dihydro-6,7-dimethoxy-4,1-(iminomethano)isoquinoline-3,10(4*H*)-dione* (**2'a**): M.p. 186.5°. IR: 1680 (CO–N). ^{1}H-NMR ($CDCl_3$): *Table 1*; additionally: 7.21, 7.01 (2*m*, 2 Ph); 3.71 (*s*, 2 MeO). ^{1}H-NMR ((D$_6$)DMSO): *Table 2*, additionally: 7.27, 7.09 (2*m*, 2 Ph); 3.69 (*s*, 2 MeO). ^{13}C-NMR ($CDCl_3$): *Table 3*; additionally: 135.1, 128.5, 128.1, 127.7 (arom. C); 55.9 (MeO); 48.4 (CH_2N). ^{13}C-NMR ((D$_6$)DMSO): *Table 3*; additionally: 136.5, 128.3, 127.7, 127.4 (arom. CH); 55.8 (MeO); 47.6 (CH_2N). Anal. calc. for $C_{26}H_{24}N_2O_4$ (428.47): C 72.88, H 5.65, N 6.54; found: C 72.7, H 5.6, N 6.4.

*1,2-Dihydro-6,7-dimethoxy-2,9-bis(4-methoxybenzyl)-4,1-(iminomethano)isoquinoline-3,10(4*H*)-dione* (**2'b**): M.p. 159°. *ΔH* = 42.4. HPLC (*Chiralcel OC*, EtOH, flow rate 30 ml/h; UV detection at 254 nm, α detection at 365 nm) 2 peaks, t_R 21 and 25 min. ^{1}H-NMR ($CDCl_3$): *Table 1*. Additionally: 6.74, 6.75 (2 MeOC_6H_4); 3.77, 3.74 (2*s*, 4 MeO). ^{1}H-NMR ((D$_6$)DMSO): *Table 2*; additionally: 7.02, 6.82 (2 MeOC_6H_4); 3.71, 3.68 (2*s*, 4 MeO). ^{13}C-NMR ((D$_6$)DMSO): *Table 3*; additionally: 158.7, 129.2, 128.4, 113.8 (arom. C); 55.9, 55.1 (MeO); 47.1 (CH_2N). MS: 489.5 ([*M* + 1]$^+$). Anal. calc. for $C_{28}H_{28}N_2O_6$ (488.55): C 68.84, H 5.78, N 5.73; found: C 68.1, H 5.6, N 5.7.

Preparation of **2'c–e**: *General Procedure.* A mixture of **2'g** (see below; 650 mg, 1.5 mmol), K_2CO_3 (1 g, 7.2 mmol), alkyl bromide (6.6 mmol), and DMF (15 ml) was stirred at 80° overnight under N_2. After being cooled, the mixture was diluted with H_2O and the resulting precipitate collected by filtration. The purification varied slightly for **2'c**, **2'd**, and **2'e** (see below).

*6,7-Dibutoxy-2,9-bis(4-butoxybenzyl)-1,2-dihydro-4,1-(iminomethano)isoquinoline-3,10(4*H*)-dione* (**2'c**): Purification by CC (SiO_2, 30 g, CH_2Cl_2/MeOH 100:0 to 98:2) afforded **2'c** (780 mg, 79%). Recrystallization from CH_2Cl_2/pentane. M.p. 93°. *ΔH* = 53.0. ^{1}H-NMR ($CDCl_3$): *Table 1*; additionally: 6.92, 6.75 (2 BuOC_6H_4); 3.87 (*m*, 4 CH_2O); 1.74 (*m*, 4 CH_2Me); 1.45 (*m*, 4 CH_2); 0.97 (*t*, 4 Me). Anal. calc. for $C_{40}H_{52}N_2O_6$ (656.86): C 73.14, H 7.98, N 4.27; found: C 73.0, H 8.0, N 4.3.

*6,7-Bis(hexyloxy)-2,9-bis[4-(hexyloxy)benzyl]-1,2-dihydro-4,1-(iminomethano)isoquinoline-3,10(4*H*)-dione* (**2'd**): Purification by CC (SiO_2, 30 g, CH_2Cl_2/MeOH 100:0 to 98:2) afforded **2'd** (780 mg, 68%). Recrystallization from CH_2Cl_2/pentane. M.p. 84°. *ΔH* = 67.0. ^{1}H-NMR ($CDCl_3$): *Table 1*; additionally: 6.92, 6.75 (2 (Hex)OC_6H_4); 3.84 (*m*, 4 CH_2O); 1.75 (*m*, 4 CH_2Me); 1.36 (*m*, 12 CH_2); 0.91 (*t*, 4 Me). Anal. calc. for $C_{48}H_{68}N_2O_6$ (769.04): C 74.96, H 8.91, N 3.64; found: C 74.9, H 8.8, N 3.5.

*6,7-Bis(dodecyloxy)-2,9-bis[4-(dodecyloxy)benzyl]-1-2-dihydro-4,1-(iminomethano)isoquinoline-3,10(4*H*)-dione* (**2'e**). Recrystallization from dioxane gave a 1st crop (755 mg). CC of the mother liquors (SiO_2, 30 g, benzene/THF 95:5) followed by recrystallization from THF/MeOH gave a 2nd crop (300 mg). Overall yield of **2'e**: 63%. M.p. 93 and 103°. ^{1}H-NMR ((D$_6$)THF): *Table 1*; additionally: 7.09, 6.87 (2 ROC$_6H_4$); 3.98 (*m*,

4 CH_2O); 1.85 (*m*, 4 CH_2Me); 1.43 (*m*, 36 CH_2); 1.02 (*t*, 4 Me). Anal. calc. for $C_{72}H_{116}N_2O_6$ (1105.72): C 78.21, H 10.57, N 2.53; found: C 78.2, H 10.6, N 2.6.

6,7-Bis(dodecyloxy)-1,2-dihydro-2,9-bis(4-methoxybenzyl)-4,1-(iminomethano)isoquinoline-3,10(4H)-dione (**2'f**). A mixture of **2'h** (see below, 690 mg, 1.5 mmol), K_2CO_3 (1 g, 7.2 mmol), 1-bromododecane (0.85 g, 3.4 mmol), and DMF (15 ml) was stirred at 80° overnight under N_2. The mixture was cooled to r.t. and diluted with H_2O and the resulting precipitate collected by filtration. CC (SiO_2, 25 g, CH_2Cl_2 then MeOH/CH_2Cl_2 2:98) followed by recrystallization from CH_2Cl_2/pentane gave pure **2'f** (585 mg). Prep. TLC (SiO_2, MeOH/CH_2Cl_2 2:98) of the mother liquors afforded a 2nd crop (138 mg). Overall yield of **2'f**: 60%. M.p.: 2 transitions; 82°, ΔH = 57.8 (attributed to a crystal → crystal transformation); 115.5°, ΔH = 50.3 (crystal → isotropic liquid). ^{1}H-NMR ($CDCl_3$): *Table 1*; additionally: 6.95, 6.76 (2 $MeOC_6H_4$); 3.80 (*m*, 2 CH_2O); 3.77 (*s*, 2 MeO); 1.75 (*m*, 2 CH_2Me); 1.27 (*m*, 18 CH_2); 0.88 (*t*, 2 Me). Anal. calc. for $C_{50}H_{72}N_2O_6$ (797.13): C 75.34, H 9.11, N 3.51; found: C 75.2, H 9.0, N 3.4.

1,2-Dihydro-6,7-dihydroxy-2,9-bis(4-hydroxybenzyl)-4,1-(iminomethano)isoquinoline-3,10(4H)-dione (**2'g**): To an ice-cold soln. of **2'b** (1.95 g, 4 mmol) in CH_2Cl_2 (20 ml) was added dropwise (30 min) BBr_3 (2.4 ml, 25 mmol) with stirring. Stirring was continued at r.t. for 5 h, and then H_2O (30 ml) was cautiously added. After 45 min, the crystalline precipitate was collected by filtration and dried. Trituration with MeOH afforded **2'g** (1.6 g, 93%). M.p. 277° (dec.; 10°/min). IR: 3400, 3200, 1680, 1640, 1615, 1595, 1510. ^{1}H-NMR ((D$_6$)DMSO): *Table 2*; additionally: 9.37, 9.12 (2 br. *s*, 4 OH); 6.90, 6.65 (2*d*, *J* = 8.5, 2 HOC_6H_4). Anal. calc. for $C_{24}H_{20}N_2O_6$ (432.43): C 66.66, H 4.66, N 6.48; found: C 66.5, H 4.75, N 6.6.

1,2-Dihydro-6,7-dihydroxy-2,9-bis(4-methoxybenzyl)-4,1-(iminomethano)isoquinoline-3,10(4H)-dione (**2'h**): To a mixture of **2'g** (1.3 g, 3 mmol), 1N NaOH (6 ml), and H_2O (15 ml), a soln. of borax (2.3 g, 6 mmol) in H_2O (30 ml) was added. The turbid mixture was stirred at r.t. for 1 h after which time it became homogeneous. *Via* two syringes were simultaneously added Me_2SO_4 (3.5 ml, 37 mmol) and 5N NaOH (3.5 ml) within 30 min. After 2.5 h stirring, the mixture was acidified with 3.6N H_2SO_4 (7.5 ml) and then refluxed for 15 min. After cooling to r.t., the resulting precipitate was collected by filtration, rinsed with H_2O, and air-dried. Trituration with MeOH gave **2'h** (1.22 g, 81%). M.p. 236–238°. ΔH = 51. ^{1}H-NMR ((D$_6$)DMSO): *Table 2*; additionally: 9.12 (br. *s*, 2 OH); 7.02, 6.82 (2*m*, 2 HOC_6H_4); 3.72 (*s*, 2 MeO). Anal. calc. for $C_{26}H_{24}N_2O_6$ (460.49): C 67.82, H 5.25, N 6.08; found: C 67.7, H 5.5, N 5.9.

6,7-Bis(acetyloxy)-1,2-dihydro-2,9-bis(4-methoxybenzyl)-4,1-(iminomethano)isoquinoline-3,10(4H)-dione (**3'b**): A mixture of **2'h** (3 g, 6.5 mmol) and Ac_2O was refluxed for 2 h. Excess Ac_2O was evaporated and the residue recrystallized from CH_2Cl_2/Et_2O to give **3'b** (2.9 g, 82%). M.p. 135°. ΔH = 41.4. ^{1}H-NMR ($CDCl_3$): *Table 1*; additionally: 6.96, 6.80 (2 $MeOC_6H_4$); 3.79 (*s*, 2 MeO); 2.26 (*s*, 2 MeCO). Anal. calc. for $C_{30}H_{28}N_2O_8$ (544.56): C 66.17, H 5.18, N 5.14; found: C 66.0, H 5.1, N 5.0.

Preparation of **3'a, c–e**: *General Procedure*. To a soln. of **2'h** (230 mg, 0.5 mmol) in pyridine (2 ml) was added excess acyl chloride (for **3'a, e**) or anhydride (for **3'c, d**). The mixture was stirred at r.t. overnight, diluted with H_2O and then extracted with CH_2Cl_2. The org. phase was washed with dil. HCl soln. (3×), and H_2O, dried, and evaporated. The residue was purified by TLC (SiO_2, 2 mm) or CC (SiO_2, 6 g/200 mg of crude product) with CH_2Cl_2/MeOH/acetone 97:1.5:1.5 as the eluent to give pure **3'**. Anal. samples were obtained by recrystallization.

6,7-Bis(benzoyloxy)-1,2-dihydro-2,9-bis(4-methoxybenzyl)-4,1-(iminomethano)isoquinoline-3,10(4H)-dione (**3'a**): Yield 89%. Recrystallized from MeOH/Et_2O. M.p. 144 and 146°. ΔH = 34.4. ^{1}H-NMR ($CDCl_3$): *Table 1*; additionally: 8.01, 7.55, 7.37 (2 PhCO); 7.01, 6.84 (2 $MeOC_6H_4$); 3.78 (*s*, 2 MeO). Anal. calc. for $C_{40}H_{32}N_2O_8$ (668.70): C 71.85, H 4.82, N 4.18; found: C 71.9, H 4.8, N 4.15.

6,7-Bis(butanoyloxy)-1,2-dihydro-2,9-bis(4-methoxybenzyl)-4,1-(iminomethano)isoquinoline-3,10(4H)-dione (**3'c**): Yield 87%. Recrystallized from CH_2Cl_2/Et_2O. M.p. 111°. ΔH = 44.6. HPLC (*Chiralcel OC*, **2'b** for conditions): 2 peaks, t_R 15 and 18 min. ^{1}H-NMR ($CDCl_3$): *Table 1*; additionally: 6.95, 6.81 (2 $MeOC_6H_4$); 3.78 (*s*, 2 MeO); 2.48 (*t*, 2 CH_2CO); 1.75 (*m* 2 CH_2); 1.02 (*t*, 2 Me). Anal. calc. for $C_{34}H_{36}N_2O_8$ (600.67): C 67.99, H 6.04, N 4.66; found: C 67.8, H 6.1, N 4.7.

6,7-Bis(hexanoyloxy)-1,2-dihydro-2,9-bis(4-methoxybenzyl)-4,1-(iminomethano)isoquinoline-3,10(4H)-dione (**3'd**): Yield 84%. Recrystallized from MeOH. M.p. 102–104°. ΔH = 40. ^{1}H-NMR ($CDCl_3$): *Table 1*; additionally: 6.95, 6.81 (2 $MeOC_6H_4$); 3.79 (*s*, 2 MeO); 2.49 (*t*, 2 CH_2CO); 1.71 (*m*, 2 CH_2Me); 1.37 (*m*, 4 CH_2); 0.96 (*t*, 2 Me). Anal. calc. for $C_{38}H_{44}N_2O_8$ (656.78): C 69.49, H 6.75, N 4.27; found: C 69.5, H 6.7, N 4.3.

6,7-Bis(dodecanoyloxy)-1,2-dihydro-2,9-bis(4-methoxybenzyl)-4,1-(iminomethano)isoquinoline-3,10(4H)-dione (**3'e**): Yield 90%. Recrystallized from Et_2O/pentane. M.p. 77°. ^{1}H-NMR ($CDCl_3$): *Table 1*; additionally: 6.95, 6.81 (2 $MeOC_6H_4$); 3.78 (*s*, 2 MeO); 2.49 (*t*, 2 CH_2CO); 1.70 (*m*, 2 CH_2Me); 1.27 (*m*, 16 CH_2); 0.89 (*t*, 2 Me). Anal. calc. for $C_{50}H_{68}N_2O_8$ (825.10): C 72.78, H 8.31, N 3.40; found: C 72.7, H 8.4, N 3.4.

6,7-Bis(benzoyloxy)-1,2-dihydro-4,1-(iminomethano)isoquinoline-3,10(4H)-dione (**3a**). To a stirred soln. of **3'a** (200 mg, 0.3 mmol) in MeCN (4 ml) was added dropwise (30 min) a soln. of CAN (1 g, 1.8 mmol) in H_2O (4 ml). Stirring was continued for 2.5 h, and 1N NaOH (3 ml) was added. The resulting precipitate was filtered and rinsed with MeCN and the filtrate evaporated at r.t. CC (SiO_2, 25 g, $CHCl_3$/MeOH/H_2O 10:5:1) followed by recrystallization from MeOH/Et_2O gave **3a** (56 mg, 44%). M.p. 234° (dec.; 10°/min). ^{1}H-NMR ((D$_6$)DMSO): *Table 2*; additionally: 7.94, 7.62, 7.47 (2 PhCO). ^{13}C-NMR ((D$_6$)DMSO): *Table 3*; additionally: 163.5 (COO); 134.2, 129.5, 128.9, 127.8 (Ph). MS: 429 ($[M + 1]^+$). Anal. calc. for $C_{24}H_{16}N_2O_6 \cdot 0.5\ CH_3OH$ (444.42): C 66.21, H 4.08, N 6.30; found: C 66.5, H 3.8, N 6.3.

6,7-Diacetoxy-1,2-dihydro-4,1-(iminomethano)isoquinoline-3,10(4H)-dione (**3b**). To a stirred soln. of **3'b** (720 mg, 1.3 mmol) in MeCN (12 ml) was added dropwise (15 min) a soln. of CAN (2.9 g, 5.3 mmol) in H_2O (12 ml). Stirring was continued for 15–30 min. The soln. was concentrated to *ca.* 1/2 the volume at r.t., and CH_2Cl_2 (10 ml) was added to give a crystalline precipitate of pure **3b** (230 mg, 58%). M.p. 256° (dec.; 10°/min). ^{1}H-NMR ((D$_6$)DMSO): *Table 2*; additionally: 2.28 (*s*, 2 MeCO). Anal. calc. for $C_{14}H_{12}N_2O_6$ (304.26): C 55.27, H 3.98, N 9.21; found: C 55.4, H 3.9, N 9.3.

6,7-Bis(butanoyloxy)-1,2-dihydro-4,1-(iminomethano)isoquinoline-3,10(4H)-dione (**3c**). As described for **3b**, from **3'c** (600 mg, 1 mmol). After the reaction, MeCN was evaporated at r.t. and CH_2Cl_2/Et_2O/pentane added. The resulting precipitate was collected by filtration, washed with pentane (320 mg), and discolored with activated carbon (*Norit*) in hot i-PrOH. Recrystallization from i-PrOH afforded pure **3c** (150 mg, 41%). M.p. 208–211°. ΔH = 40. ^{1}H-NMR ((D$_6$)DMSO): *Table 2*; additionally: 2.55 (*t*, 2 CH_2CO); 1.62 (*dt*, 2 CH_2); 0.95 (*t*, 2 Me). Anal. calc. for $C_{18}H_{20}N_2O_6$ (360.37): C 59.99, H 5.59, N 7.77; found: C 59.7, H 5.6, N 7.6.

Resolution of **3c** *by HPLC. Prochrom* column: length 23 cm and diameter 6 cm; stationary phase: *Chiralcel OC* (500 g); eluent: heptane/EtOH 1:1; flow rate 50 ml/min; UV detection at 254 nm. Three charges (800 mg each) of (±)-**3c** gave (+)-**3c** (826 mg, 69%; $[\alpha]_D^{20} = +76 \pm 2$ (c = 0.5, MeOH), e.e. ≥ 98%) and (−)-**3c** (818 mg, 68%; $[\alpha]_D^{20} = -77 \pm 2$ (c = 0.5, MeOH), e.e. ≥ 98%). Recrystallized from i-PrOH. M.p. 173.5°. ΔH = 32.2.

6,7-Bis(hexanoyloxy)-1,2-dihydro-4,1-(iminomethano)isoquinoline-3,10(4H)-dione (**3d**). As described for **3b**, from **3'd** (328 mg, 0.5 mmol). Purification by CC (SiO_2, 20 g, CH_2Cl_2 and then CH_2Cl_2/MeOH 80:20) followed by TLC (SiO_2, CH_2Cl_2/MeOH/acetone 80:10:10) gave **3d** (124 mg, 59%). M.p. 148°. ΔH = 36. ^{1}H-NMR ($CDCl_3$): *Table 1*; additionally: 7.28 (*m*, NH); 2.53 (*t*, 2 CH_2CO); 1.72 (*m*, 2 CH_2); 1.37 (*m*, 4 CH_2); 0.93 (*t*, 2 Me). ^{1}H-NMR ((D$_6$)DMSO): *Table 2*; additionally: 2.56 (*t*, 2 CH_2CO); 1.60 (*m*, 2 CH_2); 1.32 (*m*, 4 CH_2); 0.87 (*t*, 2 Me). Anal. calc. for $C_{22}H_{28}N_2O_6$ (416.47): C 63.45, H 6.78, N 6.73; found: C 63.6, H 6.9, N 6.8.

6,7-Bis(dodecanoyloxy)-1,2-dihydro-4,1-(iminomethano)isoquinoline-3,10(4H)-dione (**3e**). As described for **3b**, from **3'e** (165 mg, 0.2 mmol). Purification by 2 successive TLC (SiO_2, 1 mm, CH_2Cl_2/MeOH/acetone 80:10:10) gave **3e** (20 mg, 17%). M.p. 157.5° (160.5°, 2nd heating). ΔH = 50. ^{1}H-NMR ($CDCl_3$): *Table 1*; additionally: 7.11 (br. *d*, 2 NH); 2.52 (*t*, 2 CH_2CO); 1.71 (*m*, 2 CH_2); 1.27 (*m*, 16 CH_2); 0.88 (*t*, 2 Me). ^{1}H-NMR ((D$_6$)DMSO): *Table 2*; additionally: 2.55 (*t*, 2 CH_2CO); 1.56 (*m*, 2 CH_2); 1.23 (*m*, 16 CH_2); 0.84 (*t*, 2 Me). Anal. calc. for $C_{34}H_{52}N_2O_6 \cdot 0.5\ CH_3OH$ (600.82): C 68.97, H 9.06, N 4.66; found: C 68.7, H 8.9, N 4.35.

Dimethyl (7E,8E)-(2,5-Dibenzyl-3,6-dioxo-2,5-diazabicyclo[2.2.2]octane-7,8-diylidene)diacetate (**4'a**). To a soln. of **2'a** (107 mg, 0.25 mmol) in MeCN (4 ml) was added dropwise (30 min) a soln. of CAN (1.64 g, 3 mmol) in H_2O (4 ml) with stirring. The mixture was left at r.t. for 1 h. MeCN (10 ml) and then a soln. of $NaHCO_3$ (0.84 g, 10 mmol) in H_2O (4 ml) were added. The resulting precipitate was filtered off and rinsed with MeCN (3 × 10 ml) and the filtrate evaporated. The residue was dissolved in CH_2Cl_2 and the org. phase washed with H_2O, dried (Na_2SO_4), and evaporated: **4'a** (48 mg, 42%). Recrystallization from CH_2Cl_2/Et_2O. M.p. 143–145°. ^{1}H-NMR ($CDCl_3$): *Table 1*; additionally: 7.32, 7.12 (2*m*, 2 Ph); 3.69 (*s*, 2 CO_2Me). ^{1}H-NMR ((D$_6$)DMSO): *Table 2*; additionally: 7.28, 7.10 (2*m*, 2 Ph); 3.57 (*s*, 2 CO_2Me). ^{13}C-NMR ($CDCl_3$): *Table 3*; additionally: 134.6, 128.9, 128.2, 127.9 (arom. C); 51.7 (MeO); 48.4 (CH_2N). ^{13}C-NMR ((D$_6$)DMSO): *Table 3*; additionally: 136.2, 128.4, 127.4 (arom. C); 51.5 (MeO); 47.5 (CH_2N). Anal. calc. for $C_{26}H_{24}N_2O_6$ (460.49): C 67.82, H 5.25, N 6.08; found: C 67.85, H 5.2, N 6.1.

Dimethyl (7E,8E)-(3,6-Dioxo-2,5-diazabicyclo[2.2.2]octane-7,8-diylidene)diacetate (**4b**). To a stirred soln. of **2'b** (490 mg, 1 mmol) in MeCN (20 ml) was added dropwise (30 min) a soln. of CAN (6.58 g, 12 mmol) in H_2O (20 ml). Stirring was continued for 2 h, and then a soln. of Na_2CO_3 (1.5 g, 14 mmol) in H_2O (20 ml) was added. The resulting precipitate was filtered off, rinsed with MeCN/H_2O 1:1 (3 × 25 ml), and the filtrate evaporated at r.t. CC (SiO_2, 75 g, $CHCl_3$/MeOH/H_2O 10:5:1) of the residue (9.4 g) afforded nearly pure **4b** (120 mg) in the first fractions. A second CC (SiO_2, 2 g, CH_2Cl_2/MeOH/acetone 90:5:5) gave pure **4b** (95 mg, 33%). Recrystallization from EtOH. M.p. 260° (dec; 5°/min). IR: 3240, 3020, 1730, 1700, 1430. ^{1}H-NMR ((D$_6$)DMSO): *Table 2*; additionally: 3.57 (*s*, 2 CO_2Me). ^{13}C-NMR ((D$_6$)DMSO): *Table 3*; additionally: 51.5 (MeO). MS: 281

([M + 1]$^+$), 249 ([M + 1 − MeOH]$^+$). Anal. calc. for $C_{12}H_{12}N_2O_6$ (280.24): C 51.43, H 4.32, N 10.00, O 34.26; found: C 51.4, H 4.3, N 9.9, O 34.2.

*Dibutyl (7*E*,8*E*)-(3,6-Dioxo-2,5-diazabicyclo[2.2.2]octane-7,8-diylidene)diacetate* (**4c**). To a stirred soln. of **2'c** (650 mg, 1 mmol) in MeCN (10 ml) was added dropwise (30 min) a soln. of CAN (5.5 g, 10 mmol) in H_2O (10 ml). Stirring was continued for 2.5 h and then the mixture extracted with CH_2Cl_2. CC (SiO_2, 40 g, $CHCl_3$/MeOH/H_2O 10:5:1) of the residue followed by TLC (SiO_2, 2 mm, $CHCl_3$/MeOH/acetone 90:5:5) afforded pure **4c** (85 mg, 23%). M.p. 173°. ΔH 33.0. ^{1}H-NMR ($CDCl_3$): *Table 1*; additionally: 4.07 (*t*, 2 CH_2O); 1.63 (*m*, 2 CH_2Me); 1.38 (*m*, 2 CH_2); 0.93 (*t*, 2 Me). Anal. calc. for $C_{18}H_{24}N_2O_6$ (364.40): C 59.33, H 6.64, N 7.69; found: C 59.3, H 6.6, N 7.7.

*Didodecyl (7*E*,8*E*)-(3,6-Dioxo-2,5-diazabicyclo[2.2.2]octane-7,8-diylidene)diacetate* (**4e**). To a stirred soln. of **2'f** (318 mg, 0.4 mmol) in MeCN/THF 1:1 (8 ml) was added dropwise (30 min) a soln. of CAN (1.3 g, 2.4 mmol) in H_2O (5 ml). Stirring was continued for 2 h, and 1M Na_2CO_3 (2.4 ml) was added. The resulting precipitate was filtered off and rinsed with MeCN and THF and the filtrate evaporated at r.t. TLC (SiO_2, 2 mm, CH_2Cl_2/MeOH/acetone 8:1:1) followed by CC (SiO_2, 5 g, CH_2Cl_2/MeOH/acetone 90:5:5) and recrystallization from MeOH/Et_2O afforded **4e** (30 mg, 13%). M.p.: 2 transitions; 85°, ΔH = 36.3; 125°, ΔH = 5.0. ^{1}H-NMR ($CDCl_3$): *Table 1*; additionally: 4.06 (*t*, 2 CH_2O); 1.64 (*m*, 2 CH_2Me); 1.26 (*m*, 18 CH_2); 0.88 (*t*, 2Me). Anal. calc. for $C_{34}H_{56}N_2O_6$ (588.83): C 69.35, H 9.59, N 4.76; found: C 69.2, H 9.6, N 4.7.

*Dimethyl (7*Z*,8*Z*)-(2,5-Dibenzyl-3,6-dioxo-2,5-diazabicyclo[2.2.2]octane-7,8-diylidene)diacetate* (**24'**). A refluxed soln. of **4'a** (83 mg, 0.18 mmol) and I_2 (8 mg) in toluene (15 ml) was irradiated for 2.5 h with a 200-W lamp. The solvent was evaporated and the residue purified by TLC (SiO_2, 2 mm, AcOEt/hexane 1:1, 2 elutions). Pure **24'** (70 mg, 84%) was obtained from the lower fluorescent band. Recrystallization from MeOH. M.p. 175°. ΔH = 43.5. ^{1}H-NMR ($CDCl_3$): *Table 1*; additionally: 7.27, 7.18 (2*m*, 2 Ph); 3.67 (*s*, 2 CO_2Me). ^{13}C-NMR ($CDCl_3$): *Table 3*; additionally: 135.2, 128.5, 128.4, 128.0 (arom. C); 51.9 (MeO); 48.7 (CH_2N). Anal. calc. for $C_{26}H_{24}N_2O_6$ (460.49): C 67.82, H 5.25, N 6.08; found: C 67.7, H 5.2, N 6.1.

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