113. Catalytic Cyclophanes

Part XI [1]

A Flavo-thiazolio-cyclophane as a Biomimetic Catalyst for the Preparative-Scale Electro-oxidation of Aromatic Aldehydes to Methyl Esters[1])

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Flavo-thiazolio-cyclophane **6** was prepared on a gram scale by an 18-step synthesis (*Schemes 3* and *4*). This pathway involved the very efficient preparation of bromo-cyclophane **32** (37% yield over 13 steps), which can be readily modified to create various multiply functionalized receptors. This bromide **32** was subsequently converted into the corresponding boronic acid and connected to the 7-bromoflavin **10** (*Scheme 2*) *via Suzuki* coupling to give flavo-cyclophane **36**. The thiazolium unit was then introduced after quaternization of the tertiary amino groups of **36**. Flavo-thiazolio-cyclophane **6**, with both prosthetic groups attached in proximity to the well-defined cyclophane binding site, is a functional model for the enzyme pyruvate oxidase. In basic methanolic solution, **6** catalyzes the oxidation of aromatic aldehydes to their corresponding methyl esters. Cyclophane **6** shows saturation kinetics, and the turnover number calculated for the oxidation of naphthalene-2-carbaldehyde to methyl naphthalene-2-carboxylate ($k_{cat} = 0.22\ s^{-1}$) is one of the highest reported for an artificial enzyme. Control experiments showed that the catalytic advantages of **6** result from the macrocyclic binding and reaction site as well as from the covalent attachment of both cofactors to this site. The catalytic cycle is completed by electrochemical re-oxidation of the reduced flavin moiety at a low working electrode potential (−0.3 V *vs.* Ag/AgCl), and up to *ca.* 100 catalytic cycles can be performed on a preparative scale. The intramolecular nature of the electron transfer from the active aldehyde intermediate to the flavin is particularly conducive to the oxidation of unreactive aldehydes.

1. Introduction. – As biological catalysts, enzymes accelerate reactions by substrate binding and transition-state stabilization without altering the position of chemical equilibrium [2]. Coenzymes are low-molecular, non-peptidic molecules assisting in chemical transformations that cannot be performed by the functional groups provided by the polypeptide apoenzyme [3]. Thiamine diphosphate (ThDP, *Fig. 1, a*) is a coenzyme found in various enzymes of carbohydrate metabolite pathways [4]. ThDP-Dependent reactions include α-keto transfers (as in transketolase), non-oxidative decarboxylations of α-keto acids (as in pyruvate decarboxylase), and oxidative decarboxylations of α-keto acids (as in pyruvate oxidase). The X-ray crystal structures of transketolase [5], pyruvate decarboxylase [6], and pyruvate oxidase [7] show that the coenzyme ThDP is bound in a reactive conformation with N–C(4′) juxtaposed to C(2) (the so-called *V*-conformation) and with N(1′) interacting with a glutamate residue of the protein (*Fig. 1, b*). The role of

[1]) For a preliminary communication of parts of this work, see [1].

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the aminopyrimidine ring in the catalysis has been widely studied using ThDP analogs [8], site-directed mutagenesis [9], and computational methods [10]. While the aminopyrimidine ring is responsible for large rate accelerations in enzymatic catalysis, simple thiazolium ions behave as functional analogs of ThDP in the absence of enzyme, with their key feature being the acidity of H–C(2) [11].

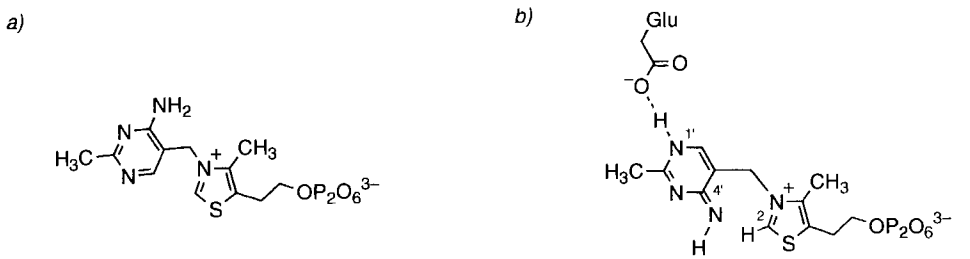
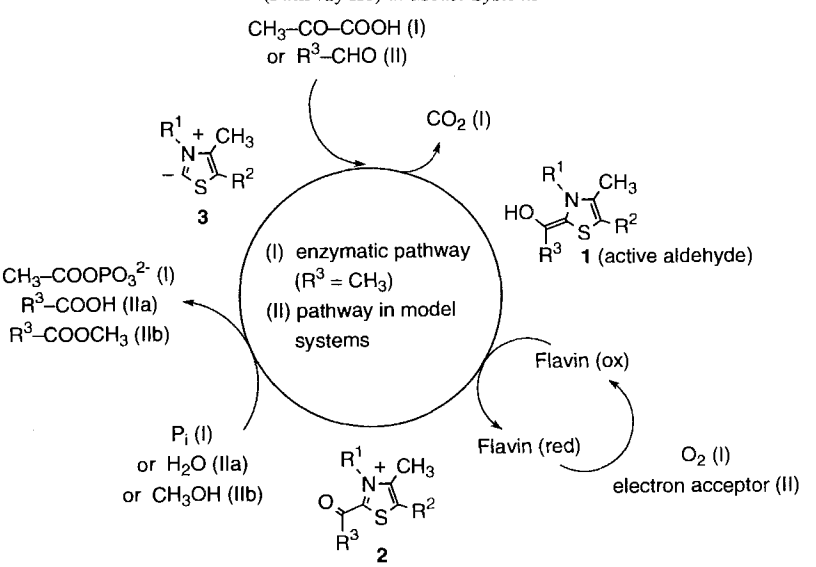


Fig. 1. a) *Thiamine diphosphate (ThDP)*, b) *the stabilized tautomeric form of ThDP as found in ThDP-dependent enzymes* [6b]

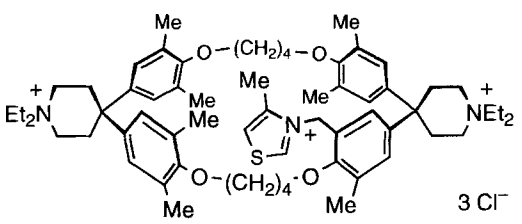
The ThDP-dependent enzyme, pyruvate oxidase, uses flavin adenine dinucleotide (FAD) as a second coenzyme and catalyzes the reaction from pyruvate to acetyl phosphate [7] [12] (*Scheme 1, Pathway I*), the latter being an important energy-rich metabolite for the production of ATP in lactic acid bacteria [13]. ThDP-Mediated decarboxylation of pyruvate generates an active aldehyde, **1**, which is oxidized by FAD. The resulting reduced flavin ($FADH_2$) is re-oxidized by dioxygen. Finally, the 2-acetylthiazolium intermediate **2**, produced by oxidation of the active aldehyde, reacts with inorganic phosphate (P_i) to give acetyl phosphate under regeneration of the thiazolium ylide **3**.

Scheme 1. *Catalytic Cycles for the Conversion of Pyruvate to Acetyl Phosphate Catalyzed by Pyruvate Oxidase* (Pathway I) *and for the Oxidation of an Aldehyde to a Carboxylic Acid* (Pathway IIa) *or Methyl Ester* (Pathway IIb) *in Model Systems*



In a similar reaction sequence, aldehydes are oxidized in either H_2O or alcohols to carboxylic acids or esters, respectively (*Scheme 1*, *Pathways IIa* and *IIb*). These conversions have been catalyzed by simple thiazolium ions [14], thiazolium micelles [15], and thiazolio-cyclodextrins [16] in the presence of various oxidizing agents such as nitrobenzene [14a–c], ferricyanide [16], disulfides [14e], and flavins [14d] [15].

In earlier work, we reported the catalytic use of thiazolio-cyclophane **4**, which contains a binding site for aromatic substrates [17]. In basic methanolic solution, a bound aromatic aldehyde reacted to give the active aldehyde which was subsequently oxidized, *via* transfer of a hydride equivalent to the added flavin derivative **5**, forming an acylthiazolium intermediate. This intermediate rapidly reacted with the solvent to afford a methyl ester, while the thiazolium ylide was regenerated. The resultant dihydroflavin was reoxidized electrochemically at a low anodic potential (−0.3 V *vs.* AgCl). This combination of biomimetic chemistry with electrocatalysis [18] provided an efficient one-pot preparation of aromatic esters from aldehydes under mild conditions. However, CPK modeling studies indicated that the active aldehyde intermediate encapsulated in the cavity was not readily accessible for intermolecular oxidation by an external flavin molecule. We, therefore, felt that this electron-transfer step would be facilitated by the covalent incorporation of the flavin moiety into the catalytic receptor. Efficient trapping of the active aldehyde by the oxidizing agent would enhance the reaction rate and suppress side reactions such as the benzoin condensation [17].



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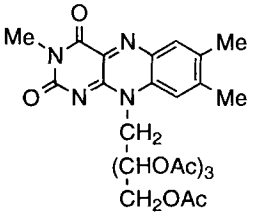

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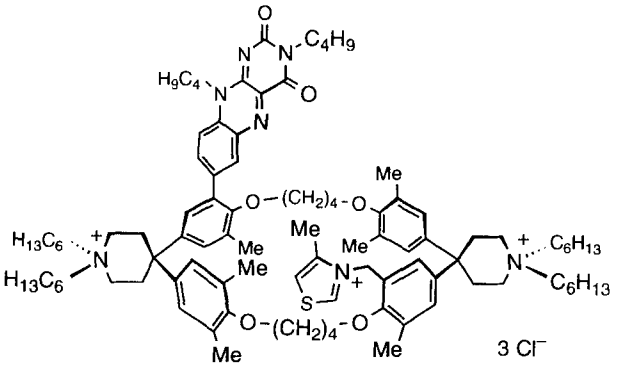
In this paper, we describe the synthesis and catalytic properties of cyclophane **6**, the first synthetic functional model of pyruvate oxidase that combines a well-defined binding site [19] with both flavin and thiazolium prosthetic groups. The catalytic ability of flavo-thiazolio-cyclophane **6** is compared to our previously published system {**4** + **5**} [17], the non-macrocyclic bis(coenzyme) derivative **7**, and the simple system {*N*-benzylthiazolium ion **8** + flavin **9**}.

2. Results and Discussion. – 2.1. *Synthesis.* The preparation of **6** was accomplished by an 18-step route, which readily afforded gram quantities. In the key-step of the synthesis, a 7-bromoflavin was attached to a cyclophane-(boronic acid) *via* a *Suzuki* cross-coupling reaction [20], which provides a convenient and general synthesis of 7-arylflavins. The thiazolium unit was introduced into the resulting flavo-cyclophane receptor after quaternization of its tertiary amino groups.

2.1.1. *Synthesis of Flavin Derivatives with Substituents at C(7).* 7-Bromoflavin **10** was synthesized according to the method of *Yoneda et al.* [21]. Treatment of uracil derivative **11** [21a] with excess Br_2, followed by reduction of crude dibrominated material with



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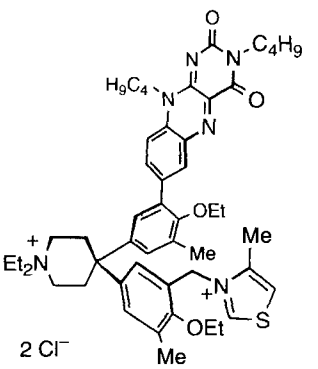

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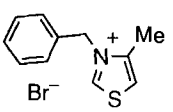

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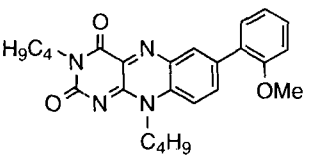

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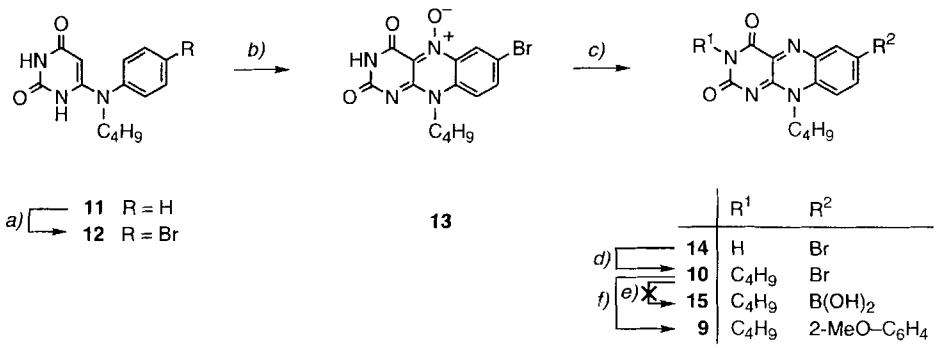
Na_2SO_3 in aqueous AcOH gave the selectively monobrominated compound **12**, which underwent a nitrosative cyclization to afford flavin-N^5-oxide **13** (*Scheme 2*). The reduction of **13** to flavin **14** proved to be surprisingly difficult: while the reaction was incomplete in aqueous $Na_2S_2O_4$ [21a], reduction with the *Vilsmeier* reagent ($DMF/POCl_3$) [21c] led to partial formation of the corresponding 7-bromo-8-chloroflavin. The reduction was finally achieved by thermal deoxygenation in DMF [21b], and the crude product **14** was alkylated with 1-bromobutane to afford flavin **10**.

Scheme 2. *Synthesis of 7-Arylflavin* **9**

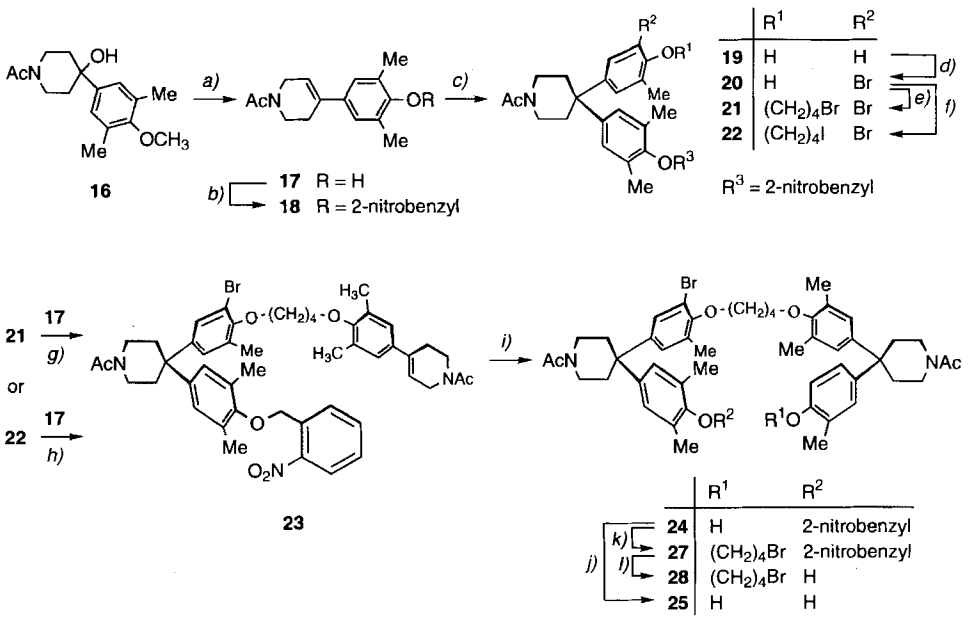


a) Br_2, EtOH, r.t., 30 min, then Na_2SO_3, aq. AcOH, 81%. *b*) $NaNO_2$, AcOH, r.t., 2 h, 88%. *c*) DMF, reflux, 5 h. *d*) BuBr, Cs_2CO_3, DMF, r.t., 16 h, 80% (from **13**). *e*) BuLi or *t*-BuLi, THF, −78°, then $(MeO)_3B$, then H^+/H_2O, 0%. *f*) 2-MeO-$C_6H_4B(OH)_2$, $[PdCl_2(PPh_3)_2]$, aq. Na_2CO_3, benzene EtOH, reflux, 16 h, 77%.

We then investigated the potential of 7-bromoflavin **10** as a precursor for 7-arylflavins *via Suzuki* cross-coupling reaction [20]. Attempts to convert **10** into flavin-7-(boronic acid) **15** were unsuccessful, but **10** could be smoothly coupled to 2-methoxybenzene-1-(boronic acid) to give **9** in 77% yield. The debromination of **10**, which may occur as a side reaction, was completely suppressed by exclusion of oxygen. Therefore, 7-arylflavins can be easily prepared *via Suzuki* coupling.

2.1.2. *Synthesis of Flavo-thiazolio-cyclophane* **6**. The synthesis of cyclophane **6** started with the readily available tertiary alcohol **16** [17]. Treatment of **16** with excess BBr_3 effected both dehydration and ether cleavage [22] to give phenol **17**, which was converted to its 2-nitrobenzyl ether **18** (*Scheme 3*). Addition of 2-methylphenol to the C=C bond of **18** in the presence of $BF_3 \cdot OEt_2$ afforded **19**. Contrary to an unsubstituted benzyl-ether protective group [22a], the 2-nitrobenzyl ether was stable under these *Friedel-Crafts* conditions. Phenol **19** was brominated in the *ortho*-position yielding **20**, which was alkylated with 1,4-dibromobutane or 1,4-diiodobutane in the presence of radical inhibitor 2,6-di(*tert*-butyl)-4-methylphenol (BHT) to afford alkyl bromide **21** and iodide **22**, respectively. A *Williamson* reaction between another equiv. of phenol **17** and alkyl halide **21** or **22** then led to **23**. In both cases, the unexpected slow cleavage of the 2-nitrobenzyl ether was observed as a side reaction. With the more reactive iodide **22**, however, since the reaction time was shorter, a significantly higher yield of the desired

Scheme 3. *Synthesis of Cyclization Precursors* **25** *and* **28**

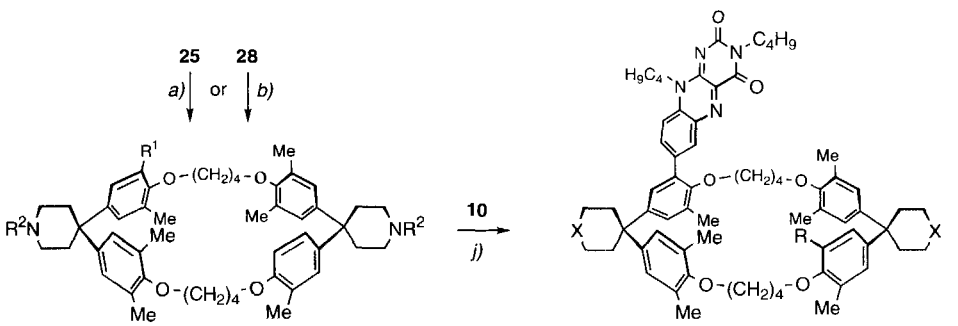


a) BBr_3, CH_2Cl_2, reflux, 3 h, 93%. *b*) 2-Nitrobenzyl chloride, K_2CO_3, MeCN, reflux, 5 h, 98%. *c*) 2-Methylphenol, $BF_3 \cdot OEt_2$, CH_2Cl_2, 50°, 24 h, 93%. *d*) Br_2, CH_2Cl_2, 0°, 20 min, 92%. *e*) 1,4-Dibromobutane, K_2CO_3, BHT, acetone, reflux, 2 h, 93%. *f*) 1,4-Diiodobutane, K_2CO_3, BHT, acetone, reflux, 4 h, 91%. *g*) Cs_2CO_3, acetone, 40°, 24 h, 60%. *h*) Cs_2CO_3, acetone, 40°, 6 h, 80%. *i*) 2-Methylphenol, $BF_3 \cdot OEt_2$, CH_2Cl_2, 50°, 24 h, 96%. *j*) *hv*, THF, r.t., 3 d, 87%. *k*) 1,4-Dibromobutane, K_2CO_3, MeCN, reflux, 24 h, 91%. *l*) *hv*, BHT, THF, r.t., 20 h, 96%.

product was achieved. The fourth aromatic ring of cyclophane precursor **24** was introduced by a *Friedel-Crafts* alkylation reaction of **23** with 2-methylphenol.

Dihydroxy compound **25** was obtained by photolytic debenzylation of **24** [23]. The 2-nitrobenzyl ether in **24** could also be cleaved reductively with Pd-C/$HCOONH_4$ in THF [24] (the same reaction in MeOH, however, also led to debromination) or under basic conditions in DMF (K_2CO_3, 100°, 5 min), but not with $BF_3 \cdot OEt_2$/EtSH [25] or $BF_3 \cdot OEt_2/Me_2S$ [26]. Compound **25** was reacted with 1,4-dibromobutane to give bromo-cyclophane **26** (*Scheme 4*, *a*). Since high dilution is required for a satisfactory yield (41% at $c = 1$ mM compared to 21% at $c = 10$ mM), the synthesis of large amounts of **26** is rather cumbersome. Therefore, an alternative route to cyclophane **26** involving an intramolecular rather than a bimolecular macrocyclization was expected to be more convenient. To that end, phenol **24** was alkylated with 1,4-dibromobutane to afford **27**, which was photolytically cleaved without breakage of the sensitive C–Br bonds to give phenol **28** (*Scheme 3*, *k* and *l*). Radical inhibitor BHT suppressed the accumulation of various decomposition products of 2-nitrosobenzaldehyde resulting from the cleavage of the 2-nitrobenzyl-ether protective group [23]; since these compounds strongly absorb at $\lambda = 300-350$ nm, their presence prevents the desired photoreaction from completion. The ω-bromoalkylated phenol **28** underwent an intramolecular macrocyclization to afford **26** in an excellent 83% yield (*Scheme 4*, *b*). In this reaction, **28** was slowly added

Scheme 4. *Synthesis of Flavo-thiazolio-cyclophane* **6**



		R^1	R^2
	26	Br	Ac
c)	**29**	Br	Et
e) d) ✗	**30**	$B(OH)_2$	Et
	33	Br	H
f)	**34**	Br	COC_5H_{11}
h) g)	**32**	Br	C_6H_{13}
i)	**35**	$B(OH)_2$	C_6H_{13}

		R	X
	36	H	N–C_6H_{13}
k)	**31**	H	NEt
	37	H	$N^+(C_6H_{13})_2Cl^-$
l)	**38**	CH_2Cl	$N^+(C_6H_{13})_2Cl^-$
m)	**6**	CH_2–$(C_4H_5NS)^+Cl^-$	$N^+(C_6H_{13})_2Cl^-$

a) 1,4-Dibromobutane, Cs_2CO_3, MeCN, reflux, 48 h, 41%. *b*) Cs_2CO_3, MeCN, reflux, 24 h, 83%. *c*) DIBAL-H, CH_2Cl_2, r.t., 16 h, 87%. *d*) BuLi, TMEDA, THF, −78°, then $(MeO)_3B$, then H^+/H_2O, 0%. *e*) KOH, $MeOCH_2CH_2OH$, reflux, 8 h, 95%. *f*) $C_5H_{11}COCl$, Et_3N, THF, r.t., 30 min, 95%. *g*) $BH_3 \cdot THF$, THF, reflux, 24 h, 93%. *h*) $C_5H_{11}COOH$, $NaBH_4$, THF, 55°, 16 h, 72%. *i*) BuLi, TMEDA, THF, −78°, 30 min, then $(MeO)_3B$, then H^+/H_2O. *j*) $[PdCl_2(PPh_3)_2]$, aq. Na_2CO_3, benzene EtOH, reflux, 20 h, 56% (from **32**). *k*) $C_6H_{13}I$, MeCN, reflux, 4 h, then ion exchange (Cl^-), 88%. *l*) Aq. CH_2O, HCl (*g*), AcOH/conc. aq. HCl, 40°, 2 h, 75%. *m*) 4-Methylthiazole, 80°, 16 h, 67%.

to a suspension of Cs_2CO_3 in MeCN in order to keep its concentration in solution low and, therefore, minimize polymerization.

The amide groups in **26** were then reduced with DIBAL-H [27] to afford the bis(tertiary amine) **29** (*Scheme 4*). Attempts to convert bromide **29** into boronic acid **30** as a precursor of flavo-cyclophane **31** were not successful, presumably because of the poor solubility of **29**. Therefore, cyclophane **32** with two hexyl groups for enhanced solubility was synthesized. This was achieved by hydrolysis [28] of the amide groups in **26** to the bis(secondary amine) **33**; subsequent acylation with hexanoyl chloride gave **34**, which was reduced with $BH_3 \cdot THF$ [29] to afford **32**. Compound **32** was also obtained by reductive alkylation [30] of **33** with $NaBH_4$ in hexanoic acid/THF. Boronic acid **35** was then successfully prepared from bromo-cyclophane **32** by metallation with BuLi/TMEDA, followed by treatment with excess $(MeO)_3B$ and aqueous workup. *Suzuki* coupling [20] of **35** with 7-bromoflavin **10** gave flavo-cyclophane **36**. The anisotropic ring current of the flavin in **36** results in remarkable upfield ^1H shifts of the adjacent $O-(CH_2)_4-O$ bridge of the cyclophane ($\Delta\delta = 0.41-0.23$ ppm, compared to **32**) and the Me groups ($\Delta\delta = 0.13$ ppm) of the adjacent aromatic ring (*Fig. 2*).

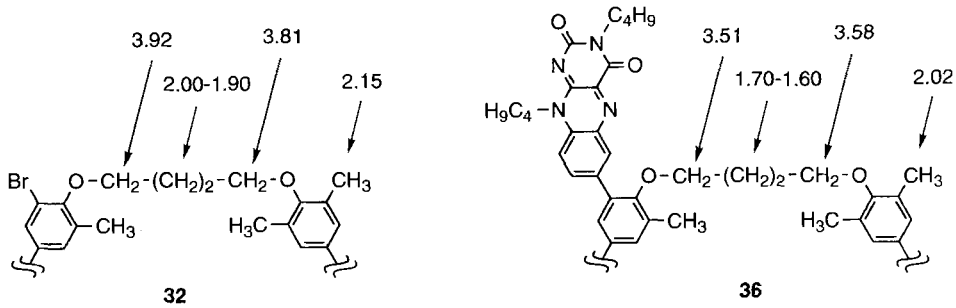


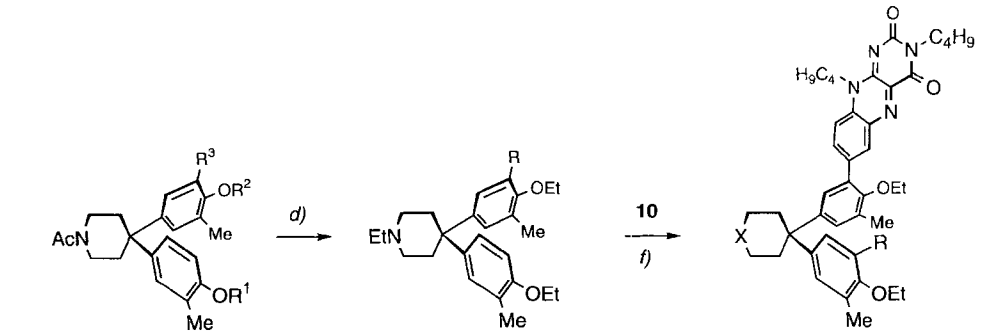
Fig. 2. *Differences in chemical shift* [ppm] *of* ^1H *signals in flavo-cyclophane* **36** *compared to bromo-cyclophane* **32** *as a consequence of the anisotropic ring current of the flavin*

Quaternization of the amino groups in **36** with 1-iodohexane followed by ion exchange led to receptor **37**. Chloromethylation of **37** with CH_2O/HCl in AcOH/conc. aqueous HCl at 40° [17] (heating was necessary because of the surprisingly low reactivity of phenolic ether **37**) yielded the chloromethyl derivative **38**. The flavin moiety was completely inert under these harsh reaction conditions. Heating **38** in 4-methylthiazole followed by chromatography on reversed-phase silica gel (C_{18}) furnished the slightly H_2O soluble flavo-thiazolio-cyclophane **6**.

2.1.3. *Synthesis of Flavo-thiazolio-cleft* **7**. The synthesis of the model system **7** started with dihydroxy compound **39** [28], which was alkylated with 1.3 equiv. of EtI to give a mixture of diethoxy derivative **40**, monoethoxy derivative **41**, and unreacted **39**. After removal of **39** by extraction with aqueous NaOH, the desired compound **41** was separated from **40** by flash chromatography (*Scheme 5*). Selective bromination of **41** in the *ortho*-position to the OH group (Br_2/(*t*-Bu)NH_2 [31]) yielded **42**, which was alkylated to afford **43**. Flavo-thiazolio-cleft **7** was then obtained from **43** *via* **44**–**48** by a similar sequence to that described for the preparation of **6**.

2.2. *Spectroscopic Characterization of Flavo-thiazolio-cyclophane* **6**. The ^1H-NMR spectrum of **6** ($CDCl_3$) showed the characteristic signals of the thiazolium moiety

Scheme 5. *Synthesis of Flavo-thiazolio-cleft* **7**



		R^1	R^2	R^3
a)	**39**	H	H	H
	40	Et	Et	H
b)	**41**	Et	H	H
c)	**42**	Et	H	Br
	43	Et	Et	Br

		R
e)	**44**	Br
	45	$B(OH)_2$

		R	X
g)	**46**	H	NEt
h)	**47**	H	$N^+Et_2Cl^-$
i)	**48**	CH_2Cl	$N^+Et_2Cl^-$
	7	CH_2–(C_4H_5NS)$^+Cl^-$	$N^+Et_2Cl^-$

a) EtI, K_2CO_3, DMF, 60°, 2 h, 43% (**41**), 26% (**40**). *b*) Br_2, (*t*-Bu)NH_2, BHT, PhMe, −78° → 0°, 4 h, 77%. *c*) EtI, K_2CO_3, BHT, DMF, 60°, 4 h, 96%. *d*) BH_3 · THF, THF, reflux, 24 h, 93%. *e*) BuLi, TMEDA, THF, −78°, 40 min, then $(MeO)_3B$, then H^+/H_2O. *f*) [$PdCl_2(PPh_3)_2$], aq. Na_2CO_3, PhMe/EtOH, reflux, 20 h, 53% (from **45**). *g*) EtI, r.t., 24 h, then ion exchange (Cl^-), 77%. *h*) Aq. CH_2O, HCl (*g*), AcOH/conc. aq. HCl, r.t., 2 h, 72%. *i*) 4-Methylthiazole, 80°, 2 h, 58%.

(H–C(2) and CH_2–N(3)) at 10.96 and 5.70 ppm, respectively. These remarkable upfield shifts (the corresponding signals appear at 11.91 and 5.95 ppm, respectively, in cleft **7**, and at 11.36 and 6.06 ppm, respectively, in the simple thiazolium ion **8**) are probably a result of the shielding ring current of the flavin. Self-complexation, as had been deduced from the upfield shifts of all thiazolium protons in thiazolio-cyclophane **4** in D_2O ($\Delta\delta = 0.28–0.70$ ppm [17]), is not likely to occur in $CDCl_3$; moreover, the chemical shifts of the thiazolium signals H–C(5) and Me–C(4) are almost identical in **6** and in **7**. The ^{13}C-NMR spectrum, recorded in $(CD_3)_2SO$, showed 56 of the 87 signals expected from the time-averaged C_s symmetry of the molecule, *i.e.*, most individual resonances of the various alkyl groups, the piperidinium rings, and the spiro C-atoms are not resolved because of very similar chemical environments. The signals at 57.8 (N–CH_2–$(CH_2)_4$Me) and 141.3–139.8 ppm (*C*(arom.)–C(spiro)) are broad and can only be observed at a relatively low field and elevated temperatures because of the slow ring inversion of the piperidinium rings. The resonances of the thiazolium C-atoms appear at 161.0 (C(2)), 148.9 (C(4)), 122.3 (C(5)), 52.2 (CH_2–N(3)), and 13.0 ppm (*Me*–C(4)). The UV/VIS and fluorescence spectra of **6** and **37** are very similar, and comparison with the simple 7-arylflavin **9** showed that the flavin moiety is the only significant chromophore at $\lambda > 250$ nm. No electronic interaction between the flavin and thiazolium moieties in **6** was observed by UV/VIS spectroscopy.

2.3. *^{1}H-NMR Binding Studies.* Flavo-thiazolio-cyclophane **6** forms stable complexes with naphthalene-2-carbaldehyde and benzaldehyde in D_2O/CD_3OD 3:2 with association constants K_a (300 K) of 2900 and 160 l mol^{-1}, respectively (*Table 1*). The stability

of these complexes is similar to that determined for the corresponding associations of thiazolio-cyclophane **4** [17]. A comparison with the complexes formed by flavo-cyclophane **37** reveals that the complexes of **6** are 0.2–0.3 kcal mol^{-1} less stable, presumably owing to self-complexation of the thiazolium ring within the cavity in the protic solvent environment as was previously reported for **4**. The complexation of **6** with aromatic guests in MeOH is significantly weaker. To determine the maximum catalytic advantage that might be obtained by complexation, naphthalene-2-carbaldehyde was chosen for the kinetic studies due to its greater strength of binding.

Table 1. *Association Constants (K_a) and Complexation Free Enthalpies ($-\Delta G°$) for Complexes of Flavo-cyclophane* **37** *and Flavo-thiazolio-cyclophane* **6** *at 300 K As Well As the Calculated and the Maximum Observed Complexation-Induced Shifts $\Delta\delta_{sat}$ and $\Delta\delta_{max\ obs}$ Determined by ^{1}H-NMR Binding Titrations*

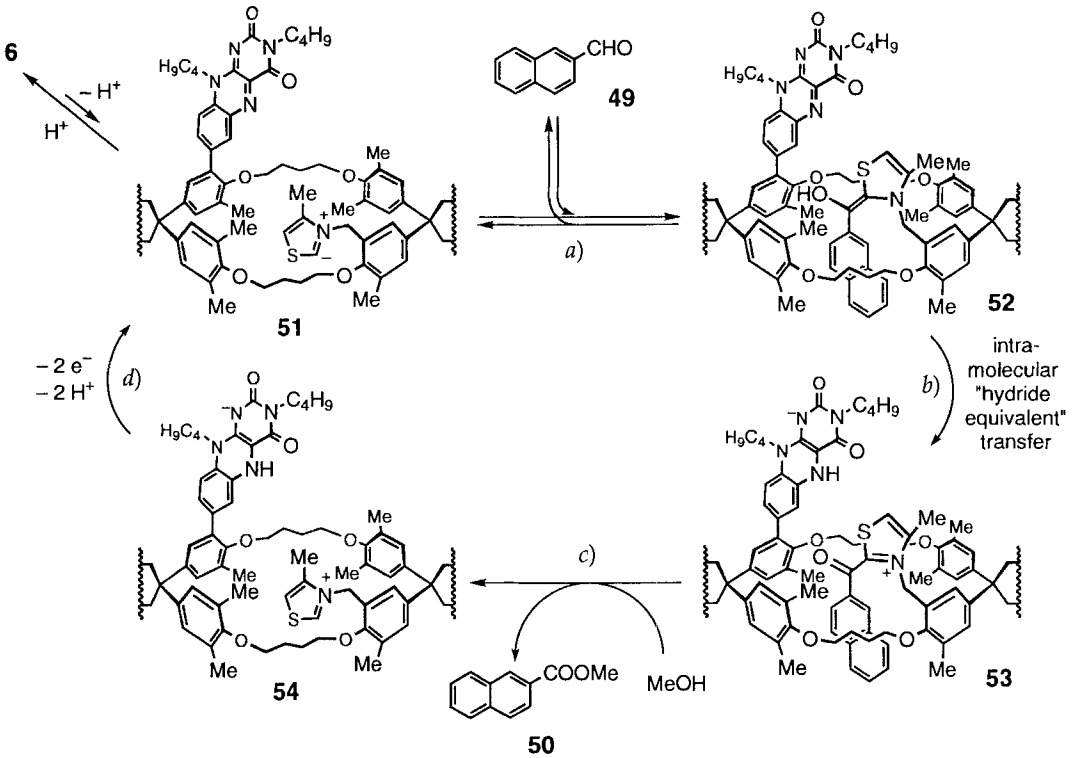
Host (c [mM])	Guest (c [mM])	K_a [a]) [$l mol^{-1}$]	$-\Delta G°$ [kcal mol^{-1}]	$\Delta\delta_{sat}$ [b]) [ppm] ($\Delta\delta_{max\ obs}$ [ppm])	Observed signal	Solvent
6 (0.15–3)	Naphthalene-2-carbaldehyde (0.5)	2900	4.8	−0.91 (−0.80)	Ar–CHO	D_2O/CD_3OD 3:2
6 (0.15–3)	Benzaldehyde (0.5)	160	3.0	−1.54 (−1.09)	Ar–CHO	D_2O/CD_3OD 3:2
37 (0.15–3)	Naphthalene-2-carbaldehyde (0.5)	5200	5.1	−0.99 (−0.92)	Ar–CHO	D_2O/CD_3OD 3:2
37 (0.5)	Benzaldehyde (0.75–15)	210	3.2	−0.32 (−0.23)	CH_2O	D_2O/CD_3OD 3:2
6 (10)	Naphthalene-2-carbaldehyde (5–100)	26	1.9	+0.29 (+0.21)	$ArCH_2$–N(3,thia)	CD_3OD
6 (10)	Methyl naphthalene-2-carboxylate (5–100)	42	2.2	+0.25 (+0.20)	$ArCH_2$–N(3,thia)	CD_3OD
6 (10)	Benzaldehyde (20–400)	2.2	0.5	−0.63 (−0.29)	CH_2O	CD_3OD
6 (10)	4-Methoxy-benzaldehyde (20–400)	3.9	0.8	−0.20 (−0.13)	Ar–H	CD_3OD

[a]) Uncertainties in K_a: ±15%. [b]) Negative sign: upfield shift.

2.4. *Catalytic Cycles for the Oxidation of Naphthalene-2-carbaldehyde to Its Corresponding Carboxylic-Acid Derivatives.* The oxidation of naphthalene-2-carbaldehyde (**49**) to methyl naphthalene-2-carboxylate (**50**) in MeOH is catalyzed by flavo-thiazolio-cyclophane **6** in the presence of base. A plausible catalytic cycle for this supramolecular reaction is shown in *Scheme 6*. Thiazolium ylide **51** is formed by deprotonation of **6** with Et_3N and forms active aldehyde intermediate **52** with the complexed substrate **49** (*a*). Subsequent transfer of a hydride equivalent from the active aldehyde to the flavin moiety in **52** leads to the 2-acylthiazolium intermediate **53** (*b*). This intermediate then reacts with

the solvent (MeOH) producing **50** and **54**, which represents the reduced flavin form of **6** (*c*). Re-oxidation of the flavin moiety in **54** and deprotonation of the thiazolium ion regenerate the catalyst in its reactive ylide form **51** (*d*).

Scheme 6. *Catalytic Cycle for the Oxidation of Naphthalene-2-carbaldehyde* (**49**) *to Methyl Naphthalene-2-carboxylate Catalyzed by Flavo-thiazolio-cyclophane* **6**



By changing the nucleophile which, in step *c*, reacts with the 2-acylthiazolium intermediate **53**, the catalytic cycle could represent a versatile one-pot oxidation of aldehydes to a variety of carboxylic-acid derivatives. Stable 2-acylthiazolium compounds, which react with H_2O and alcohols to give carboxylic acids and esters, respectively [32], have also been reported to react with thiols to afford thioesters [33]. The reaction of 2-acylthiazolium compounds with amines (with the exception of hydroxylamines [33] [34]), however, is not known in biological or model systems. The only related reaction reported is the conversion of a 2-benzoylbenzothiazolium salt with $BuNH_2$ to give *N*-butylbenzamide [35]; benzothiazolium ions, however, are known to be more reactive than thiazolium salts because of the lower basicity of the ylide leaving group [36].

2.5. *Determination of the Initial Rate of the Oxidation of Naphthalene-2-carbaldehyde* (**49**) *to Methyl Naphthalene-2-carboxylate* (**50**) *Catalyzed by* **6**. The initial rate of the oxidation of **49** to **50** was determined at 300 K by adding Et_3N (50 mM) to a degassed methanolic solution of **6** (0.5 mM) and **49** (2–50 mM) under anaerobic conditions. The course of the reaction was followed by monitoring the exponential decrease in ab-

sorbance of the visible flavin chromophore (λ = 455 nm, initial absorbance $A_0 = 1$) upon reduction to the colorless (end absorbance $A_\infty \approx 0$) dihydro form (*Scheme 6, b*). The rate of disappearance of the oxidized flavin can be equated to the rate of formation of **50**, since the reaction of 2-acylthiazolium ions with MeOH is very fast under basic conditions [37]. For comparison, this oxidation reaction was also studied under similar conditions with **7** and {**8** + **9**}.

Saturation kinetics was observed with cyclophane **6**. In contrast, rates in the presence of **7** or {**8** + **9**} increased in a linear fashion with increasing substrate concentration (*Fig. 3*). An *Eadie-Hofstee* plot (*v vs. v*/[naphthalene-2-carbaldehyde]) for the reaction catalyzed by **6** gave $v_{max} = 1.1 \cdot 10^{-4}$ M s^{-1} and $K_M = 21$ mM. The turnover number $k_{cat} = v_{max}/[\mathbf{6}]$ was calculated to be 0.22 s^{-1}; this value represents *ca.* 20-fold acceleration in comparison to the reaction catalyzed by the bimolecular system {**4** + **5**} [17] [38], and is one of the highest turnover numbers reported for an artificial enzyme [39]. Apparently, intramolecular electron transfer from the active aldehyde form of **4** to flavin **5** was rate-determining for steric reasons; catalyst **6** enables this step to occur intramolecularly, which results in a highly enhanced reaction rate.

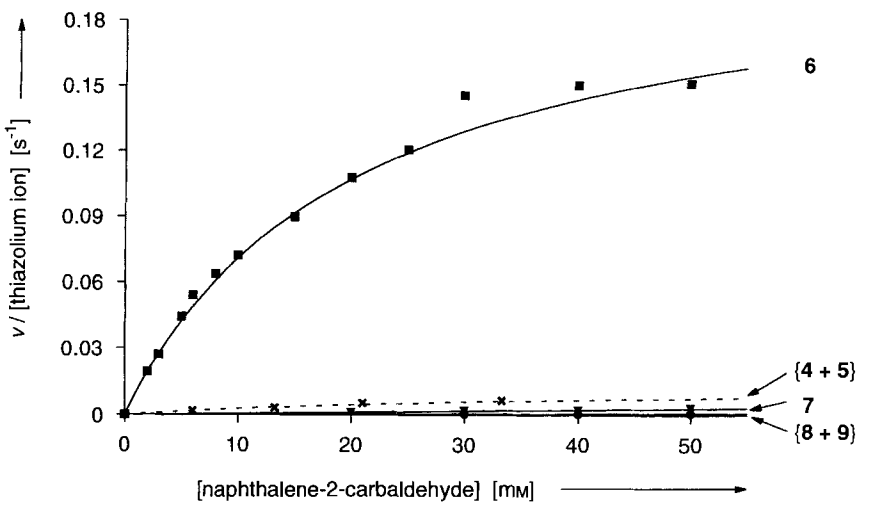


Fig. 3. *Plot of relative initial rates* vs. *substrate concentrations for the oxidation at 300 K of naphthalene-2-carbaldehyde to methyl naphthalene-2-carboxylate catalyzed by* **6**, **7**, *and* {**8** + **9**} *in comparison to* {**4** + **5**}. For meaningful comparison, *v*/[thiazolium ion] rather than *v* is plotted, since experimental conditions required different concentrations of the various catalysts. Initial rates with {**4** + **5**} were measured under similar conditions at 303 K [38].

The *Michaelis* constant (K_M = 21 mM) is lower than the dissociation constant measured by ^{1}H-NMR titration ($K_d = K_a^{-1}$ = 38 mM). This could be due to the unproductive binding conformation leading to the active aldehyde intermediate **55** (*Fig. 4, a*), in which the intramolecular electron transfer would have to occur through the naphthalene ring. Intermolecular oxidation of **55** by an external flavin cannot be ruled out, but would be slow for steric reasons, as has been shown for the bimolecular system {**4** + **5**} [17] [38]. Since the absorbance of the flavin chromophore rapidly approaches $A_\infty \approx 0$, the intermolecular oxidation of **55** to the 2-acylthiazolium intermediate **56** (*Fig. 4, b*) is unlikely. It is more likely that **55** reacts back to ylide **51**, and then aldehyde **49** is complexed again

productively leading to active aldehyde **52**. The value of K_M is *ca.* 0.5 K_d, from which it is proposed that the two active aldehyde conformers **55** and **52** are formed in a *ca.* 1:1 ratio.

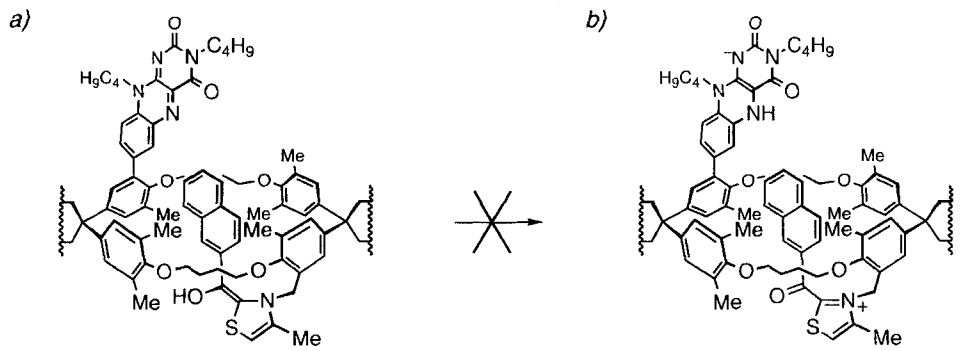


Fig. 4. a) *Unproductive conformation* (**55**) *of the active aldehyde intermediate* **52**, b) *unlikely conformation* (**56**) *of the 2-acylthiazolium intermediate* **53**

The apparent second-order rate constants k_{cat}/K_M for **6** and {**4** + **5**} were compared with the calculated second-order rate constants for the catalyst systems **7** and {**8** + **9**}, which lack the macrocyclic binding site. This revealed that the reaction with **6** is 190-fold and 730-fold faster than with **7** and {**8** + **9**}, respectively (*Table 2*). The large increase in reaction rate with **6** is a result of the intramolecular nature of all the key steps in the catalytic cycle. The formation of the methyl ester **50** was confirmed by ^{1}H-NMR spectroscopy. A comparison with authentic samples of **49** and **50** showed that no by-product was formed.

Table 2. *Oxidation of Naphthalene-2-carbaldehyde* (**49**) *to Methyl Naphthalene-2-carboxylate in the Presence of Et_3N in MeOH*

Catalyst	Second-order rate constant [$M^{-1}\,s^{-1}$]
Flavo-thiazolio-cyclophane **6**	$k_{cat}/K_M = 11$[a])
Thiazolio-cyclophane **4** and flavin **5**	$k_{cat}/K_M = 0.37$[b])
Flavo-thiazolio-cleft **7**	$k_2 = 0.058$
Thiazolium ion **8** and 7-arylflavin **9**	$k_2 = 0.015$

[a]) $k_{cat} = 0.22\ s^{-1}$, $K_M = 21$ mM. [b]) $k_{cat} = 0.013\ s^{-1}$, $K_M = 37$ mM; data from [38].

The thiazolium-catalyzed oxidation of aldehydes to carboxylic-acid derivatives has been shown to be first-order in thiazolium ion and zero-order in the oxidizing agent (flavin or Fe^{III}) [15–17] (the zero-order dependence in the flavin concentration was confirmed with the system {**8** + **9**} at [**9**] = 0.5–2 mM; at higher flavin concentrations, the reproducibility of the results was poor). The second-order rate constant for the oxidation of an active aldehyde intermediate by a flavin has been estimated to be $\geq 6100\ M^{-1}\,s^{-1}$ [40]. Therefore, the accelerations observed with **6** and **7** in comparison to {**4** + **5**} and {**8** + **9**}, respectively, cannot be expressed in terms of an effective molarity [2].

2.6. *Preparative-Scale Oxidation of Aromatic Aldehydes Mediated by Bis(coenzyme) Catalysis.* To employ **6** as a catalyst on a preparative scale, the reduced form of its flavin moiety needs to be re-oxidized (*Scheme 6, d*). Attempts to regenerate this oxidized form under aerobic conditions (as is the case for pyruvate oxidase, *Scheme 1*) were unsuccessful [1]. While **6** is almost indefinitely stable in pure MeOH, its thiazolium moiety is very air-sensitive in the presence of base in this solvent [17]. Poor conversion of naphthalene-2-carbaldehyde to naphthalene-2-carboxylic acid was also observed in aqueous phosphate buffer at pH 7.5, where the thiazolium ion is more stable against oxidative destruction. In both cases, however, only *ca.* 1 equiv. of ester or acid was formed with 1 equiv. of catalyst. Therefore, we turned to an electrochemical regeneration of the oxidized flavin form.

2.6.1. *Electrochemical Properties of Flavo-thiazolio-cyclophane* **6**. In protic solvents, the reversible electrochemical reduction of the flavin moiety in **6** leads directly to the dihydro form in two overlapping one-electron steps [41]. To evaluate the application of **6** in electro-oxidation reactions, we investigated its cyclic voltammetric behavior. The cyclic voltammogram (CV) of **6** in MeOH, measured at a glassy carbon electrode, showed a *quasi*-reversible (ΔE_p = 70 mV) reduction of the flavin moiety at *ca.* −0.47 V *vs.* Ag/AgCl (*Fig. 5, a*). The reduction potentials of the flavin moieties of **6** and **37** were equal within experimental error; moreover, the value measured for the riboflavin derivative **5** under similar conditions was in the same range ($E^{\circ\prime} \approx -0.50$ V *vs.* Ag/AgCl [17] [42]).

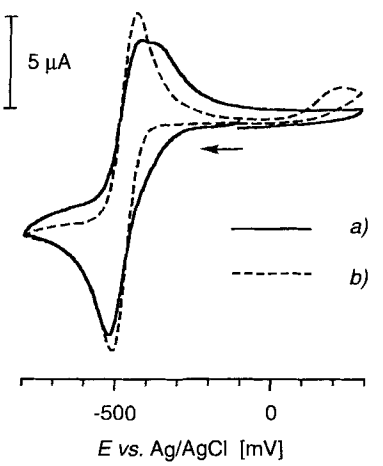


Fig. 5. *Cyclic voltammograms of flavo-thiazolio-cyclophane* **6** (1 mM) *in a 50 mM* Et_4NBr *soln.* a) *in MeOH and* b) *in MeOH/*Et_3N *100:1 (v/v), recorded 1 h after addition of* Et_3N. Scan rate 20 mV s^{-1}, 300 K, glassy carbon working electrode.

Addition of Et_3N led to an increase in the peak currents and to the formation of an irreversible anodic signal, which reached a maximum after *ca.* 1 h (E_{pa} = + 0.23 V *vs.* Ag/AgCl; *Fig. 5, b*). This can be explained by the slow conversion of thiazolium moiety of **6** into an oxidizable ene-thiolate; accordingly, no additional anodic peak was observed in the CV of flavo-cyclophane **37** [17] [43]. The absence of a cathodic peak indicates that this oxidation is irreversible at the electrode, which is in accord with the sensitivity of the thiazolium ion towards O_2 in basic MeOH.

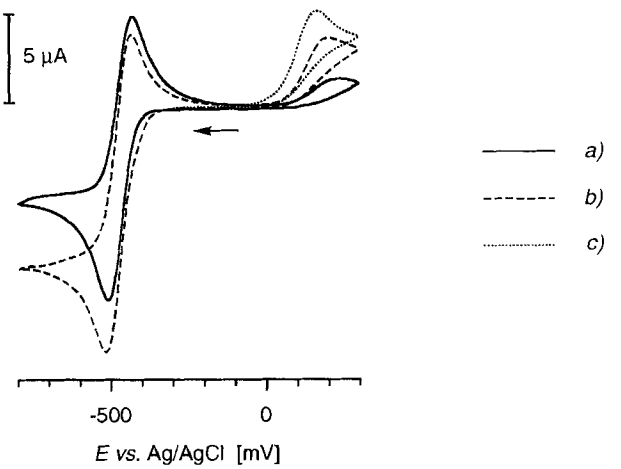


Fig. 6. *Cyclic voltammograms of* a) *flavo-thiazolio-cyclophane* **6** (1 mM), b) *flavo-thiazolio-cleft* **7** (1 mM), *and* c) *3-benzyl-4-methylthiazolium bromide* **8** (1 mM) *in a 50 mM soln. of* Et_4NBr *in MeOH/*Et_3N *100:1 (v/v).* Scan rate 20 mV s^{-1}, 300 K, glassy carbon working electrode.

A comparison of the CVs of flavo-thiazolio-cyclophane **6**, cleft **7**, and the simple thiazolium ion **8** (*Fig. 6*) showed that the oxidative destruction of the thiazolium moiety in **6** (E_{pa} = + 0.23 V *vs.* Ag/AgCl) occurred at a higher potential than in **7** (E_{pa} = + 0.20 V) and **8** (E_{pa} = + 0.16 V). This anodic oxidation is also slower in **6** than in model compounds **7** and **8** as judged from the anodic currents (i_{pa} (**6**) > i_{pa} (**7**) > i_{pa} (**8**)). Similar observations were made with thiazolio-cyclophane **4** in comparison with a thiazolio-cleft and **8** [17]. Presumably, the bulky and positively charged cyclophane moiety hinders the access of the thiazolium moiety to the electrode surface.

Considerably higher potentials are required for the oxidation of the thiazolium moiety of **6** at a Pt working electrode (E_{pa} > + 0.3 V *vs.* Ag/AgCl), while the reduction potential for the flavin moiety ($E^{\circ\prime}$ = – 0.47 V) remains unchanged in comparison to the glassy carbon electrode (*Fig. 7, a*). It should, therefore, be possible to re-oxidize the reduced flavin moiety of **6** without destroying the thiazolium unit at a Pt working electrode using potentials between $E^{\circ\prime}$ and *ca.* 0 V.

A comparison of the CV of **6** to that of the simple 7-arylflavin **9** (*Fig. 7, b*) revealed that the anodic peak current i_{pa} of **6** is lower by almost 50%. The anodic re-oxidation of the reduced flavin in **6** seems to be hindered for steric reasons and possibly also due to the presence of the positive charges in the cyclophane unit. It may be anticipated that the advantage found for **6** in comparison to {**8** + **9**}, *i.e.*, the higher initial rate, is reduced, if the re-oxidation step becomes rate-determining.

2.6.2. *Indirect Electro-oxidation of Aromatic Aldehydes with Flavo-thiazolio-cyclophane* **6** *as a Redox Mediator.* The CV experiments discussed above illustrated that **6** should be suitable as a redox catalyst in indirect electro-oxidations [18]. To investigate the stability of **6** under the reaction conditions, a degassed solution of **6** (1 mM) in MeOH/Et_3N 100:1 (*v/v*) was electrolyzed at a glassy carbon working electrode potential of –0.2 V *vs.* Ag/AgCl. Thiazolium salt **8** was stable under these conditions, *i.e.*, the cyclic voltammogram was stable over at least 24 h after the anodic peak of the thiazolium oxidation

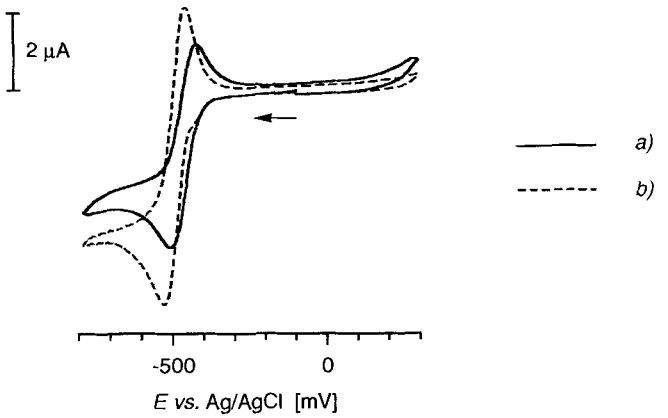


Fig. 7. *Cyclic voltammograms of* a) *flavo-thiazolio-cyclophane* **6** (1 mM; $i_a \approx 3.1$ μA) *and* b) *7-arylflavin* **9** (1 mM; $i_a \approx 5.6$ μA) *in a 50 mM soln. of* Et_4NBr *in* $MeOH/Et_3N$ *100:1* (*v*/*v*). Scan rate: 20 mV s^{-1}, 300 K, Pt working electrode.

had reached a maximum (after *ca.* 1 h). In the case of **6**, the cyclic voltammograms measured during the electrolysis revealed that the peak currents of both the *quasi*-reversible flavin reduction and of the irreversible thiazolium oxidation slowly decreased (*Fig. 8*). Since the charge transferred for 24 h ($Q = \int i_a dt$) was less than 0.005 C (Coulombs), electrochemical oxidation could not account for the oxidative destruction of the thiazolium unit. It, therefore, appeared that both prosthetic groups were destroyed chemically. In contrast, thiazolio-cyclophane **4** was reported to be far more stable under similar conditions, with a decrease of the anodic thiazolium signal (i_{pa}) of only *ca.* 20% over 21 h [17].

First electrolysis experiments on a preparative scale were subsequently carried out at Pt foil working and glassy carbon counter electrodes, with 150 mM aldehyde concentra-

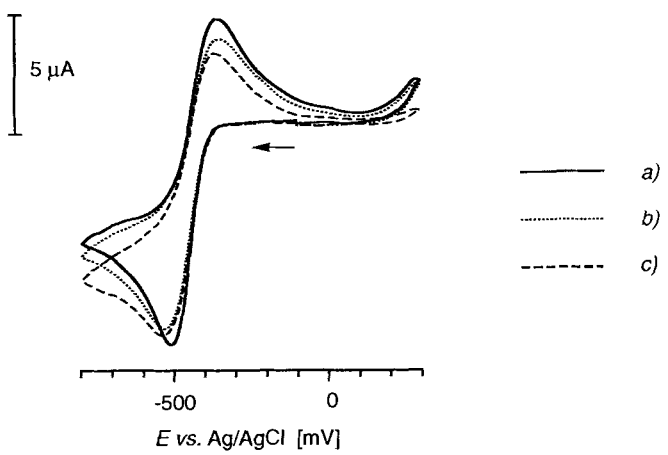


Fig. 8. *Cyclic voltammograms of* **6** (1 mM) *after electrolysis in a 50 mM soln. of* Et_4NBr *in* $MeOH/Et_3N$ *100:1* (*v*/*v*) *at a glassy carbon working electrode at* −*0.2 V* (*vs.* Ag/AgCl) *for* a) *1 h*, b) *6 h*, c) *24 h*. Scan rate: 20 mV s^{-1}, 308 K.

tion, Et_3N (150 mM) as base, and Et_4NBr (50 mM) as supporting electrolyte. These conditions were found to be optimal for electro-oxidations on a preparative scale with the bimolecular system {**4** + **5**} [17]. Since aldehydes were converted to the corresponding acetals by **6** in methanolic electrolyte solutions in the absence of base, the bis(coenzyme) catalyst was added to a solution of aldehyde in the basic electrolyte solution under exclusion of O_2. After an electrolysis time of 16 h at 300 K, however, only trace amounts of methyl benzoate were obtained from benzaldehyde, and a negligible anodic current was measured.

It became clear that the glassy carbon counter electrode was not suitable for the regeneration of **6**: the cyclic voltammogram of **6** revealed the absence of an anodic peak for the flavin re-oxidation (*Fig. 9, a*), while there was a significant anodic current with a Pt wire counter electrode (*Fig. 9, b*). The cyclic voltammogram of riboflavin derivative **5**, on the other hand, was independent of the counter electrode, and a large anodic current was observed under both sets of experimental conditions described in *Fig. 9*.

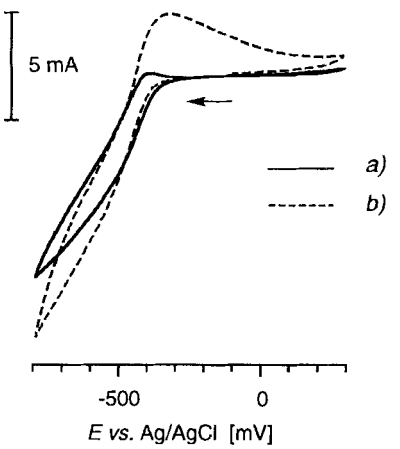


Fig. 9. *Cyclic voltammograms of flavo-thiazolio-cyclophane* **6** (5 mM) *in a 50 mM soln. of* Et_4NBr *in* $MeOH/Et_3N$ *50:1* (*v/v*) *at* a) *a glassy carbon counter electrode and* b) *a Pt wire counter electrode.* Scan rate: 20 mV s^{-1}, 308 K, Pt foil (50 × 12 × 10 mm) working electrode.

Under the same reaction conditions, the electro-oxidation of 4-formylbenzonitrile gave methyl 4-cyanobenzoate in 37% yield. The anodic current passed during the reaction was also very small; on the other hand, the aldehyde had completely reacted. We, therefore, suspected that the aldehyde itself might be able to oxidize the active aldehyde intermediate. Indeed, 4-formylbenzonitrile is irreversibly reduced at low potentials ($E_{pc} = -1.15$ V *vs.* Ag/AgCl), while benzaldehyde is not electroactive at potentials higher than -1.2 V *vs.* Ag/AgCl (*Fig. 10*).

From this irreversible reduction, a reduction potential slightly lower than -1 V *vs.* Ag/AgCl may be estimated. Apparently this potential is sufficient for the oxidation of the active aldehyde intermediate of 4-formylbenzonitrile. Since this intermediate is not an isolable compound, its reduction potential is difficult to determine. *Jordan* and coworkers estimated this potential for the active aldehyde formed from benzaldehyde to be ≤ -0.67 V *vs.* Ag/AgCl [40]. Our observation might suggest that this potential could

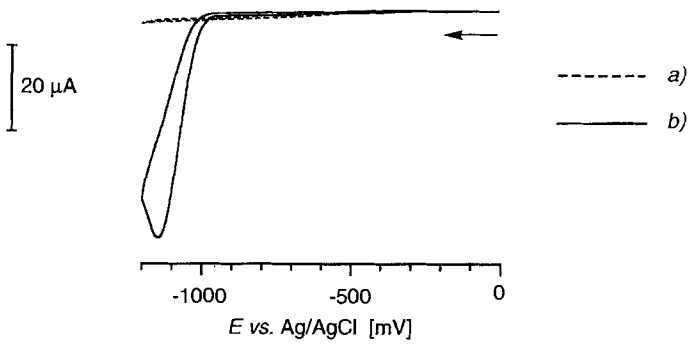
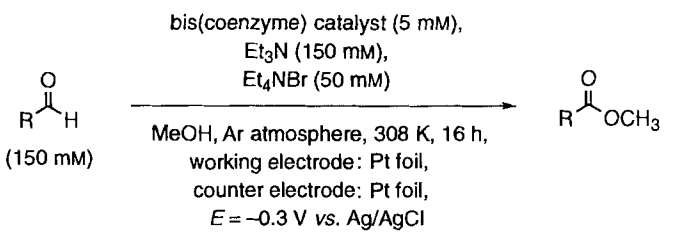


Fig. 10. *Cyclic voltammograms of* a) *benzaldehyde* (1 mM) *and* b) *4-formylbenzonitrile* (1 mM) *in a 50 mM soln. of* Et_4NBr *in* $MeOH/Et_3N$ *100:1* (*v*/*v*). Scan rate 20 $mV\,s^{-1}$, 308 K, glassy carbon working electrode.

be significantly lower. It needs to be considered, however, that the CN group can strongly shift a reduction potential; moreover, the subsequent reaction, *i.e.*, the methanolysis of the 2-acetylthiazolium intermediate, is irreversible.

These preliminary experiments showed the way for the successful use of flavo-thiazolio-cyclophane **6** on a preparative scale. Under the conditions outlined in *Scheme 7*, a 48% yield of methyl benzoate was obtained from the electro-oxidation of benzaldehyde, which corresponds to 14 catalytic cycles according to *Scheme 6* (*Table 3*, *Entry 1*). This shows that **6** is both a chemical catalyst and a redox mediator. The isolated yield is very similar to that obtained with {**4** + **5**} [17]. The aldehyde had reacted almost completely; the side products, however, could not be identified but did not include benzoin, which is the product of thiazolium-catalyzed reactions of aldehydes in the absence of oxidizing agents [44]. The yields obtained with flavo-thiazolio-cleft **7** or with the simple system {**8** + **9**} (*Entries 2* and *3*) were much lower. The intramolecular catalytic cycle provided by **6** (*Scheme 6*), therefore, is evidently advantageous in spite of the low association constant for the complex formed by benzaldehyde (*Table 1*).

Scheme 7. *Preparative-Scale Oxidation of Aromatic Aldehydes to the Corresponding Methyl Esters*



Under the same conditions, the oxidation of naphthalene-2-carbaldehyde (**49**) with **6** gave methyl ester **50** in 78% yield (*Entry 4*). With lower amounts of catalyst (1/150 equiv.), **50** was isolated in 64% yield after a reaction time of 48 h, which corresponds to almost 100 catalytic cycles (*Entry 5*). This result shows that bis(coenzyme)-cyclophane **6** is a functional catalyst with a high turnover, even though its stability in basic methanol is limited. As expected, cleft **7** was less effective at catalyzing this reaction (*Entry 6*).

Table 3. *Electrochemical Oxidation of Aldehydes in 50 mM Solution of Et_4NBr in MeOH at a Pt Electrode, 308 K.* For conditions, see *Scheme 7.*

Entry	Aldehyde	Bis(coenzyme) catalyst	Time [h]	Yield of ester[a]) [%]	Aldehyde recovered[a]) [%]	Turnover
1	Benzaldehyde	**6**	16	48	1	14
2	Benzaldehyde	**7**	16	28	13	8
3	Benzaldehyde	{**8** + **9**}	16	19	41	6
4	Naphthalene-2-carbaldehyde	**6**	16	78	2	23
5	Naphthalene-2-carbaldehyde	**6**[b])	48	64	24	96
6	Naphthalene-2-carbaldehyde	**7**	16	59	7	18
7	Naphthalene-2-carbaldehyde	{**8** + **9**}	16	81	7	24
8	Naphthalene-2-carbaldehyde	{**8** + **9**}	24	87	5	26
9	Naphthalene-2-carbaldehyde	**8**	16	3	32[c])	1
10	Naphthalene-2-carbaldehyde	–	16	–	98	–
11	4-Methoxybenzaldehyde	**6**	16	44	46	13
12	4-Methoxybenzaldehyde	{**8** + **9**}	16	15	71	5

[a]) Isolated yields. [b]) [**6**] = 1 mM. [c]) Naphthoin **57** was isolated as the main product (59% yield).

Rather surprisingly, the simple system {**8** + **9**} proved to be superior to **6**: the yield of **50** was 81% after 16 h and 87% after 24 h (*Entries 7* and *8*).

To explain the high yield obtained with {**8** + **9**}, we monitored the course of the anodic current i_a during the reaction (*Fig. 11*). The total charges transferred were 270 C and 263 C for **6** and {**8** + **9**}, respectively. This corresponds to current yields of 84% and 89%, respectively. In the reaction with catalyst **6**, the maximal anodic current ($i_{a,max}$ = 12 mA) is reached after *ca.* 1 min already and then decreases by *ca.* 30%, presumably because of the formation of an ene-thiolate from the thiazolium moiety [43], which results in a lower apparent concentration of the catalyst. After *ca.* 1 h, **6** and the corresponding ene-thiolate reach an equilibrium, and i_a is almost constant over several hours (the slow decrease of i_a is probably a consequence of the slow decomposition of **6**). Finally, i_a decreases exponentially to reach the terminal value of *ca.* 1.5 mA. During the period of constant i_a, **6** is largely saturated with its substrate and performs chemical catalysis at the maximal rate. Since one would expect a much faster conversion of the aldehyde from the initial rate measured ($k_{cat} = 0.22\ s^{-1}$), it is most likely that the re-oxidation of the reduced flavin **54** at the electrode, *i.e.*, the heterogeneous electron transfer, is the rate-limiting step of the reaction.

In the reaction catalyzed by the simple bimolecular system {**8** + **9**}, i_a increases more slowly reaching a maximum after *ca.* 10 min, then decreases exponentially to a terminal current of *ca.* 1.5 mA. The maximum current ($i_{a,max}$ = 16 mA), however, is significantly higher than in the case of **6**. The higher anodic current for **9** in comparison to **6** (*Fig. 8*) proved to be favorable for the catalysis. For the optimization of the anodic re-oxidation in the system {**8** + **9**}, an excess of flavin **9** could be used as has been done with {**4** + **5**} [17]. For compound **6**, however, the flavin concentration can obviously not be altered.

Control experiments were carried out in order to prove that the oxidation of naphthalene-2-carbaldehyde (**49**) to methyl naphthalene-2-carboxylate (**50**) is an indirect electro-oxidation with the thiazolium ion as the chemical catalyst and the flavin as the redox mediator. Attempts to obtain **50** in the presence of **8** but in the absence of redox

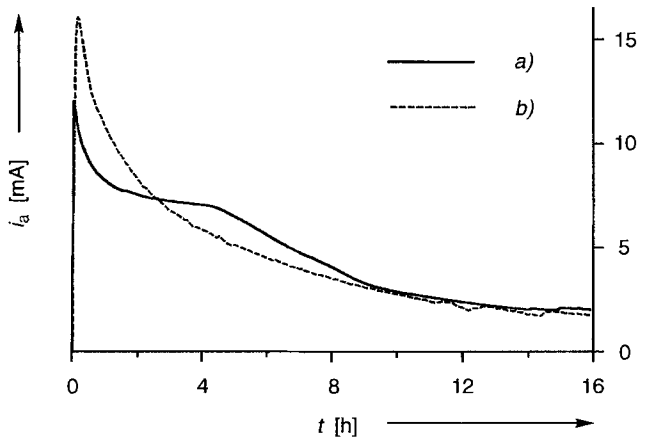
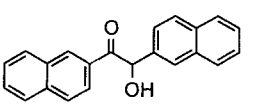


Fig. 11. *Anodic current* (i_a) *during the electro-oxidation of naphthalene-2-carbaldehyde to methyl naphthalene-2-carboxylate catalyzed by* a) *flavo-thiazolio-cyclophane* **6** (*Table 3, Entry 4*) *and* b) *thiazolium ion* **8** *and flavin* **9** (*Table 3, Entry 7*)

catalyst **9** gave only a 3% yield, *i.e.*, the direct anodic oxidation of the active aldehyde intermediate is hardly possible because of an unfavorable overpotential. Instead, naphthoin **57** was isolated as the main product (*Entry 9*). Finally, no ester **50** was formed in the absence of a thiazolium catalyst, and aldehyde **49** was recovered almost quantitatively (*Entry 10*).



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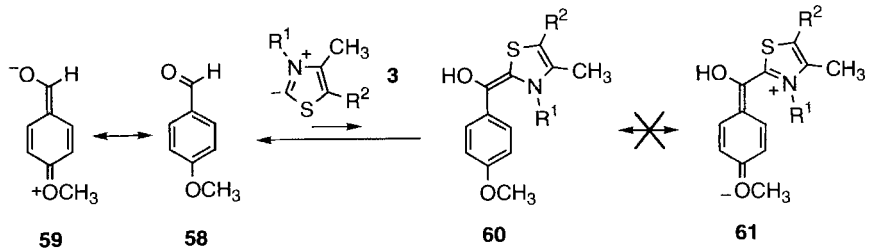
We also investigated the electro-oxidation of naphthalene-2-carbaldehyde (**49**) in the presence of amines or thiols for the one-pot preparation of the corresponding carboxamides and thioesters, respectively. These experiments were performed under similar conditions to those outlined in *Scheme 7*. While the solvent MeOH could compete with the amine or thiol, we hoped that the latter would be the stronger nucleophiles (the competitive solvent was necessary, since amines or thiols do not promote the complexation of **6** with aromatic substrates because of their low polarity, not even in combination with dipolar aprotic co-solvents such as MeCN or Me_2SO). Reactions run in the presence of NH_3, $MeNH_2$, or EtSH (the latter with excess Et_3N added as a base and at a slightly lower working electrode potential in order to prevent its anodic oxidation) rapidly led to destruction of the thiazolium catalyst, possibly *via* a nucleophilic attack at the benzylic CH_2 position. On the other hand, a 39% yield of methyl naphthalene-2-carboxylate (**50**) was isolated from the oxidation of 2-naphthaldehyde in MeOH in the presence of Et_2NH. Apparently, Et_2NH did not destroy the catalyst as rapidly as the smaller nucleophiles, but was too bulky to effect a nucleophilic attack at the C=O group of intermediate **53**. Finally, reactions run with amine or thiol nucleophiles in H_2O or CF_3CH_2OH instead of MeOH were not successful either.

In the electro-oxidation of 4-methoxybenzaldehyde (**58**), the advantage of flavo-thiazolio-cyclophane **6** was most apparent. In the case of the simple system {**8** + **9**}, the reaction was very slow; only 15% ester was formed after 16 h, which corresponds to five catalytic cycles (*Table 3*, *Entry 12*). The low reactivity of **58** is a result of the 4-MeO substituent, which both renders the nucleophilic attack of thiazolium ylide **3** more difficult (the low electrophilicity of the carbonyl center of **58** is illustrated by the important resonance structure **59**) and destabilizes the active aldehyde intermediate **60**, *i.e.*, the resonance structure **61** does not contribute to the stabilization of **60** (*Scheme 8*).

Scheme 8. *Unfavorable Formation of an Active Aldehyde Intermediate*, **60**, *from 4-Methoxybenzaldehyde* (**58**)



Flavo-thiazolio-cyclophane **6** is a superior catalyst (*Entry 11*) as compared to {**8** + **9**} in the electro-oxidation of unreactive 4-methoxybenzaldehyde (**58**) for the following reasons: *i*) The encounter of **58** ($\Delta G^\circ = -0.8$ kcal mol^{-1}; *Table 1*) with ylide **51** is promoted because of host-guest complexation. The complex of **58** is by 0.3 kcal mol^{-1} more stable than that of benzaldehyde, presumably because of the larger dipole in the guest [45]. *ii*) The apolar cavity of the receptor stabilizes ylide **3** (which corresponds to ylide **51** in *Scheme 6*) and active aldehyde **60**, which are both less polar than the thiazolium ion in **6** [17]. *iii*) The energy-rich active aldehyde intermediate is effectively trapped by the proximal flavin. This irreversible electron transfer competes successfully with the back-reaction to aldehyde **58** and ylide **51**. Thus, methyl 4-methoxybenzoate was isolated in 44% yield after 16 h, which corresponds to 13 catalytic cycles, and the unreacted starting material recovered (46%), showing that side reactions are largely suppressed (*Entry 11*). The maximum anodic current ($i_{a,max} = 6.3$ mA) was much lower than in the reaction with benzaldehyde or naphthalene-2-carbaldehyde ($i_{a,max} \approx 12$ mA) and was only reached after *ca.* 15 min. Therefore, the electrochemical regeneration of the oxidized flavin is probably no longer rate-limiting. This is the first example reported for a thiazolium-catalyzed oxidation of an unreactive aromatic aldehyde.

Finally, the oxidation of 4-formylbenzonitrile was investigated. Contrary to a 4-MeO group, a 4-CN group both activates the C=O group for nucleophilic attack by a thiazolium ylide and stabilizes the active aldehyde. Good yields (65–95%) have been reported in the electro-oxidation of reactive aldehydes with thiazolio-cyclophane **4** or thiazolium ion **8** [17]. The riboflavin derivative **5** acting as a redox mediator in these conversions was capable of performing a rapid electron transfer at the anode and was used in a threefold excess with respect to the thiazolium catalyst thus accelerating the potentially rate-determining re-oxidation step. In the reactions catalyzed by **6**, flavin re-oxidation was rate-determining even in the case of the moderately reactive benzaldehyde and naphthalene-2-carbaldehyde. Therefore, **6** was not expected to be a superior

catalyst, but the yields of 35 and 31% with **6** and {**8** + **9**}, respectively (*Table 4*, *Entries 1* and *2*), were lower than expected. Analogously to the attempted electro-oxidation using a glassy carbon electrode, the starting material had reacted completely. The numerous side products, however, could not be identified.

Table 4. *Oxidation of 4-Formylbenzonitrile to Methyl 4-Cyanobenzoate in MeOH under the Conditions Shown in* Scheme 7

Entry	Catalyst	*E vs.* Ag/AgCl [V]	Yield of ester[a]) [%]	Aldehyde recovered[a]) [%]
1	**6**	−0.3	35	–
2	{**8** + **9**}	−0.3	31	–
3	**8**	−0.3	29	5
4	**8**	–	59	5
5	–	−0.3	–	77

[a]) Isolated yields.

Control experiments showed that the flavin has very little influence on the oxidation reaction (*Table 4*). The yield obtained with **8** in the absence of **9** was very similar to that obtained with {**8** + **9**} (*Entry 3*) and was even higher, when no potential was applied affording methyl 4-cyanobenzoate in 59% yield (*Entry 4*). This confirmed the assumption that 4-formylbenzonitrile might act as an oxidizing agent in a similar manner to 4-nitrobenzaldehyde [14a] [42]. This homogeneous electron transfer is rapid and cannot be prevented by the flavin, since it is mainly present in its reduced form. Moreover, aldehyde (*Entry 5*), ester (*ca.* 10% decomposition over 16 h), and presumably the reactive intermediates in particular have only a limited stability under these electrolysis conditions.

3. Conclusions. – Flavo-thiazolio-cyclophane **6**, with the two coenzyme analogs arranged in proximity to a well-defined binding site, is a functional supramolecular catalyst for the oxidation of aromatic aldehydes to the corresponding methyl esters in MeOH. In initial rate studies, **6** showed large rate accelerations in comparison to simpler bis(coenzyme) catalysts. The rate enhancements are a result of the macrocyclic binding and reaction site providing a favorable intramolecular, enzyme-like catalytic cycle. While the flavin moiety cannot be re-oxidized under aerobic conditions because of the sensitivity of the thiazolium unit, CV investigations showed that the oxidized flavin form of **6** can be electrochemically regenerated at a working electrode potential of −0.3 V *vs.* Ag/AgCl without affecting the thiazolium moiety. Thus, **6** is a homogeneous, supramolecular chemical catalyst as well as a heterogeneous redox mediator, and up to *ca.* 100 catalytic cycles can be performed. The efficient intramolecular trapping of the active aldehyde formed in the catalytic cycle by the flavin allowed the reaction to be performed on a preparative scale, even in the case of the unreactive 4-methoxybenzaldehyde. The present investigation suggests that the combination of biomimetic chemistry with electrocatalysis represents a valuable approach for the development of new selective and environmentally viable methods of chemical transformation.

Experimental Part

General. Reagents and solvents were purchased reagent grade and used without further purification unless stated otherwise. THF was distilled from sodium benzophenone ketyl under N_2. Et_4NBr was dried (120°, 100 mbar, 16 h) before use. Petroleum ether (p.e.) consisted of a fraction with a boiling range of 60–95°. Compounds **5** [46], **8** [47], **11** [21a], **39** [28], and **50** [48] were prepared according to the published procedures. Amides and thioesters serving as reference compounds in electrolysis experiments were synthesized from the corresponding acid chlorides and amines or thiols, respectively. All reactions were performed in standard glassware under Ar unless stated otherwise. Irradiations were carried out using a 250-W medium pressure Hg lamp equipped with a *Pyrex* cooler. Evaporation was performed at H_2O-aspirator pressure; the term *in vacuo* refers to a pressure of *ca.* 0.1 Torr. Column chromatography (CC): silica gel *60* (63–200 μm) from *Macherey-Nagel*. Flash chromatography (FC): silica gel *60* (40–63 μm) from *Macherey-Nagel*. Reversed-phase chromatography: silica gel *100* (C_{18}, fully end-capped) from *Fluka*. Ion-exchange chromatography: *Dowex 1 × 8*, strongly basic anion exchange resin (Cl^-), 200–400 mesh. TLC: glass sheets covered with silica gel *60* F_{254} from *Merck*, visualization by UV light. Unless stated otherwise, products were dried for 24 h at 0.1 Torr prior to spectral and anal. characterization. M.p.: *Büchi 510* apparatus; uncorrected. UV/VIS (λ_{max} [nm] (lg ε)): *Varian Cary 5*, 10^{-5} M soln. in MeCN, at r.t. Fluorescence ($\lambda_{max.\ em.}$ [nm]): *Spex 212 Fluorolog*, 10^{-7}–10^{-5} M soln. in MeCN, at r.t., $\lambda_{exc.}$ = 420 nm. IR ($\tilde{\nu}$ [cm^{-1}]): *Perkin-Elmer 1600 FT-IR*. ^{1}H- and ^{13}C-NMR (δ *vs.* Me_4Si [ppm]): *Bruker ARX-300*, *AMX-400*, and *AMX-500* instruments at r.t., unless stated otherwise; multiplicities (^{13}C-NMR) from DEPT experiments. MS (*m/z*, (% base peak)): *VG-TRIBRID* instrument for EI (70 eV) and a *VG-ZAB-2SEQ* for FAB (3-nitrobenzyl-alcohol matrix). Elemental analyses were effected by the *Mikrolabor* in the *Laboratorium für Organische Chemie*, ETH-Zürich. The *Chemical Abstracts Registry Service* provided the names for **25**, **26**, and **28**. Names for other macrocycles were derived from the name of **26**.

Complexation Studies. All ^{1}H-NMR titration data were acquired on a *Bruker* 500-MHz NMR spectrometer thermostated to ± 0.1 K at 300 K. For each binding study, 10 titration samples (0.7 ml) were prepared with *Gilson Pipetman* (200 μl and 1000 μl) pipettes from stock solns. of hosts and guests. Quantitative binding data (K_a, ΔG°, $\Delta\delta_{sat}$) were obtained with the nonlinear least-squares curve-fitting program *Associate V. 1.6* [27a].

Kinetic Studies. For the determination of initial rates of the oxidation reaction of naphthalene-2-carbaldehyde to methyl naphthalene-2-carboxylate, a mixture of methanolic stock solns. of naphthalene-2-carbaldehyde (2.5–62.5 mM, 480 μl) and bis(coenzyme) catalyst (120 μl) was purged with Ar for 4 min in a 0.2-cm optical cuvette. The cuvette was then stoppered and thermostated to 300 K in a *Varian Cary 5* instrument for 2 min. Et_3N (4.2 μl, 30 μmol) was added, the soln. was shaken, and the decrease of the visible flavin chromophore at the wavelength λ was subsequently monitored. This exponential decrease was preceded by a short incubation time with constant absorbance. The wavelength λ was chosen in such a manner that the initial absorbance was A_0 = 1.0: λ = 455.0, 505.2, and 510.4 nm for **6**, **7**, and {**8** + **9**}, respectively. Initial velocities were calculated by standard linear-regression analysis using the initial linear portions (*i.e.*, the initial 5–10% of the exponential decrease or *ca.* 0.5 s) of absorbance *vs.* time plots. Experiments were run in triplicate with the concentrations of bis(coenzyme) catalyst stock solns. being [**6**] = 2.5 mM, [**7**] = 10 mM ([**8**] = 50 mM and [**9**] = 10 mM), respectively. An *Eadie-Hofstee* plot (v *vs.* v/[naphthalene-2-carbaldehyde]) was used to calculate the maximal velocity (v_{max}) and the *Michaelis* constant (K_M) for the reaction catalyzed by **6**. The v_{max} and K_M values obtained from the saturation kinetics data with the nonlinear least-squares curve fitting program *Associate V. 1.6* [27a] were identical to those determined from the *Eadie-Hofstee* plot; moreover, *Associate V. 1.6* determined the accuracies of the v_{max} and K_M values to be ±7% and ±14%, respectively. The turnover number (k_{cat}) was calculated by dividing the maximal velocity v_{max} by the concentration of the catalyst **6**. The second-order rate constants for the reactions catalyzed by **7** and {**8** + **9**} were calculated by taking the slope of the line created by plotting v *vs.* [naphthalene-2-carbaldehyde] and dividing by the concentration of the thiazolium catalyst (**7** and **8**, resp.).

Cyclic Voltammetry. Experiments were performed on a *EG & G Princeton Applied Research Potentiostat/Galvanostat* model *273* in a thermostated three-electrode cell with a Ag/AgCl/3M aq. NaCl reference electrode (*BAS MF-2063*), an Au counter electrode (*BAS MF-2014*, d = 1.6 mm), and a Pt (*BAS MF-2013*, d = 1.6 mm) or glassy carbon (*BAS MF-2012*, d = 3.0 mm) working electrode. A soln. of 10 μmol of the electroactive compound in a 50 mM Et_4NBr soln. in MeOH (10 ml) was purged with Ar for 10 min; then degassed Et_3N (0.1 ml) was added, and the experiment started.

Electrolysis Experiments. Electrochemical oxidations of aldehydes were performed on a *EG & G Princeton Applied Research Potentiostat/Galvanostat* model *263A* in a thermostated three-electrode cell using a Ag/AgCl/3M aq. NaCl reference electrode (*BAS MF-2063*), a Pt foil (50 × 12 × 0.1 mm) working electrode, and a Pt foil (12 × 10 × 0.1 mm) counter electrode. In a typical experiment, the aldehyde (1.5 mmol) and Et_3N (1.5 mmol) were

dissolved in a 50 mM soln. of Et_4NBr in MeOH (5 ml), and the soln. was purged with Ar for 20 min. After addition of a degassed soln. of the bis(coenzyme) catalyst (**6**, **7**, or {**8** + **9**}; 50 μmol) in a 50 mM soln. of Et_4NBr in MeOH (5 ml), the temp. was set at 308 K and the electrolysis started. The working electrode potential was −0.3 V *vs.* Ag/AgCl. After 16 h, CH_2Cl_2 was added, and the soln. was washed with H_2O (40 ml), dried ($MgSO_4$), and evaporated. The products were isolated by FC (10 g of SiO_2, CH_2Cl_2).

*6-[(4-Bromophenyl)butylamino]-1*H*-pyrimidine-2,4-dione* (**12**). A suspension of **11** (10.8 g, 41.6 mmol) [21a] in EtOH (10 ml) was treated at 0° with Br_2 (33.3 g, 208 mmol). The orange solid formed was allowed to stand for 30 min at r.t., then a soln. of Na_2SO_3 (40 g, 320 mmol) in AcOH/H_2O 1:1 (200 ml) was added, and the suspension was refluxed for 30 min. Evaporation gave a white solid residue which was washed with H_2O (1000 ml) and filtered. Recrystallization from EtOH/AcOH 8:1 (*ca.* 450 ml) afforded **12** (11.4 g, 81%). White crystals. M.p. 254–256°. IR (KBr): 3417*w* (br.), 3128*w*, 2958*m*, 1703*s*, 1646*s*, 1620*s*, 1578*s*, 1488*m*, 1370*m*, 1211*m*, 534*w*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 10.46 (br. *s*, 1 H); 10.32 (br. *s*, 1 H); 7.63 (*dm*, *J* = 8.7, 2 H); 7.22 (*dm*, *J* = 8.7, 2 H); 4.34 (*d*, *J* = 1.1, 1 H); 3.60 (*m*, 2 H); 1.50–1.40 (*m*, 2 H); 1.30–1.20 (*m*, 2 H); 0.84 (*t*, *J* = 7.3, 3 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 163.7 (*s*); 153.9 (*s*); 151.1 (*s*); 141.7 (*s*); 132.6 (*d*); 129.4 (*d*); 119.5 (*s*); 78.7 (*d*); 50.8 (*t*); 29.0 (*t*); 19.1 (*t*); 13.6 (*q*). FAB-MS: 338/340 (100/99, MH^+). Anal. calc. for $C_{14}H_{16}BrN_3O_2$ (338.21): C 49.72, H 4.77, N 12.42, Br 23.63; found: C 49.45, H 4.53, N 12.31, Br 23.81.

*7-Bromo-10-butylbenzo[*g*]pteridine-2,4(3*H*,10*H*)-dione 5-Oxide* (**13**). $NaNO_2$ (11.6 g, 169 mmol) was added to a suspension of **12** (11.4 g, 33.7 mmol) in AcOH (100 ml) in a flask open to the air. After stirring for 2 h, H_2O (400 ml) was added and the suspension stored for 2 h at 4°. The precipitate was filtered, washed with H_2O, and dried (80°, 100 mbar, 16 h): **13** (10.8 g, 88%). Orange solid. M.p. 235° (dec.; aq. AcOH). UV/VIS: 272 (4.62), 325 (3.75), 338 (3.88), 354 (3.78), 459 (3.84). Fluorescence: $\lambda_{max.\ em.}$ = 517 nm. IR (KBr): 3438*w* (br.), 3109*w*, 3028*w*, 2956*w*, 1693*s*, 1664*s*, 1534*s*, 1221*m*, 1184*m*, 1114*w*, 445*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 11.22 (br. *s*, 1 H); 8.41 (*d*, *J* = 2.3, 1 H); 8.09 (*dd*, *J* = 9.3, 2.3, 1 H); 7.95 (*d*, *J* = 9.3, 1 H); 4.51 (*m*, 2 H); 1.70–1.60 (*m*, 2 H); 1.50–1.40 (*m*, 2 H); 0.95 (*t*, *J* = 7.3, 3 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 156.3 (*s*); 154.3 (*s*); 152.7 (*s*); 137.6 (*d*); 134.6 (*s*); 133.0 (*s*); 126.1 (*s*); 122.6 (*d*); 119.5 (*d*); 117.5 (*s*); 44.0 (*t*); 28.6 (*t*); 19.2 (*t*); 13.6 (*q*). FAB-MS: 365/367 (99/100, MH^+). Anal. calc. for $C_{14}H_{13}BrN_4O_3$ (365.19): C 46.05, H 3.59, N 15.34; found: C 46.09, H 3.62, N 15.18.

*7-Bromo-3,10-dibutylbenzo[*g*]pteridine-2,4(3*H*,10*H*)-dione* (**10**) *and 7-Bromo-10-butylbenzo[*g*]pteridine-2,4-(3*H*,10*H*)-dione* (**14**). A soln. of **13** (365 mg, 1.00 mmol) in DMF (2 ml) was refluxed for 5 h in the dark. After evaporation, the residue **14** was stirred at r.t. in DMF (4 ml) for 16 h with Cs_2CO_3 (652 mg, 2.00 mmol) and BuBr (1.37 g, 10.0 mmol). Filtration, evaporation, and FC (10 g of SiO_2; cyclohexane/AcOEt 1:1) gave **10** (325 mg, 80%).

Data of **14**: Orange solid. M.p. 275° (dec.; EtOH/AcOH). UV/VIS: 271 (4.48), 323 (3.62), 444 (3.85). Fluorescence: $\lambda_{max.\ em.}$ = 508 nm. IR (KBr): 3422*w* (br.), 3156*w*, 3100*w*, 3033*w*, 2957*m*, 2811*w*, 1711*m*, 1658*s*, 1602*m*, 1549*s*, 1511*m*, 1248*m*, 818*m*, 447*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 11.46 (br. *s*, 1 H); 8.35 (*d*, *J* = 2.0, 1 H); 8.06 (*dd*, *J* = 9.2, 2.0, 1 H); 7.92 (*d*, *J* = 9.2, 1 H); 4.51 (*m*, 2 H); 1.75–1.60 (*m*, 2 H); 1.55–1.40 (*m*, 2 H); 0.95 (*t*, *J* = 7.3, 3 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 159.3 (*s*); 155.4 (*s*); 150.3 (*s*); 139.7 (*s*); 136.9 (*d*); 135.6 (*s*); 133.2 (*d*); 131.7 (*s*); 118.3 (*d*); 117.5 (*s*); 44.1 (*t*); 28.4 (*t*); 19.4 (*t*); 13.6 (*q*). FAB-MS: 349/351 (77/100, MH^+). Anal. calc. for $C_{14}H_{13}BrN_4O_2$ (349.19): C 48.16, H 3.75, N 16.04; found: C 47.90, H 3.83, N 15.74.

Data of **10**: Orange solid. M.p. 211–213° (EtOH/AcOEt). UV/VIS: 274 (4.66), 325 (3.82), 446 (3.98). Fluorescence: $\lambda_{max.\ em.}$ = 506 nm. IR ($CHCl_3$): 3007*w*, 2963*w*, 1711*m*, 1659*s*, 1606*s*, 1588*m*, 1555*s*, 1245*w*, 1183*m*, 814*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.45 (*d*, *J* = 2.3, 1 H); 7.95 (*dd*, *J* = 9.2, 2.3, 1 H); 7.51 (*d*, *J* = 9.2, 1 H); 4.66 (*m*, 2 H); 4.10 ('*t*', *J* = 7.5, 2 H); 1.90–1.75 (*m*, 2 H); 1.75–1.65 (*m*, 2 H); 1.60–1.50 (*m*, 2 H); 1.50–1.35 (*m*, 2 H); 1.03 (*t*, *J* = 7.3, 3 H); 0.96 (*t*, *J* = 7.3, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.0 (*s*); 155.3 (*s*); 148.6 (*s*); 138.2 (*d* + *s*); 136.4 (*s*); 135.3 (*d*); 131.7 (*s*); 119.1 (*s*); 116.5 (*d*); 44.8 (*t*); 42.0 (*t*); 29.8 (*t*); 29.1 (*t*); 20.2 (*t*, 2×); 13.8 (*q*, 2×). FAB-MS: 405/407 (96/100, MH^+). Anal. calc. for $C_{18}H_{21}BrN_4O_2$ (405.30): C 53.34, H 5.22, N 13.82; found: C 53.43, H 5.40, N 14.01.

*3,10-Dibutyl-7-(2-methoxyphenyl)benzo[*g*]pteridine-2,4(3*H*,10*H*)-dione* (**9**). To a soln. of **10** (405 mg, 1.00 mmol) and 2-methoxybenzene-1-boronic acid (152 mg, 1.00 mmol) [49] in benzene (20 ml) and EtOH (5 ml) was added 0.2M aq. Na_2CO_3 soln. (10 ml, 2.0 mmol). The two-phase mixture was purged with Ar for 10 min and, after addition of $[PdCl_2(PPh_3)_2]$ (35.1 mg, 50.0 μmol), was refluxed for 16 h. Dilution with AcOEt (40 ml), washing with sat. aq. $NaHCO_3$ soln. (40 ml) and sat. aq. NaCl soln. (40 ml), drying ($MgSO_4$), and FC (20 g of SiO_2; hexane/AcOEt 3:2 → 1:1) gave **9** (333 mg, 77%). Orange foam. M.p. 78–82° (aq. MeOH). UV/VIS: 278 (4.53), 332 (3.79), 453 (3.91). Fluorescence: $\lambda_{max.\ em.}$ = 543 nm. IR ($CHCl_3$): 3008*w*, 1706*m*, 1654*s*, 1620*m*, 1590*s*, 1552*s*, 1528*m*, 1466*w*, 1435*w*, 1249*w*, 1188*m*, 1027*w*, 820*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.52 (*d*, *J* = 2.1, 1 H); 8.13 (*dd*, *J* = 9.0, 2.1, 1 H); 7.64 (*d*, *J* = 9.0, 1 H); 7.45–7.35 (*m*, 2 H); 7.10 (*td*, *J* = 7.5, 1.0, 1 H); 7.05 (br. *d*, *J* = 8.3, 1 H); 4.80–4.70 (*m*, 2 H); 4.12 ('*t*', *J* = 7.5, 2 H); 3.87 (*s*, 3 H); 1.95–1.85 (*m*, 2 H); 1.80–1.70

(*m*, 2 H); 1.65–1.55 (*m*, 2 H); 1.50–1.40 (*m*, 2 H); 1.05 (*t*, *J* = 7.4, 3 H); 0.97 (*t*, *J* = 7.4, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 159.7 (*s*); 156.5 (*s*); 155.7 (*s*); 148.6 (*s*); 137.5 (*d*); 137.07 (*s*); 137.04 (*s*); 136.0 (*s*); 133.4 (*d*); 131.4 (*s*); 130.6 (*d*); 130.0 (*d*); 127.3 (*s*); 121.3 (*d*); 114.5 (*d*); 111.5 (*d*); 55.6 (*q*); 44.7 (*t*); 41.9 (*t*); 29.9 (*t*); 29.2 (*t*); 20.25 (*t*); 20.24 (*t*); 13.86 (*q*); 13.80 (*q*). FAB-MS: 433 (100, MH$^+$). Anal. calc. for $C_{25}H_{28}N_4O_3 \cdot {}^1/_3\ H_2O$ (438.53): C 68.47, H 6.58, N 12.77; found: C 68.47, H 6.60, N 12.68.

1-Acetyl-1,2,3,6-tetrahydro-4-(4-hydroxy-3,5-dimethylphenyl)pyridine (**17**). Br_3B (56.4 g, 225 mmol) was slowly added at −78° to a soln. of **16** (13.9 g, 50.0 mmol) [17] in CH_2Cl_2 (550 ml). The ice bath was removed, and the resulting suspension was refluxed for 3 h, then carefully quenched with MeOH (50 ml) at 0°. Washing with H_2O (400 ml), 2M aq. HCl soln., and sat. aq. NaCl soln. (400 ml), drying ($MgSO_4$), evaporation, and recrystallization from PhMe (*ca.* 200 ml) provided air-sensitive **17** (11.4 g, 93%). White crystals. M.p. 147–149° (dec.). IR ($CHCl_3$): 3605*w*, 3376*w* (br.), 3006*m*, 1626*s*, 1489*m*, 1450*s*, 1243*m*, 1172*s*, 980*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 6.99, 6.98 (2*s*, 2 H); 5.93, 5.87 (2*m*, 1 H); 5.37 (br. *s*, 1 H); 4.20, 4.09 (2*dd*, *J* = 5.7, 2.7, 2 H); 3.79, 3.63 (2*t*, *J* = 5.8, 2 H); 2.54, 2.49 (2*m*, 2 H); 2.258, 2.257 (2*s*, 6 H); 2.16, 2.13 (2*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 169.5, 169.3 (2*s*); 152.2, 152.1 (2*s*); 136.5, 134.5 (2*s*); 132.27, 132.20 (2*s*); 125.25, 125.22 (2*d*); 123.30, 123.29 (2*s*); 118.8, 117.1 (2*d*); 45.8, 42.2 (2*t*); 43.5, 38.5 (2*t*); 28.0, 27.2 (2*t*); 21.8, 21.4 (2*q*); 16.2 (*q*). EI-MS: 43 (32), 159 (27), 174 (21), 188 (37), 202 (57), 245 (100, M^+). Anal. calc. for $C_{15}H_{19}NO_2$ (245.32): C 73.44, H 7.81, N 5.71; found: C 73.34, H 7.78, N 5.61.

1-Acetyl-4-{3,5-dimethyl-4-[(2-nitrophenyl)methoxy]phenyl}-1,2,3,6-tetrahydropyridine (**18**). A suspension of **17** (11.4 g, 46.5 mmol) and 2-nitrobenzyl chloride (10.4 g, 60.4 mmol) in MeCN (150 ml) was purged with Ar for 10 min. K_2CO_3 (12.8 g, 92.9 mmol) was added, and the mixture was refluxed for 5 h. Filtration, evaporation, dilution with PhMe (150 ml), washing with 2M aq. NaOH soln. (2 × 150 ml) and sat. aq. NaCl soln. (150 ml), drying ($MgSO_4$), and evaporation gave a yellow oil which solidified overnight at 4°. This solid was suspended in p.e. (200 ml), and the mixture was refluxed for 2 h, then stored for 16 h at 4°. The precipitate was filtered and dried to give **18** (17.4 g, 98%). Yellow powder. M.p. 117–118° (CH_3NO_2). IR ($CHCl_3$: 3006*w*, 1628*s*, 1526*s*, 1448*m*, 1342*m*, 1167*m*, 1020*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.20–8.15 (*m*, 2 H); 7.77 (*td*, *J* = 7.8, 1.2, 1 H); 7.51 (*tm*, *J* = 7.8, 1 H); 7.07, 7.06 (2*s*, 2 H); 6.02, 5.95 (2*m*, 1 H); 5.23 (*s*, 2 H); 4.23, 4.12 (2*dd*, *J* = 5.7, 2.7, 2 H); 3.81, 3.65 (2*t*, *J* = 5.7, 2 H); 2.57, 2.52 (2*m*, 2 H); 2.28 (*s*, 6 H); 2.17, 2.15 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 169.4, 169.2 (2*s*); 155.0, 154.8 (2*s*); 146.5 (*s*); 136.50, 136.47 (2*s*); 136.37, 134.4 (2*s*); 134.7 (*s*); 134.1 (*d*); 130.91, 130.88 (2*s*); 128.3 (*d*); 128.1 (*d*); 125.68, 125.63 (2*d*); 124.8 (*d*); 120.5, 118.7 (2*d*); 70.1 (*t*); 45.8, 42.2 (2*t*); 43.4, 38.3 (2*t*); 28.0, 27.2 (2*t*); 21.9, 21.5 (2*q*); 16.5 (*q*). EI-MS: 43 (32), 78 (34), 136 (43), 174 (37), 202 (100), 244 (67), 380 (16, M^+). Anal. calc. for $C_{22}H_{24}N_2O_4$ (380.45): C 69.46, H 6.36, N 7.36; found: C 69.47, H 6.54, N 7.39.

1-Acetyl-4-{3,5-dimethyl-4-[(2-nitrophenyl)methoxy]phenyl}-4-(4-hydroxy-3-methylphenyl)piperidin (**19**). A soln. of **18** (17.4 g, 45.7 mmol), 2-methylphenol (14.8 g, 137 mmol), and $BF_3 \cdot OEt_2$ (19.5 g, 137 mmol) in CH_2Cl_2 (15 ml) was stirred at 50°. After 24 h, the reaction was quenched with MeOH (30 ml) and the soln. was diluted with CH_2Cl_2 (200 ml), washed with H_2O (200 ml) and sat. aq. NaCl soln. (200 ml), dried ($MgSO_4$), and concentrated. Most of the excess *o*-cresol was distilled off *in vacuo* at 90°. CC (500 g of SiO_2; CH_2Cl_2, then CH_2Cl_2/MeOH 30:1) and evaporation afforded a brown foam, from which **19** (20.7 g, 93%) precipitated on addition of $MeNO_2$ (20 ml). White solid. M.p. 182–184°. IR ($CHCl_3$): 3600*w*, 3322*w* (br.), 3004*w*, 1625*s*, 1526*s*, 1455*m*, 1343*m*, 1147*w*, 1022*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.20–8.15 (*m*, 2 H); 7.74 (*td*, *J* = 7.8, 1.2, 1 H); 7.49 (*tm*, *J* = 7.8, 1 H); 6.97 (br. *d*, *J* = 2.2, 1 H); 6.91 (*dd*, *J* = 8.4, 2.2, 1 H); 6.88 (*s*, 2 H); 6.76 (*d*, *J* = 8.4, 1 H); 6.72 (*s*, 1 H); 5.19 (*s*, 2 H); 3.75–3.70 (*m*, 1 H); 3.65–3.60 (*m*, 1 H); 3.55–3.45 (*m*, 2 H); 2.35–2.30 (*m*, 4 H); 2.22 (*s*, 3 H); 2.21 (*s*, 6 H); 2.11 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 169.3 (*s*); 153.4 (*s*); 152.8 (*s*); 146.4 (*s*); 142.7 (*s*); 137.4 (*s*); 134.9 (*s*); 134.1 (*d*); 130.7 (*s*); 129.4 (*d*); 128.3 (*d*); 128.0 (*d*); 127.4 (*d*); 125.3 (*d*); 124.8 (*d*); 124.2 (*s*); 114.9 (*d*); 69.9 (*t*); 43.8 (*t*); 43.7 (*s*); 38.9 (*t*); 36.9 (*t*); 36.0 (*t*); 21.4 (*w*); 16.7 (*q*); 16.4 (*q*). FAB-MS: 489 (100, MH$^+$). Anal. calc. for $C_{29}H_{32}N_2O_5$ (488.59): C 71.29, H 6.60, N 5.73; found: C 71.08, H 6.67, N 5.79.

1-Acetyl-4-(3-bromo-4-hydroxy-5-methylphenyl)-4-{3,5-dimethyl-4-[(2-nitrophenyl)methoxy]phenyl}-piperidine (**20**). Br_2 (10.1 g, 63.2 mmol) was added dropwise to a soln. of **19** (20.6 g, 42.1 mmol) in CH_2Cl_2 (150 ml) at 0°. The soln. was stirred for 20 min at 0°, then washed with sat. aq. Na_2SO_3 soln. (200 ml) and sat. aq. NaCl soln. (200 ml), dried ($MgSO_4$), and concentrated. The crude product was recrystallized (MeOH, 50 ml), the mother liquor was filtered through a plug (SiO_2; CH_2Cl_2/MeOH 50:1), evaporated, and the residue also recrystallized (MeOH, 10 ml) to afford **20** in a combined yield of 21.9 g (92%). White solid. M.p. 162–163°. IR ($CHCl_3$): 3523*w*, 3400*w* (br.), 3004*m*, 1628*s*, 1526*s*, 1483*m*, 1455*m*, 1342*m*, 1152*m*, 1021*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.17 (br. *dd*, *J* = 7.8, 1.2, 1 H); 8.16 (*dd*, *J* = 7.8, 1.2, 1 H); 7.75 (*td*, *J* = 7.8, 1.2, 1 H); 7.50 (*tm*, *J* = 7.8, 1 H); 7.16 (*d*, *J* = 2.1, 1 H); 6.93 (br. *d*, *J* = 2.1, 1 H); 6.88 (*s*, 2 H); 5.67 (*s*, 1 H); 5.21 (*s*, 2 H); 3.75–3.60 (*m*, 2 H); 3.55–3.45 (*m*, 2 H); 2.40–2.30 (*m*, 4 H); 2.26 (*s*, 3 H); 2.23 (*s*, 6 H); 2.09 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$):

168.9 (*s*); 153.6 (*s*); 148.7 (*s*); 146.5 (*s*); 141.7 (*s*); 139.6 (*s*); 134.8 (*s*); 134.1 (*d*); 130.9 (*s*); 129.0 (*d*); 128.2 (*d*); 128.0 (*d*); 127.6 (*d*); 127.4 (*d*); 125.9 (*s*); 124.8 (*d*); 110.3 (*s*); 69.9 (*t*); 43.7 (*s*); 43.6 (*t*); 38.6 (*t*); 36.8 (*t*); 35.9 (*t*); 21.4 (*q*); 17.1 (*q*); 16.7 (*q*). FAB-MS 567/569 (100/97, MH$^+$). Anal. calc. for $C_{29}H_{31}BrN_2O_5$ (567.48): C 61.38, H 5.51, N 4.94, Br 14.08; found: C 61.37, H 5.51, N 4.89, Br 14.28.

1-Acetyl-4-[3-bromo-4-(4-bromobutoxy)-5-methylphenyl]-4-{3,5-dimethyl-4-[(2-nitrophenyl)methoxy]phenyl}-piperidine (**21**). To a soln. of **20** (284 mg, 0.500 mmol) and 2,6-di(*tert*-butyl)-4-methylphenol (11.0 mg, 50.0 µmol) in acetone (4 ml) were added 1,4-dibromobutane (1.08 g, 5.00 mmol) and K_2CO_3 (207 mg, 1.50 mmol), and the mixture was refluxed for 2 h. Filtration, evaporation, and CC (10 g of SiO_2, CH_2Cl_2/MeOH 80:1) gave **21** (327 mg, 93%). White foam. IR ($CHCl_3$): 3006*w*, 1628*s*, 1526*s*, 1455*m*, 1343*m*, 1153*w*, 1022*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.20–8.15 (*m*, 2 H); 7.75 (*td*, J = 7.8, 1.2, 1 H); 7.50 (*tm*, J = 7.8, 1 H); 7.24 (*d*, J = 2.2, 1 H); 6.96 (br. *d*, J = 2.2, 1 H); 6.88 (*s*, 2 H); 5.21 (*s*, 2 H); 3.90 (*t*, J = 6.1, 2 H); 3.75–3.65 (*m*, 1 H); 3.65–3.55 (*m*, 1 H); 3.53 (*t*, J = 6.7, 2 H); 3.50–3.45 (*m*, 2 H); 2.40–2.20 (*m*, 4 H); 2.28 (*s*, 3 H); 2.23 (*s*, 6 H); 2.20–2.10 (*m*, 2 H); 2.09 (*s*, 3 H); 2.00–1.90 (*m*, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 168.9 (*s*); 153.7 (*s*); 152.4 (*s*); 146.5 (*s*); 143.8 (*s*); 141.3 (*s*); 134.8 (*s*); 134.1 (*d*); 133.0 (*s*); 131.0 (*s*); 129.3 (*d*); 129.0 (*d*); 128.3 (*d*); 128.1 (*d*); 127.4 (*d*); 124.8 (*d*); 117.5 (*s*); 71.5 (*t*); 69.9 (*t*); 43.9 (*s*); 43.5 (*t*); 38.5 (*t*); 36.7 (*t*); 35.8 (*t*); 33.7 (*t*); 29.5 (*t*); 28.8 (*t*); 21.4 (*q*); 17.2 (*q*); 16.7 (*q*). FAB-MS: 701/703/705 (57/100/53, MH$^+$). Anal. calc. for $C_{33}H_{38}Br_2N_2O_5$ (702.49): C 56.42, H 5.45, N 3.99; found: C 56.30, H 5.54, N 3.95.

1-Acetyl-4-[3-bromo-4-(4-iodobutoxy)-5-methylphenyl]-4-{3,5-dimethyl-4-[(2-nitrophenyl)methoxy]phenyl}-piperidine (**22**). To a soln. of **20** (12.6 g, 22.1 mmol) and 2,6-di(*tert*-butyl)-4-methylphenol (488 mg, 2.21 mmol) in acetone (180 ml) were added 1,4-diiodobutane (34.3 g, 111 mmol) and K_2CO_3 (9.18 g, 66.4 mmol), and the mixture was refluxed for 4 h. Filtration, evaporation, and CC (200 g of SiO_2; CH_2Cl_2/MeOH 80:1) afforded **22** (15.1 g, 91%). White foam. IR ($CHCl_3$): 3005*w*, 1628*s*, 1526*s*, 1455*m*, 1343*m*, 1153*w*, 1021*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.20–8.15 (*m*, 2 H); 7.74 (br. *t*, J = 7.8, 1 H); 7.50 (br. *t*, J = 7.8, 1 H); 7.24 (*d*, J = 2.3, 1 H); 6.95 (br. *d*, J = 2.3, 1 H); 6.88 (*s*, 2 H); 5.21 (*s*, 2 H); 3.89 (*t*, J = 6.1, 2 H); 3.75–3.55 (*m*, 2 H); 3.55–3.45 (*m*, 2 H); 3.30 (*t*, J = 6.9, 2 H); 2.40–2.25 (*m*, 4 H); 2.27 (*s*, 3 H); 2.23 (*s*, 6 H); 2.15–2.05 (*m*, 2 H); 2.08 (*s*, 3 H); 1.95–1.90 (*m*, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 168.9 (*s*); 153.7 (*s*); 152.4 (*s*); 146.5 (*s*); 143.8 (*s*); 141.3 (*s*); 134.8 (*s*); 134.1 (*d*); 133.0 (*s*); 131.0 (*s*); 129.3 (*d*); 129.0 (*d*); 128.3 (*d*); 128.1 (*d*); 127.5 (*d*); 124.8 (*d*); 117.5 (*s*); 71.3 (*t*); 69.9 (*t*); 43.9 (*s*); 43.5 (*t*); 38.5 (*t*); 36.8 (*t*); 35.9 (*t*); 31.1 (*t*); 30.2 (*t*); 21.4 (*q*); 17.2 (*q*); 16.7 (*q*); 6.7 (*t*). FAB-MS: 749/751 (100/97, MH$^+$). Anal. calc. for $C_{33}H_{38}BrIN_2O_5$ (749.49): C 52.88, H 5.11, N 3.74; found: C 53.02, H 5.33, N 3.67.

1-Acetyl-4-{4-{4-{4-{1-acetyl-4-{3,5-dimethyl-4-[(2-nitrophenyl)methoxy]phenyl}piperidin-4-yl}-2-bromo-6-methylphenoxy}butoxy}-3,5-dimethylphenyl}-1,2,3,6-tetrahydropyridine (**23**). *Method A*: To a soln. of **22** (15.0 g, 20.0 mmol) and **17** (4.91 g, 20.0 mmol) in acetone (200 ml) was added Cs_2CO_3 (13.0 g, 40.0 mmol), and the mixture was stirred at 40° for 6 h. Filtration, evaporation, dissolution of the residue in CH_2Cl_2 (200 ml), washing with 2M aq. NaOH soln. (2 × 200 ml) and sat. aq. NaCl soln. (200 ml), drying ($MgSO_4$), evaporation, and FC (300 g of SiO_2; CH_2Cl_2/MeOH 100:1 → 40:1) yielded **23** (13.9 g, 80%). White foam. *Method B*: Compound **23** was obtained in a similar manner by reacting **21** (100 mg, 0.142 mmol), **17** (34.9 mg, 0.142 mmol), and Cs_2CO_3 (92.8 mg, 0.285 mmol) in acetone (1.5 ml) for 24 h at 40°. Yield 74.1 mg (60%). IR ($CHCl_3$): 3007*m*, 1628*s*, 1526*m*, 1477*m*, 1450*m*, 1372*w*, 1343*w*, 1153*w*, 1020*w*, 957*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.17 (br. *dd*, J = 7.8, 1.2, 1 H); 8.16 (*dd*, J = 7.8, 1.2, 1 H); 7.75 (*td*, J = 7.8, 1.2, 1 H); 7.50 (*tm*, J = 7.8, 1 H); 7.25 (*d*, J = 2.2, 1 H); 7.02, 7.01 (2*s*, 2 H); 6.97 (*dm*, J = 2.2, 1 H); 6.89 (*s*, 2 H); 5.99, 5.92 (2*m*, 1 H); 5.21 (*s*, 2 H); 4.21, 4.10 (2*dd*, J = 5.6, 2.5, 2 H); 4.00–3.95 (*m*, 2 H); 3.85–3.80 (*m*, 2 H); 3.79, 3.64 (2*t*, J = 5.8, 2 H); 3.75–3.65 (*m*, 1 H); 3.65–3.55 (*m*, 1 H); 3.55–3.45 (*m*, 2 H); 2.55, 2.50 (2*m*, 2 H); 2.40–2.25 (*m*, 4 H); 2.30 (*s*, 3 H); 2.29 (*s*, 6 H); 2.24 (*s*, 6 H); 2.16, 2.13 (2*s*, 3 H); 2.09 (*s*, 3 H); 2.10–2.00 (*m*, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 169.4, 169.2 (2*s*); 168.9 (*s*); 155.5, 155.4 (2*s*); 153.6 (*s*); 152.5 (*s*); 146.5 (*s*); 143.7 (*s*); 141.3 (*s*); 136.4, 134.5 (2*s*); 135.73, 135.69 (2*s*); 134.8 (*s*); 134.1 (*d*); 133.1 (*s*); 131.0 (*s*); 130.83, 130.80 (2*s*); 129.3 (*d*); 128.9 (*d*); 128.3 (*d*); 128.1 (*d*); 127.4 (*d*); 125.45, 125.39 (2*d*); 124.8 (*d*); 120.0, 118.4 (2*d*); 117.6 (*s*); 72.4 (*t*); 72.0 (*t*); 69.9 (*t*); 45.8, 42.1 (2*t*); 43.9 (*s*); 43.5 (*t*); 43.4, 38.3 (2*t*); 38.5 (*t*); 36.7 (*t*); 35.8 (*t*); 28.0, 27.2 (2*t*); 27.10 (*t*); 27.01 (*t*); 21.9, 21.48 (2*q*); 21.41 (*q*); 17.2 (*q*); 16.7 (*q*); 16.5 (*q*). FAB-MS: 866/868 (100/99, MH$^+$). HR-FAB-MS: 866.3366 (MH$^+$, $C_{48}H_{57}BrN_3O_7^+$; calc. 866.3375).

1-Acetyl-4-{4-{4-{4-{1-acetyl-4-{3,5-dimethyl-4-[(2-nitrophenyl)methoxy]phenyl}piperidin-4-yl}-2-bromo-6-methylphenoxy}butoxy}-3,5-dimethylphenyl}-4-(4-hydroxy-3-methylphenyl)piperidine (**24**). A soln. of **23** (12.0 g, 13.8 mmol), 2-methylphenol (7.48 g, 69.2 mmol), and $BF_3 \cdot OEt_2$ (5.89 g, 41.5 mmol) in CH_2Cl_2 (10 ml) was stirred at 50° for 24 h. After quenching with MeOH (10 ml) at 0°, the soln. was diluted with CH_2Cl_2 (100 ml), washed with H_2O (100 ml) and sat. aq. NaCl soln. (100 ml), dried ($MgSO_4$), and evaporated. The product **24** (13.0 g, 96%) was isolated by FC (200 g of SiO_2; CH_2Cl_2 to elute excess *o*-cresol, then CH_2Cl_2/MeOH

50:1 → 30:1). White foam. IR ($CHCl_3$): 3600*w*, 3344*w* (br.), 3006*m*, 1627*s*, 1526*m*, 1455*m*, 1372*w*, 1342*m*, 1264*m*, 1152*m*, 991*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.17 (br. *dd*, *J* = 7.8, 1.2, 1 H); 8.16 (*dd*, *J* = 7.8, 1.2, 1 H); 7.74 (*td*, *J* = 7.8, 1.2, 1 H); 7.49 (*tm*, *J* = 7.8, 1 H); 7.24 (*d*, *J* = 2.2, 1 H); 7.18 (br. *s*, 1 H); 6.95 (br. *d*, *J* = 2.2, 1 H); 6.94 (br. *d*, *J* = 2.1, 1 H); 6.879 (*s*, 2 H); 6.878 (*dd*, *J* = 8.4, 2.1, 1 H); 6.83 (*s*, 2 H); 6.74 (*d*, *J* = 8.4, 1 H); 5.21 (*s*, 2 H); 3.95 (br. *t*, *J* = 5.5, 2 H); 3.82 (br. *t*, *J* = 5.5, 2 H); 3.75–3.65 (*m*, 2 H); 3.65–3.55 (*m*, 2 H); 3.55–3.40 (*m*, 4 H); 2.40–2.25 (*m*, 8 H); 2.28 (*s*, 3 H); 2.230 (*s*, 6 H); 2.222 (*s*, 6 H); 2.20 (*s*, 3 H); 2.09 (*s*, 3 H); 2.08 (*s*, 3 H); 2.05–2.00 (*m*, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 169.14 (*s*); 169.11 (*s*); 153.9 (*s*); 153.7 (*s*); 152.9 (*s*); 152.5 (*s*); 146.5 (*s*); 143.7 (*s*); 141.9 (*s*); 141.2 (*s*); 137.3 (*s*); 134.8 (*s*); 134.1 (*d*); 133.1 (*s*); 131.0 (*s*); 130.5 (*s*); 129.4 (*d*); 129.2 (*d*); 128.9 (*d*); 128.3 (*d*); 128.1 (*d*); 127.4 (*d*); 127.2 (*d*); 125.3 (*d*); 124.8 (*d*); 124.2 (*s*); 117.6 (*s*); 114.8 (*d*); 72.5 (*t*); 71.8 (*t*); 69.9 (*t*); 43.84 (*s*); 43.78 (*t*); 43.62 (*s*); 43.56 (*t*); 38.9 (*t*); 38.7 (*t*); 36.9 (*t*); 36.7 (*t*); 36.0 (*t*); 35.8 (*t*); 27.09 (*t*); 27.01 (*t*); 21.4 (*q*, 2 ×); 17.2 (*q*); 16.7 (*q*, 2 ×); 16.4 (*q*). FAB-MS: 974/976 (91/100, MH^+). HR-FAB-MS: 974.4156 (MH^+, $C_{55}H_{65}BrN_3O_8^+$; calc. 974.3950).

1-Acetyl-4-{4-{4-{4-[1-acetyl-4-(4-hydroxy-3,5-dimethylphenyl)piperidin-4-yl]-2-bromo-6-methylphenoxy}-butoxy}-3,5-dimethylphenyl}-4-(4-hydroxy-3-methylphenyl)piperidine (**25**). A soln. of **24** (569 mg, 0.583 mmol) in THF (10 ml) was irradiated at r.t. for 3 d. Dissolving the resultant suspension in CH_2Cl_2 (10 ml), evaporation, and FC (15 g of SiO_2; CH_2Cl_2/MeOH 50:1 → 20:1) yielded **25** (424 mg, 87%). White foam. IR ($CHCl_3$): 3603*w*, 3333*w* (br.), 3005*m*, 1626*s*, 1478*m*, 1455*s*, 1376*w*, 1264*m*, 1155*w*, 992*w*, 956*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.19 (*d*, *J* = 2.2, 1 H); 6.98 (br. *s*, 1 H); 6.95–6.90 (*m*, 2 H); 6.87 (*dd*, *J* = 8.4, 2.3, 1 H); 6.81 (*s*, 2 H); 6.79 (*s*, 2 H); 6.73 (*d*, *J* = 8.4, 1 H); 5.35 (br. *s*, 1 H); 3.93 (br. *t*, *J* = 5.7, 2 H); 3.81 (br. *t*, *J* = 5.7, 2 H); 3.80–3.40 (*m*, 8 H); 2.40–2.20 (*m*, 8 H); 2.25 (*s*, 3 H); 2.210 (*s*, 6 H); 2.201 (*s*, 6 H); 2.192 (*s*, 3 H); 2.07 (*s*, 6 H); 2.05–2.00 (*m*, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 169.2 (*s*, 2 ×); 153.9 (*s*); 152.8 (*s*); 152.4 (*s*); 150.8 (*s*); 144.3 (*s*); 141.9 (*s*); 137.4 (*s*); 136.4 (*s*); 132.9 (*s*); 130.5 (*s*); 129.4 (*d*); 129.2 (*d*); 128.8 (*d*); 127.2 (*d*); 127.0 (*d*); 125.3 (*d*); 124.1 (*s*); 123.5 (*s*); 117.5 (*s*); 114.9 (*d*); 72.4 (*t*); 71.8 (*t*); 43.8 (*t*); 43.6 (*s*, (2 ×) + *t*); 38.9 (*t*); 38.7 (*t*); 36.9 (*t*); 36.7 (*t*); 36.0 (*t*); 35.9 (*t*); 27.07 (*t*); 26.98 (*t*); 21.3 (*q*, 2 ×); 17.1 (*q*); 16.7 (*q*); 16.46 (*q*); 16.37 (*q*). FAB-MS: 839/841 (100/99, MH^+). Anal. calc. for $C_{48}H_{59}BrN_2O_6$ (839.92): C 68.64, N 7.08, N 3.34; found: C 68.41, H 7.23, N 3.36.

1-Acetyl-4-{4-{4-{4-{1-acetyl-4-{1-acetyl-4-[4-(4-bromobutoxy)-3-methylphenyl]piperidin-4-yl}-2,6-dimethylphenoxy}butoxy}-3-bromo-5-methylphenyl}-4-{3,5-dimethyl-4-[(2-nitrophenyl)methoxy]phenyl}}piperidine (**27**). A mixture of phenol **24** (12.9 g, 13.2 mmol), 1,4-dibromobutane (28.6 g, 132 mmol), and K_2CO_3 (5.49 g, 39.7 mmol) was refluxed for 24 h in MeCN (65 ml). Filtration, evaporation, and CC (200 g of SiO_2, CH_2Cl_2/MeOH 50:1) afforded **27** (13.3 g, 91%). White foam. IR ($CHCl_3$): 3005*w*, 1627*s*, 1526*m*, 1455*m*, 1343*w*, 1252*m*, 1152*w*, 992*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.17 (br. *dd*, *J* = 7.8, 1.2, 1 H); 8.16 (br. *dd*, *J* = 7.8, 1.2, 1 H); 7.75 (*td*, *J* = 7.8, 1.2, 1 H); 7.50 (*tm*, *J* = 7.8, 1 H); 7.24 (*d*, *J* = 2.1, 1 H); 7.00–6.95 (*m*, 2 H); 6.96 (br. *d*, *J* = 2.1, 1 H); 6.88 (*s*, 2 H); 6.83 (*s*, 2 H); 6.71 (*dm*, *J* = 9.3, 1 H); 5.21 (*s*, 2 H); 4.00–3.90 (*m*, 2 H); 3.96 (*t*, *J* = 5.9, 2 H); 3.85–3.80 (*m*, 2 H); 3.75–3.55 (*m*, 4 H); 3.50–3.45 (*m*, 4 H); 3.49 (*t*, *J* = 6.6, 2 H); 2.40–2.25 (*m*, 8 H); 2.29 (*s*, 3 H); 2.232 (*s*, 6 H); 2.228 (*s*, 6 H); 2.17 (*s*, 3 H); 2.10–2.00 (*m*, 2 H); 2.09 (*s*, 3 H); 2.07 (*s*, 3 H); 2.05–2.00 (*m*, 4 H); 1.95–1.90 (*m*, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 168.87 (*s*); 168.84 (*s*); 155.1 (*s*); 153.9 (*s*); 153.6 (*s*); 152.5 (*s*); 146.5 (*s*); 143.7 (*s*); 141.7 (*s*); 141.3 (*s*); 138.0 (*s*); 134.8 (*s*); 134.1 (*d*); 133.1 (*s*); 131.0 (*s*); 130.6 (*s*); 129.3 (*d*, 2 ×); 128.9 (*d*); 128.3 (*d*); 128.1 (*d*); 127.4 (*d*); 127.2 (*d*); 126.6 (*s*); 125.1 (*d*); 124.8 (*d*); 117.6 (*s*); 110.5 (*d*); 72.4 (*t*); 71.7 (*t*); 69.9 (*t*); 66.7 (*t*); 43.9 (*s*); 43.69 (*t*); 43.65 (*d*); 43.5 (*t*); 38.7 (*t*); 38.5 (*t*); 36.9 (*t*); 36.7 (*t*); 36.0 (*t*); 35.9 (*t*); 33.5 (*t*); 29.7 (*t*); 28.0 (*t*); 27.11 (*t*); 27.02 (*t*); 21.4 (*q*, 2 ×); 17.2 (*q*); 16.69 (*q*, 2 ×); 16.61 (*q*). FAB-MS: 1108/1110/1112 (57/100/63, MH^+). Anal. calc. for $C_{59}H_{71}Br_2N_3O_8$ (1110.05): C 63.84, H 6.45, N 3.79; found: C 63.76, H 6.54, N 3.81.

1-Acetyl-4-{4-{4-{4-{1-acetyl-4-[4-(4-bromobutoxy)-3-methylphenyl]piperidin-4-yl}-2,6-dimethylphenoxy}-butoxy}-3-bromo-5-methylphenyl}-4-(4-hydroxy-3,5-dimethylphenyl)piperidine (**28**). A soln. of **27** (4.00 g, 3.60 mmol) and 2,6-di(*tert*-butyl)-4-methylphenol (800 mg, 3.63 mmol) in THF (300 ml) was irradiated at r.t. for 20 h. Evaporation and FC (150 g of SiO_2; CH_2Cl_2/MeOH 70:1 → 30:1) gave **28** (3.38 g, 96%). White foam. IR ($CHCl_3$): 3600*w*, 3400*w* (br.), 3006*m*, 1627*s*, 1479*m*, 1455*m*, 1377*w*, 1252*m*, 1153*w*, 992*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.20 (*d*, *J* = 2.2, 1 H); 7.00–6.95 (*m*, 2 H); 6.93 (br. *d*, *J* = 2.2, 1 H); 6.83 (*s*, 2 H); 6.80 (*s*, 2 H); 6.70 (*dm*, *J* = 9.3, 1 H); 5.50 (br. *s*, 1 H); 3.95 (*t*, *J* = 5.9, 2 H); 3.95–3.90 (*m*, 2 H); 3.85–3.80 (*m*, 2 H); 3.80–3.55 (*m*, 4 H); 3.55–3.40 (*m*, 4 H); 3.48 (*t*, *J* = 6.6, 2 H); 2.40–2.25 (*m*, 8 H); 2.26 (*s*, 3 H); 2.22 (*s*, 6 H); 2.21 (*s*, 6 H); 2.17 (*s*, 3 H); 2.10–2.00 (*m*, 2 H); 2.07 (*s*, 6 H); 2.05–2.00 (*m*, 4 H); 2.00–1.90 (*m*, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 168.9 (*s*, 2 ×); 155.1 (*s*); 153.9 (*s*); 152.3 (*s*); 150.9 (*s*); 144.4 (*s*); 141.7 (*s*); 138.0 (*s*); 136.4 (*s*); 132.9 (*s*); 130.6 (*s*); 129.25 (*d*); 129.21 (*d*); 128.8 (*d*); 127.2 (*d*); 127.0 (*d*); 126.6 (*s*); 125.1 (*d*); 123.5 (*s*); 117.5 (*s*); 110.5 (*d*); 72.4 (*t*); 71.7 (*t*); 66.7 (*t*); 43.69 (*t*); 43.62 (*s*, 2 ×); 43.57 (*t*); 38.7 (*t*); 38.6 (*t*); 36.8 (*t*); 36.7 (*t*); 35.97 (*t*); 35.87 (*t*); 33.5 (*t*); 29.7 (*t*); 28.0 (*t*); 27.1 (*t*); 27.0 (*t*); 21.4 (*q*, 2 ×); 17.1 (*q*); 16.69 (*q*); 16.61 (*q*); 16.5 (*q*). FAB-MS: 973/975/977 (57/100/57, MH^+). Anal. calc. for $C_{52}H_{66}Br_2N_2O_6$ (974.92): C 64.06, H 6.82, N 2.87; found: C 63.94, H 6.76, N 2.88.

1,1''-Diacetyl-20'-bromo-5',14',29',32',33',36'-hexamethyldispiro[piperidine-4,2'-[7,12,22,27]tetraoxapentacyclo[26,2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta[3,5,13,15,18,20,28,30,31,33,35,37]dodecaene-17',4''-piperidine] (**26**). *Method A* (*intramolecular*): A soln. of **28** (7.37 g, 7.56 mmol) in MeCN (500 ml) was added over 30 h to a suspension of Cs_2CO_3 (14.8 g, 45.4 mmol) in refluxing MeCN (250 ml), and the mixture was refluxed for another 24 h. Filtration, evaporation, and FC (150 g of SiO_2; CH_2Cl_2/MeOH 50:1) yielded a white foam from which the product was precipitated by addition of EtOH (10 ml). After washing with Et_2O and drying (120°, 100 mbar, 3 h), **26** (5.58 g, 83%) was obtained. *Method B* (*bimolecular*): A soln. of **25** (411 mg, 0.489 mmol), 1,4-dibromobutane soln. (0.5M in MeCN, 0.98 ml, 0.49 mmol), and Cs_2CO_3 (957 mg, 2.94 mmol) in MeCN (490 ml) was refluxed for 48 h. The product **26** was isolated as described in *Method A* (179 mg, 41%). White powder. M.p. > 300°. IR ($CHCl_3$): 3004*m*, 1627*s*, 1500*w*, 1472*m*, 1454*s*, 1376*w*, 1251*m*, 1152*w*, 992*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.14 (*d*, *J* = 2.2, 1 H); 6.93 (br. *d*, *J* = 2.1, 1 H); 6.90 (br. *d*, *J* = 2.2, 1 H); 6.87 (*dd*, *J* = 8.6, 2.1, 1 H); 6.79 (*s*, 2 H); 6.75 (*s*, 2 H); 6.64 (*d*, *J* = 8.6, 1 H); 3.98 (br. *t*, *J* = 5.7, 2 H); 3.93 (br. *t*, *J* = 6.3, 2 H); 3.82 (br. *t*, *J* = 6.3, 2 H); 3.78 (br. *t*, *J* = 6.4, 2 H); 3.70–3.55 (*m*, 4 H); 3.50–3.40 (*m*, 4 H); 2.35–2.20 (*m*, 8 H); 2.21 (*s*, 3 H); 2.17 (*s*, 6 H); 2.16 (*s*, 6 H); 2.10 (*s*, 3 H); 2.05 (*s*, 6 H); 2.05–1.90 (*m*, 8 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 168.8 (*s*, 2×); 154.9 (*s*); 154.2 (*s*); 153.8 (*s*); 152.2 (*s*); 143.7 (*s*); 141.5 (*s*); 140.5 (*s*); 138.4 (*s*); 132.9 (*s*); 130.6 (*s*); 130.5 (*s*); 129.1 (*d*); 128.7 (*d*); 128.5 (*d*); 127.0 (*d*); 126.8 (*d*); 126.5 (*s*); 125.1 (*d*); 117.5 (*s*); 111.2 (*d*); 73.1 (*t*); 72.4 (*t*); 71.8 (*t*); 67.1 (*t*); 43.6 (*t*); 43.5 (*t*); 43.34 (*s*); 43.26 (*s*); 38.6 (*t*); 38.5 (*t*); 36.4 (*t*); 36.2 (*t*); 35.5 (*t*); 35.3 (*t*); 27.3 (*t*); 27.1 (*t*); 26.5 (*t*); 25.6 (*t*); 21.40 (*q*); 21.37 (*q*); 17.2 (*q*); 16.90 (*q*); 16.81 (*q*); 16.6 (*q*). FAB-MS: 893/895 (98/100, *M*H$^+$). Anal. calc. for $C_{52}H_{65}BrN_2O_6$ (894.01): C 69.86, H 7.33, N 3.13, O 10.74, Br 8.94; found: C 69.95, H 7.38, N 3.10, O 10.99, Br 8.69.

1,1''-Diethyl-20'-bromo-5',14',29',32',33',36'-hexamethyldispiro[piperidine-4,2'-[7,12,22,27]tetraoxapentacyclo[26,2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta[3,5,13,15,18,20,28,30,31,33,35,37]dodecaene-17',4''-piperidene] (**29**). To a soln. of **26** (447 mg, 0.500 mmol) in CH_2Cl_2 (10 ml) was added DIBAL-H (1M in CH_2Cl_2, 10.0 ml, 10.0 mmol) dropwise at 0°. After stirring for 16 h at r.t., the mixture was quenched by careful addition of MeOH (*ca.* 0.5 ml). CH_2Cl_2 (20 ml) and 2M aq. NaOH soln. (40 ml) were added, and the resulting suspension was stirred at r.t., until a clear two-phase mixture had formed (30 min). Washing of the org. layer with sat. aq. NaCl soln. (40 ml), drying ($MgSO_4$), and evaporation provided a white solid, which was stirred for 1 h in Et_2O (50 ml), filtered, and dried to yield **29** (375 mg, 87%). White powder. M.p. 290–292° (dec.; PhMe/Et_2O). IR ($CHCl_3$): 2950*s*, 1600*w*, 1506*m*, 1474*s*, 1450*m*, 1383*w*, 1310*w*, 1250*m*, 1156*m*, 1132*s*, 1012*m*, 660*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.15 (*d*, *J* = 2.2, 1 H); 6.95 (br. *d*, *J* = 2.1, 1 H); 6.90 (br. *d*, *J* = 2.2, 1 H); 6.86 (*dd*, *J* = 8.6, 2.1, 1 H); 6.79 (*s*, 2 H); 6.75 (*s*, 2 H); 6.62 (*d*, *J* = 8.6, 1 H); 3.97 (br. *t*, *J* = 5.9, 2 H); 3.92 (br. *t*, *J* = 6.5, 2 H); 3.81 (br. *t*, *J* = 6.5, 2 H); 3.78 (br. *t*, *J* = 6.6, 2 H); 2.55–2.30 (*m*, 16 H); 2.30 (*q*, *J* = 7.2, 4 H); 2.20 (*s*, 3 H); 2.155 (*s*, 6 H); 2.147 (*s*, 6 H); 2.09 (*s*, 3 H); 2.05–1.90 (*m*, 8 H); 1.034 (*t*, *J* = 7.2, 3 H); 1.032 (*t*, *J* = 7.2, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 154.5 (*s*); 153.9 (*s*); 153.4 (*s*); 151.9 (*s*); 144.9 (br. *s*); 142.5 (br. *s*); 141.9 (br. *s*); 139.8 (br. *s*); 132.4 (*s*); 130.2 (*s*); 130.0 (*s*); 129.4 (*d*); 129.1 (*d*); 128.9 (*d*); 127.3 (*d*); 127.1 (*d*); 126.1 (*s*); 125.3 (*d*); 117.2 (*s*); 111.0 (*d*); 73.0 (*t*); 72.4 (*t*); 71.7 (*t*); 67.1 (*t*); 52.43 (*t*); 52.38 (*t*); 50.3 (*t*); 50.1 (*t*); 43.25 (*s*); 43.18 (*s*); 36.0 (*t*); 35.9 (*t*); 27.2 (*t*); 27.1 (*t*); 26.5 (*t*); 25.7 (*t*); 17.2 (*q*); 16.89 (*q*); 16.82 (*q*); 16.6 (*q*); 12.2 (*q*, 2×). FAB-MS: 865/867 (99/100, *M*H$^+$). Anal. calc. for $C_{52}H_{69}BrN_2O_4$ (866.04): C 72.12, H 8.03, N 3.23; found: C 71.96, H 7.87, N 3.14.

20'-Bromo-5',14',29',32',33',36'-hexamethyldispiro[piperidine-4,2'-[7,12,22,27]tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta[3,5,13,15,18,20,28,30,31,33,35,37]dodecaene-17',4''-piperidine] (**33**). A soln. of **26** (8.19 g, 9.16 mmol) and KOH (10.3 g, 183 mmol) in degassed 2-methoxyethanol (150 ml) was refluxed for 8 h. After evaporation of about half of the solvent, H_2O (60 ml) was added and the suspension obtained was stored overnight at 4°. The crude product was filtered, washed with H_2O, and dried (100°, 100 mbar, 5 h), then dissolved in hot EtOH (60 ml). Addition of H_2O (60 ml), filtration of the precipitate, and drying (120°, 100 mbar, 3 h) gave **33** (7.06 g, 95%). White powder. M.p. 267–269° (dec.). IR ($CHCl_3$): 3289*w* (sh), 2933*s*, 1605*w*, 1504*s*, 1485*s*, 1377*w*, 1294*w*, 1250*m*, 1156*m*, 1134*m*, 1012*w*, 889*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.16 (*d*, *J* = 2.1, 1 H); 6.96 (br. *d*, *J* = 2.3, 1 H); 6.90 (br. *d*, *J* = 2.1, 1 H); 6.87 (*dd*, *J* = 8.6, 2.3, 1 H); 6.80 (*s*, 2 H); 6.75 (*s*, 2 H); 6.63 (*d*, *J* = 8.6, 1 H); 3.98 (br. *t*, *J* = 5.8, 2 H); 3.92 (br. *t*, *J* = 6.5, 2 H); 3.81 (br. *t*, *J* = 6.5, 2 H); 3.77 (br. *t*. *J* = 6.6, 2 H); 2.90–2.80 (*m*, 8 H); 2.30–2.20 (*m*, 8 H); 2.20 (*s*, 3 H); 2.162 (*s*, 6 H); 2.154 (*s*, 6 H); 2.10 (*s*, 3 H); 2.00–1.90 (*m*, 8 H); 1.52 (br. *s*, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 154.6 (*s*); 153.9 (*s*); 153.4 (*s*); 151.9 (*s*); 145.1 (*s*); 143.0 (*s*); 142.2 (*s*); 140.0 (*s*); 132.5 (*s*); 130.2 (*s*); 130.1 (*s*); 129.2 (*d*); 128.9 (*d*); 128.7 (*d*); 127.1 (*d*); 126.9 (*d*); 126.1 (*s*); 125.2 (*d*); 117.3 (*s*); 111.1 (*d*); 73.0 (*t*); 72.4 (*t*); 71.7 (*t*); 67.1 (*t*); 43.54 (*s*); 43.46 (*s*); 43.40 (*t*); 43.3 (*t*); 37.5 (*t*); 37.3 (*t*); 27.3 (*t*); 27.1 (*t*); 26.5 (*t*); 25.7 (*t*); 17.2 (*q*); 16.89 (*q*); 16.81 (*q*); 16.6 (*q*). FAB-MS: 809/811 (100/98, *M*H$^+$). Anal. calc. for $C_{48}H_{61}BrN_2O_4$ (809.94): C 71.18, H 7.59, N 3.46; found: C 71.25, H 7.65, N 3.39.

20'-Bromo-1,1''-dihexanoyl-5',14',29',32',33',36'-hexamethyldispiro[piperidine-4,2'-[7,12,22,27]tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta[3,5,13,15,18,20,28,30,31,33,35,37]dodecaene-17',4''-piperidine] (**34**).

A soln. of hexanoyl chloride (3.99 g, 29.6 mmol) in THF (50 ml) was added over 30 min to a soln. of **33** (6.00 g, 7.41 mmol) and Et_3N (3.75 g, 37.0 mmol) in THF (100 ml) at r.t., and the suspension formed was stirred for another 30 min. Et_2O (200 ml) and 2M aq. NaOH soln. (200 ml) were added, and the two-phase mixture was stirred for 30 min. Removal of the aq. layer, washing with 2M aq. HCl (200 ml) and sat. aq. NaCl soln. (200 ml), drying ($MgSO_4$), evaporation, and CC (100 g of SiO_2; hexane/AcOEt 2:1 → 1:1) yielded **34** (7.05 g, 95%). White foam. M.p. 215–217° (benzene/p.e.). IR ($CHCl_3$): 3003*w*, 2957*m*, 1623*s*, 1504*w*, 1455*m*, 1377*w*, 1248*m*, 1151*m*, 1009*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.15 (*d*, *J* = 2.1, 1 H); 6.94 (br. *d*, *J* = 2.3, 1 H); 6.90 (br. *d*, *J* = 2.1, 1 H); 6.87 (*dd*, *J* = 8.6, 2.3, 1 H); 6.79 (*s*, 2 H); 6.75 (*s*, 2 H); 6.64 (*d*, *J* = 8.6, 1 H); 3.98 (br. *t*, *J* = 5.8, 2 H); 3.93 (br. *t*, *J* = 6.4, 2 H); 3.81 (br. *t*, *J* = 6.4, 2 H); 3.78 (br. *t*, *J* = 6.4, 2 H); 3.70–3.55 (*m*, 4 H); 3.50–3.40 (*m*, 4 H); 2.35–2.20 (*m*, 12 H); 2.21 (*s*, 3 H); 2.165 (*s*, 6 H); 2.158 (*s*, 6 H); 2.10 (*s*, 3 H); 2.05–1.95 (*m*, 8 H); 1.65–1.55 (*m*, 4 H); 1.45–1.35 (*m*, 8 H); 0.88 (br. *t*, *J* = 6.9, 6 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 171.6 (*s*, 2×); 154.9 (*s*); 154.3 (*s*); 153.8 (*s*); 152.2 (*s*); 143.8 (*s*); 141.6 (*s*); 140.6 (*s*); 138.5 (*s*); 132.9 (*s*); 130.6 (*s*); 130.5 (*s*); 129.1 (*d*); 128.7 (*d*); 128.5 (*d*); 127.0 (*d*); 126.8 (*d*); 126.5 (*s*); 125.1 (*d*); 117.5 (*s*); 111.2 (*d*); 73.1 (*t*); 72.4 (*t*); 71.8 (*t*); 67.1 (*t*); 43.43 (*s*); 43.34 (*s*); 42.9 (*t*); 42.8 (*t*); 38.7 (*t*); 38.5 (*t*); 36.5 (*t*); 36.4 (*t*); 35.5 (*t*); 35.4 (*t*); 33.40 (*t*); 33.36 (*t*); 31.7 (*t*, 2×); 27.3 (*t*); 27.1 (*t*); 26.5 (*t*); 25.7 (*t*); 25.16 (*t*); 25.12 (*t*); 22.5 (*t*, 2×); 17.2 (*q*); 16.90 (*q*); 16.81 (*q*); 16.6 (*q*); 14.0 (*q*, 2×). FAB-MS: 1005/1007 (100/100, MH^+). Anal. calc. for $C_{60}H_{81}BrN_2O_6$ (1006.23): C 71.62, H 8.11, N 2.78; found: C 71.39, H 8.29, N 2.78.

20′-Bromo-1,1″-dihexyl-5′,14′,29′,32′,33′,36′-hexamethyldispiro[piperidine-4,2′-[7,12,22,27]tetraoxapentacyclo-[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta[3,5,13,15,18,20,28,30,31,33,35,37]dodecaene-17′,4″-piperidine] (**32**). *Method A* (*reduction of* **34**): BH_3 · THF (1M in THF, 22 ml, 22 mmol) was added dropwise to a soln. of **34** (1.12 g, 1.11 mmol) in THF (50 ml) at r.t., and the colorless soln. was refluxed for 24 h. Quenching with MeOH (10 ml) at 0° and evaporation gave a white residue, which was taken up in 5% ethanolic H_2SO_4 soln. (20 ml). This soln. was then refluxed for 4 h. Dilution with AcOEt (100 ml), washing with 2M aq. NaOH soln. (2 × 100 ml) and sat. aq. NaCl soln. (100 ml), drying ($MgSO_4$), evaporation, and FC (15 g of SiO_2; CH_2Cl_2/acetone 2:1) gave **32** (1.01 g, 93%). *Method B* (*reductive alkylation of* **33**): $NaBH_4$ (672 mg, 17.8 mmol) was added portionwise to a soln. of **33** (719 mg, 0.888 mmol) in hexanoic acid (9 ml) and THF (20 ml) at 50–55°, and tbe viscous soln. formed was stirred 16 h at 50–55°. After cooling, 5% ethanolic H_2SO_4 soln. (20 ml) was added, and the resulting suspension was refluxed for 3 h. After addition of AcOEt (100 ml) and 2M aq. NaOH soln. and stirring for 1 h at r.t., the aq. layer was removed. Washing with 2M aq. NaOH soln. (3 × 100 ml) and sat. aq. NaCl soln. (100 ml), drying ($MgSO_4$), evaporation, and FC (15 g of SiO_2; CH_2Cl_2/acetone 2:1) afforded **32** (625 mg, 72%). White foam. M.p. 161–164° (PhMe/p.e.). IR ($CHCl_3$): 2932*s*, 1500*w*, 1472*m*, 1379*w*, 1250*m*, 1132*m*, 1011*w*, 659*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.15 (*d*, *J* = 2.1, 1 H); 6.95 (br. *d*, *J* = 2.2, 1 H); 6.90 (br. *d*, *J* = 2.1, 1 H); 6.87 (*dd*, *J* = 8.6, 2.2, 1 H); 6.79 (*s*, 2 H); 6.75 (*s*, 2 H); 6.62 (*d*, *J* = 8.6, 1 H); 3.97 (br. *t*, *J* = 5.9, 2 H); 3.92 (br. *t*, *J* = 6.5, 2 H); 3.81 (br. *t*, *J* = 6.5, 2 H); 3.77 (br. *t*, *J* = 6.6, 2 H); 2.50–2.30 (*m*, 16 H); 2.25–2.20 (*m*, 4 H); 2.20 (*s*, 3 H); 2.154 (*s*, 6 H); 2.146 (*s*, 6 H); 2.09 (*s*, 3 H); 2.00–1.90 (*m*, 8 H); 1.50–1.40 (*m*, 4 H); 1.30–1.20 (*m*, 12 H); 0.856 (br. *t*, *J* = 7.1, 3 H); 0.853 (br. *t*, *J* = 6.7, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 154.5 (*s*); 153.9 (*s*); 153.4 (*s*); 151.8 (*s*); 144.9 (br. *s*); 142.8 (br. *s*); 142.1 (br. *s*); 140.0 (br. *s*); 132.4 (*s*); 130.1 (*s*); 130.0 (*s*); 129.4 (*d*); 129.1 (*d*); 128.9 (*d*); 127.3 (*d*); 127.1 (*d*); 126.1 (*s*); 125.4 (*d*); 117.2 (*s*); 111.0 (*d*); 73.0 (*t*); 72.4 (*t*); 71.7 (*t*); 67.1 (*t*); 59.1 (*t*); 59.0 (*t*); 50.8 (*t*); 50.6 (*t*); 43.22 (*s*); 43.15 (*s*); 36.1 (*t*); 35.9 (*t*); 31.8 (*t*, 2×); 27.41 (*t*); 27.37 (*t*); 27.25 (*t*); 27.12 (*t*, 2×); 27.07 (*t*); 26.5 (*t*); 25.7 (*t*); 22.6 (2*t*); 17.2 (*q*); 16.88 (*q*); 16.82 (*q*); 16.6 (*q*); 14.0 (*q*, 2×). FAB-MS: 977/979 (100/72, MH^+). Anal. calc. for $C_{60}H_{85}BrN_2O_4$ (978.26): C 73.67, H 8.76, N 2.86; found: C 73.57, H 8.70, N 2.88.

3,10-Dibutyl-7-{1,1″-dihexyl-14′,19′,29′,32′,36′,37′-hexamethyldispiro[piperidine-4,2′-[7,12,22,27]tetraoxa-pentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta[3,5,13,15,18,20,28,30,31,33,35,37]dodecaene-17′,4″-piperidin]-5′yl}benzo[g]pteridine-2,4(3H,10H)-dione (**36**). BuLi (1.6M in hexane, 16.0 ml, 25.6 mmol) was added at −78° to a soln. of TMEDA (2.97 g, 25.6 mmol) in THF (50 ml). A soln. of **32** (5.00 g, 5.11 mmol) in THF (25 ml) was added dropwise after 10 min, then after 30 min the mixture was treated with $(MeO)_3B$ (10.6 g, 102 mmol). The suspension formed was allowed to warm to r.t. and stirred overnight. After quenching with sat. aq. NH_4Cl soln. (50 ml), the mixture was neutralized with sat. aq. $NaHCO_3$ soln. (100 ml) and diluted with Et_2O (100 ml). The org. layer was collected, dried ($MgSO_4$), and evaporated, yielding **35**. This crude material was dissolved together with **10** (2.07 g, 5.11 mmol) in benzene (50 ml), EtOH (13 ml), and 0.5M aq. Na_2CO_3 soln. (52 ml, 26 mmol). The two-phase mixture was purged for 10 min with Ar and, after addition of $[PdCl_2(PPh_3)_2]$ (179 mg, 0.256 mmol), refluxed for 20 h. Washing with sat. aq. $NaHCO_3$ soln. (100 ml) and sat. aq. NaCl soln. (100 ml), drying ($MgSO_4$), evaporation, and filtration through a plug (SiO_2; CH_2Cl_2/acetone 10:1 → 1:1) gave an orange oil, which was purified by FC (200 g of SiO_2; hexane/AcOEt/Et_3N 100:50:0.5 → 100:50:3) to yield **36** (3.49 g, 56%). Orange foam. UV/VIS: 283 (4.71), 335 (3.89), 453 (4.00). Fluorescence: $\lambda_{max.\ em.}$ = 526 nm. IR ($CHCl_3$): 2933*m*, 1706*w*, 1655*m*, 1619*w*, 1590*m*, 1551*s*, 1469*w*, 1379*w*, 1345*w*, 1249*w*, 1188*w*, 1135*w*, 1012*w*. ^{1}H-NMR (400 MHz, $CDCl_3$):

8.41 (*d*, *J* = 2.0, 1 H); 8.24 (*dd*, *J* = 9.0, 2.0, 1 H); 7.59 (*d*, *J* = 9.0, 1 H); 7.13 (*d*, *J* = 2.2, 1 H); 6.99 (br. *d*, *J* = 2.2, 1 H); 6.96 (br. *d*, *J* = 2.0, 1 H); 6.834 (*dd*, *J* = 8.6, 2.0, 1 H); 6.827 (*s*, 2 H); 6.75 (*s*, 2 H); 6.64 (*d*, *J* = 8.6, 1 H); 4.80–4.70 (*m*, 2 H); 4.14 ('*t*', *J* = 7.5, 2 H); 4.03 (br. *t*, *J* = 5.7, 2 H); 3.79 (br. *t*, *J* = 6.3, 2 H); 3.58 (br. *t*, *J* = 5.9, 2 H); 3.51 (br. *t*, *J* = 6.7, 2 H); 2.55–2.35 (*m*, 16 H); 2.30–2.20 (*m*, 4 H); 2.24 (*s*, 3 H); 2.18 (*s*, 6 H); 2.12 (*s*, 3 H); 2.02 (*s*, 6 H); 2.00–1.85 (*m*, 6 H); 1.80–1.55 (*m*, 8 H); 1.50–1.40 (*m*, 6 H); 1.30–1.20 (*m*, 12 H); 1.05 (*t*, *J* = 7.3, 3 H); 0.98 (*t*, *J* = 7.3, 3 H); 0.850 (br. *t*, *J* = 6.9, 3 H); 0.845 (br. *t*, *J* = 6.9, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 159.6 (*s*); 155.6 (*s*); 154.6 (*s*); 153.9 (*s*); 153.2 (*s*); 152.7 (*s*); 148.6 (*s*); 143.6 (br. *s*); 142.9 (br. *s*); 142.2 (br. *s*); 139.3 (br. *s*); 138.4 (*s*); 137.6 (*d*); 137.1 (*s*); 136.1 (*s*); 132.4 (*d*); 131.8 (*s*); 131.5 (*s*); 130.94 (*s*); 130.87 (*d*); 130.3 (*s*); 129.8 (*s*); 128.9 (br. *d*); 127.2 (*d*); 127.0 (*d*); 126.4 (br. *d*); 126.2 (*s*); 125.4 (*d*); 114.3 (*d*); 111.3 (*d*); 73.2 (*t*); 71.9 (*t*); 71.6 (*t*); 67.1 (*t*); 58.8 (*t*, 2×); 50.6 (2*t*); 44.8 (*t*); 43.1 (*s*); 43.0 (*s*); 41.9 (*t*); 35.7 (*t*); 35.5 (*t*); 31.72 (*t*); 31.70 (*t*); 29.9 (*t*); 29.2 (*t*); 27.3 (*t*, 3×); 26.9 (*t*); 26.7 (*t*); 26.6 (*t*); 26.3 (*t*); 25.7 (*t*); 22.6 (*t*, 2×); 20.2 (*t*, 2×); 16.95 (*q*); 16.92 (*q*); 16.67 (*q*); 16.59 (*q*); 14.0 (*q*, 2×); 13.86 (*q*); 13.82 (*q*). FAB-MS: 1224 (100, MH$^+$). HR-FAB-MS: 1223.7968 (MH$^+$, $C_{78}H_{107}N_6O_6^+$; calc. 1223.8246).

*20'-{3,10-Dibutyl-2,4(3*H*,10*H*)-dioxobenzo[g]pteridin-7-yl}-1,1,1'',1''-tetrahexyl-5',14',29',32',33',36'-hexamethyldispiro[piperidinium-4,2'-[7,12,22,27]tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta[3,5,13,15,18,20,28,30,31,33,35,37]dodecaene-17',4''-piperidinium] Dichloride* (**37**). A soln. of **36** (3.44 g, 2.81 mmol) in Et_2O (100 ml) was washed with 2M aq. NaOH soln. (100 ml), dried ($MgSO_4$), and evaporated. After addition of 1-iodohexane (50 ml) and MeCN (50 ml), the soln. was refluxed for 4 h, then concentrated, and most of the excess 1-iodohexane was removed *in vacuo* at 60°. FC (150 g of SiO_2; CH_2Cl_2/acetone 8:1 → 3:1), followed by ion-exchange (50 g of *Dowex 1×8*; MeOH) gave an orange foam which was taken up in MeCN (10 ml) and precipitated by addition of Et_2O (200 ml). Drying the precipitate (120°, 100 mbar, 4 h) afforded **37** (3.68 g, 88%). Hygroscopic orange powder. M.p. 201–202° (dec.). UV/VIS: 283 (4.72), 334 (3.90), 453 (4.01). Fluorescence: $\lambda_{max.\ em.}$ = 526 nm. IR ($CHCl_3$): 3667*w*, 3345*w* (br.), 2933*s*, 2467*w*, 1706*w*, 1655*m*, 1620*w*, 1590*m*, 1552*s*, 1468*w*, 1378*w*, 1344*w*, 1251*m*, 1187*w*, 1150*w*, 1009*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.36 (*d*, *J* = 2.0, 1 H); 8.27 (*dd*, *J* = 9.0, 2.0, 1 H); 7.68 (*d*, *J* = 9.0, 1 H); 7.12 (*d*, *J* = 2.3, 1 H); 7.05 (br. *s*, 1 H); 6.95–6.90 (*m*, 2 H); 6.87 (*s*, 2 H); 6.80 (*s*, 2 H); 6.72 (*d*, *J* = 8.4, 1 H); 4.80–4.70 (*m*, 2 H); 4.13 ('*t*', *J* = 7.5, 2 H); 4.03 (br. *t*, *J* = 5.7, 2 H); 3.80 (br. *t*, *J* = 6.4, 2 H); 3.75–3.30 (*m*, 16 H); 3.61 (br. *t*, *J* = 6.2, 2 H); 3.50 (br. *t*, *J* = 6.9, 2 H); 2.80–2.55 (*m*, 8 H); 2.25 (*s*, 3 H); 2.21 (*s*, 6 H); 2.13 (*s*, 3 H); 2.06 (*s*, 6 H); 2.00–1.85 (*m*, 6 H); 1.80–1.55 (*m*, 16 H); 1.50–1.40 (*m*, 2 H); 1.40–1.20 (*m*, 24 H); 1.05 (*t*, *J* = 7.4, 3 H); 0.98 (*t*, *J* = 7.4, 3 H); 0.90–0.80 (*m*, 12 H). ^{13}C-NMR (75 MHz, $(CDCl_2)_2$, 95°): 159.6 (*s*); 155.8 (*s*); 155.4 (*s*); 155.2 (*s*); 154.5 (*s*); 154.1 (*s*); 149.0 (*s*); 140.3 (*s*); 139.5 (*s*); 138.2 (*s*); 137.7 (*d*); 137.5 (*s*); 136.1 (*s*); 135.7 (*s*); 133.5 (*s*); 132.5 (*d*); 132.2 (*s*); 132.02 (*s*); 131.94 (*s*); 131.5 (*s*); 130.0 (*d*); 128.1 (*d*); 126.4 (*d*); 126.3 (*d*); 125.1 (*d*); 124.5 (*d*); 115.1 (*d*); 112.7 (*d*); 74.5 (*t*); 73.6 (*t*); 72.2 (*t*); 67.9 (*t*); 60.5 (br. *t*, 2×); 59.6 (br. *t*, 2×); 56.5 (*t*, 2×); 45.2 (*t*); 42.0 (*s*, 2×); 41.8 (*t*); 31.3 (*t*, 4×); 30.2 (*t*, 2×); 30.0 (*t*); 29.5 (*t*); 29.3 (*t*); 26.8 (*t*); 26.7 (*t*); 26.4 (*t*, 4×); 26.1 (*t*); 22.5 (*t*, 4×); 22.2 (*t*, 4×); 20.4 (*t*, 2×); 17.25 (*q*); 17.17 (*q*); 16.9 (*q*); 16.7 (*q*); 14.0 (*q*, 6×); 2 quaternary C signals are obscured. FAB-MS: 697.0 (100, [M – 2 Cl]$^{2+}$ ($^{13}C_1{}^{12}C_{89}H_{132}N_6O_6{}^{2+}$)), 1308 (52, [$M$ – C_6H_{13} – 2 Cl]$^+$ ($^{12}C_{84}H_{119}N_6O_6{}^+$)), 1393 (60, [$M$ – H – 2 Cl]$^+$), 1428 (52, [M – H – Cl]$^+$). Anal. calc. for $C_{90}H_{132}Cl_2N_6O_6 \cdot 1.5\ H_2O$ (1492.02): C 72.45, H 8.99, N 5.63; found: C 72.20, H 8.87, N 5.60. H_2O (P_2O_5) calc.: 1.81; found: 1.85.

*5'-(Chloromethyl)-20'-{3,10-dibutyl-2,4(3*H*,10*H*)-dioxobenzo[g]pteridin-7-yl}-1,1,1'',1''-tetrahexyl-14',29',32',33',36',37'-hexamethyldispiro[piperidinium-4,2'-[7,12,22,27]tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta[3,5,13,15,18,20,28,30,31,33,35,37]dodecaene-17',4''-piperidinium] Dichloride* (**38**). A slow stream of HCl gas was bubbled through a degassed soln. of **37** (4.00 g, 2.68 mmol) in AcOH (40 ml), conc. aq. HCl soln. (40 ml), and 37% aq. HCOH soln. (20 ml, 0.27 mol) at 0°. After 30 min, the temp. was raised to 40°, and the HCl gas stream was maintained for a total of 2 h. The soln. was then poured into ice (200 g), diluted with CH_2Cl_2 (600 ml), and neutralized by careful addition of 2M aq. Na_2CO_3 soln. (800 ml). Removal of the org. layer, washing with sat. aq. NaCl soln. (600 ml), drying ($MgSO_4$), evaporation, and FC (200 g of SiO_2; CH_2Cl_2/acetone/MeOH 10:3:1 → 6:3:1) gave an orange foam, which was dissolved in MeCN (20 ml) and precipitated by addition of Et_2O (200 ml). Filtration and drying (60°, 100 mbar, 3 h) gave **38** (3.17 g, 75%). Hygroscopic orange powder. M.p. 195–197°. UV/VIS: 283 (4.71), 335 (3.88), 452 (4.03). Fluorescence: $\lambda_{max.\ em.}$ = 526 nm. IR ($CHCl_3$): 3667*w*, 3333*w* (br.), 2933*m*, 2456*w*, 1706*w*, 1655*m*, 1617*w*, 1590*m*, 1552*s*, 1477*w*, 1378*w*, 1005*w*, 660*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.37 (*d*, *J* = 2.1, 1 H); 8.19 (br. *d*, *J* = 9.1, 1 H); 7.60 (*d*, *J* = 9.1, 1 H); 7.10 (*d*, *J* = 2.0, 1 H); 7.08 (br. *d*, *J* = 1.9, 1 H); 7.01 (br. *s*, 1 H); 6.95 (br. *d*, *J* = 1.9, 1 H); 6.88 (*s*, 2 H); 6.80 (*s*, 2 H); 4.75–4.70 (*m*, 2 H); 4.57 (*s*, 2 H); 4.13 ('*t*', *J* = 7.4, 2 H); 3.92 (br. *t*, *J* = 6.6, 2 H); 3.81 (br. *t*, *J* = 6.3, 2 H); 3.75–3.30 (*m*, 18 H); 3.62 (br. *t*, *J* = 6.3, 2 H); 2.85–2.55 (*m*, 8 H); 2.22 (*s*, 3 H); 2.213 (*s*, 6 H); 2.203 (*s*, 3 H); 2.07 (*s*, 6 H); 2.05–1.95 (*m*, 4 H); 1.95–1.85 (*m*, 2 H); 1.75–1.55 (*m*, 16 H); 1.45–1.35 (*m*, 2 H); 1.35–1.20 (*m*, 24 H); 1.05 (*t*, *J* = 7.4, 3 H); 0.97 (*t*, *J* = 7.3, 3 H); 0.90–0.80 (*m*, 12 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$, 95°): 159.1 (*s*); 154.6

(*s*); 154.0 (*s*); 153.85 (*s*); 153.77 (*s*); 152.8 (*s*); 148.9 (*s*); 141.2 (*s*); 140.8 (*s*); 139.6 (*s*); 139.5 (*s*); 137.8 (*s*); 136.3 (*s*); 136.1 (*d*); 135.2 (*s*); 131.57 (*s*); 131.49 (*s*); 131.2 (*d*); 131.0 (*s*); 130.3 (*s*); 130.1 (*s*); 129.27 (*d*); 129.19 (*d*); 126.2 (*d*); 126.1 (*d*, 2×); 125.4 (*d*); 115.8 (*d*); 73.4 (*t*); 72.6 (*t*); 71.9 (*t*); 71.7 (*t*); 58.6 (br. *t*, 2×); 57.9 (br. *t*, 2×); 55.9 (*t*); 55.7 (*t*); 44.1 (*t*); 41.8 (*t*); 41.7 (*s*); 41.5 (*s*); 40.7 (*t*); 30.5 (*t*, 6×); 29.5 (*t*); 28.8 (*t*); 28.3 (*t*); 26.6 (*t*); 26.3 (*t*); 25.3 (*t*, 4×); 21.6 (*t*, 4×); 21.0 (*t*, 4×); 19.6 (*t*); 19.4 (*t*); 16.38 (*q*); 16.32 (*q*, 2×); 16.24 (*q*); 13.5 (*q*, 6×). 1 CH_2 and 2 quaternary C signals are obscured. FAB-MS: 721.0 (40, $[M - 2\,Cl]^{2+}$ ($^{13}C_1{}^{12}C_{90}H_{133}{}^{35}ClN_6O_6{}^{2+}$)), 1356 (25, $[M - C_6H_{13} - 2\,Cl]^+$ ($^{12}C_{85}H_{120}{}^{35}ClN_6O_6{}^+$)), 1441 (40, $[M - H - 2\,Cl]^+$), 1476 (100, $[M - H - Cl]^+$). Anal. calc. for $C_{91}H_{133}Cl_3N_6O_6 \cdot 4\,H_2O$ (1585.53): C 68.94, H 8.96, N 5.30, Cl 6.71; found: C 68.95, H 8.98, N 5.43, Cl 6.99.

5′-{3,10-Dibutyl-2,4(3H,10H)-dioxobenzo[g]pteridin-7-yl}-1,1,1″,1″-tetrahexyl-14′,20′,29′,32′,36′,37′-hexamethyl-33′-[(4-methyl-3-thiazolio)methyl]dispiro[piperidinium-4,2′-[7,12,22,27]tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta[3,5,13,15,18,20,28,30,31,33,35,37]dodecaene-17′,4″-piperidinium] Trichloride (**6**). A soln. of **38** (3.17 g, 2.00 mmol) in degassed 4-methylthiazole (50 ml) was heated for 16 h at 80°. Most of the excess 4-methylthiazole was then distilled off *in vacuo* at 80°, and the residue was purified twice by reversed-phase chromatography (40 g of SiO_2-C_{18}; MeOH/H_2O 1:1 → 2:1; then 40 g of SiO_2-C_{18}; H_2O/MeCN 3:2). The solvent was removed as an azeotrope with MeCN at 35° to leave an orange oil, which was diluted with MeCN (3 ml) and acetone (3 ml), and precipitated with Et_2O (30 ml). Filtration and drying (10^{-6} mbar, 16 h, r.t.) yielded **6** (2.28 g, 67%). Hygroscopic orange powder. M.p. 181–184°. UV/VIS: 283 (4.71), 334 (3.89), 453 (4.00). Fluorescence: $\lambda_{max.\,em.}$ = 5.26 nm. IR ($CHCl_3$): 3666*w*, 3350*w* (br.), 2933*m*, 2458*w*, 1706*w*, 1655*m*, 1620*w*, 1590*m*, 1552*s*, 1468*w*, 1381*w*, 1151*w*, 1004*w*, 660*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 10.96 (br. *s*, 1 H); 8.42 (*d*, *J* = 1.9, 1 H); 8.19 (*dd*, *J* = 9.0, 1.9, 1 H); 8.16 (br. *s*, 1 H); 7.74 (br. *d*, *J* = 1.5, 1 H); 7.73 (*d*, *J* = 9.0, 1 H); 7.19 (br. *s*, 1 H); 7.10 (br. *s*, 1 H); 7.06 (br. *s*, 1 H); 6.94 (*s*, 2 H); 6.89 (*s*, 2 H); 5.70 (*s*, 2 H); 4.80–4.70 (*m*, 2 H); 4.13 ('*t*', *J* = 7.5, 2 H); 3.90–3.30 (*m*, 14 H); 3.87 (br. *t*, *J* = 6.6, 2 H); 3.78 (br. *t*, *J* = 6.5, 2 H); 3.63 (br. *t*, *J* = 6.0, 2 H); 3.53 (br. *t*, *J* = 6.7, 2 H); 3.20–3.10 (*m*, 4 H); 2.85–2.55 (*m*, 4 H); 2.71 (*s*, 3 H); 2.55–2.35 (*m*, 2 H); 2.27 (*s*, 3 H); 2.22 (*s*, 3 H); 2.21 (*s*, 6 H); 2.07 (*s*, 6 H); 1.95–1.85 (*m*, 6 H); 1.75–1.55 (*m*, 16 H); 1.50–1.40 (*m*, 2 H); 1.40–1.25 (*m*, 24 H); 1.05 (*t*, *J* = 7.4, 3 H); 0.98 (*t*, *J* = 7.3, 3 H); 0.90–0.80 (*m*, 12 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$, 60°): 160.6 (*d*); 159.2 (*s*); 154.7 (*s*); 153.9 (*s*, 2×); 153.6 (*s*); 152.6 (*s*); 148.9 (*s*); 145.9 (*s*); 141.3 (br. *s*); 140.9 (br. *s*); 140.1 (br. *s*); 139.8 (br. *s*); 137.8 (*s*); 136.15 (*s*); 136.08 (*d*); 135.1 (*s*); 131.62 (*s*); 131.53 (*s*); 131.45 (*s*); 131.0 (*d*); 130.4 (*d*); 130.3 (*s*); 130.1 (*s*); 129.2 (*d*); 126.3 (*d*); 126.1 (*d*); 125.9 (*d*) 125.3 (*d*); 122.3 (*d*); 116.09 (*d*); 73.3 (*t*); 72.6 (*t*); 71.8 (*t*); 71.6 (*t*); 57.8 (br. *t*, 4×); 55.9 (*t*); 55.7 (*t*); 52.2 (*t*); 44.0 (*t*); 41.6 (*s*, 2×); 40.7 (*t*); 30.5 (*t*, 6×); 29.5 (*t*); 28.7 (*t*); 28.0 (*t*); 26.5 (*t*); 26.3 (*t*); 25.2 (*t*, 4×); 21.7 (*t*, 4×); 20.9 (*t*, 4×); 19.6 (*t*); 19.4 (*t*); 16.4 (*q*, 3×); 16.3 (*q*); 13.6 (*q*, 6×); 13.0 (*q*). 1 CH_2 and 2 quaternary C signals are obscured. FAB-MS: 703.5 (29, $[M - C_4H_5NS - 3\,Cl]^{2+}$ ($^{13}C_1{}^{12}C_{90}H_{133}N_6O_6{}^{2+}$)), 752.5 (86, $[M - H - 3\,Cl]^{2+}$ ($^{13}C_1{}^{12}C_{94}H_{137}N_7O_6S^{2+}$)), 1442 (24, $[M - C_4H_5NS - 2\,Cl]^+$), 1504 (37, $[M - 2\,H - 3\,Cl]^+$), 1540 (100, $[M - H - 2\,Cl]^+$), 1576 (20, $[M - Cl]^+$). HR-FAB-MS: 752.0185 ($[M - H - 3\,Cl]^{2+}$ ($^{12}C_{95}H_{137}N_7O_6S^{2+}$), calc. 752.0170). Anal. calc. for $C_{95}H_{138}Cl_3N_7O_6S \cdot 5\,H_2O \cdot 0.15\,Et_2O$ (1713.82): C 67.00, H 8.79, N 5.72, S 1.87; found: C 67.08, H 8.51, N 6.20, S 1.94.

1-Acetyl-4,4-bis(4-ethoxy-3-methylphenyl)piperidine (**40**) *and 4-[1-Acetyl-4-(4-ethoxy-3-methylphenyl)piperidin-4-yl]-2-methylphenol* (**41**). K_2CO_3 (41.5 g, 300 mmol) was added to a soln. of **39** (33.9 g, 100 mmol) [28] and EtI (20.3 g, 130 mmol) in DMF (200 ml), and the mixture was stirred for 2 h at 60°. Filtration, evaporation, dilution with AcOEt (500 ml), washing with 2M aq. NaOH soln. (2 × 500 ml), water (500 ml), 2M aq. HCl soln. (500 ml), sat. aq. NaCl soln. (500 ml), drying ($MgSO_4$), evaporation, and FC (200 g of SiO_2; hexane/AcOEt 2:1 → 1:3) gave **41** (15.7 g, 43%) and **40** (10.2 g, 26%).

Data of **41**: White solid. M.p. 179–180° (EtOH). IR ($CHCl_3$): 3600*w*, 3298*w* (br.), 3004*m*, 1624*s*, 1506*s*, 1477*m*, 1456*m*, 1252*s*, 1138*m*, 1040*w*, 992*w*. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 9.06 (br. *s*, 1 H); 7.04 (*d*, *J* = 2.3, 1 H); 7.02 (*dd*, *J* = 8.5, 2.3, 1 H); 6.98 (*d*, *J* = 2.4, 1 H); 6.90 (*dd*, *J* = 8.4, 2.4, 1 H); 6.78 (*d*, *J* = 8.5, 1 H); 6.67 (*d*, *J* = 8.4, 1 H); 3.96 (*q*, *J* = 7.0, 2 H); 3.45–3.35 (*m*, 4 H); 2.35–2.25 (*m*, 2 H); 2.25–2.15 (*m*, 2 H); 2.09 (*s*, 3 H); 2.07 (*s*, 3 H); 1.97 (*s*, 3 H); 1.30 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (100 MHz, $(CD_3)_2SO$): 167.9 (*s*); 154.3 (*s*); 153.1 (*s*); 138.7 (*s*); 137.0 (*s*); 128.71 (*d*); 128.61 (*d*); 125.2 (*s*); 124.9 (*d*); 124.7 (*d*); 123.3 (*s*); 114.3 (*d*); 110.8 (*d*); 62.9 (*t*); 43.0 (*t*); 42.7 (*s*); 38.0 (*t*); 35.9 (*t*); 35.2 (*t*); 21.2 (*q*); 16.2 (*q*, 2×); 14.7 (*q*). EI-MS: 43 (91), 188 (16), 231 (16), 255 (70), 281 (30), 367 (100, M^+). Anal. calc. for $C_{23}H_{29}NO_3$ (367.49): C 75.17, H 7.95, N 3.81; found: C 75.09, H 7.81, N 3.86.

Data of **40**: White foam. M.p. 114–116° (benzene/hexane). IR ($CHCl_3$): 3003*m*, 1626*s*, 1505*s*, 1477*m*, 1455*m*, 1393*w*, 1298*w*, 1249*s*, 1140*m*, 1048*m*, 992*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.00–6.95 (*m*, 4 H); 6.71 (*d*, *J* = 8.5, 2 H); 3.98 (*q*, *J* = 7.0, 4 H); 3.65–3.60 (*m*, 2 H); 3.50–3.45 (*m*, 2 H); 2.45–2.35 (*m*, 4 H); 2.17 (*s*, 6 H); 2.07 (*s*, 3 H); 1.39 (*t*, *J* = 7.0, 6 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 168.8 (*s*); 155.2 (*s*); 138.1 (*s*); 129.2 (*d*); 126.6 (*s*);

125.0 (*d*); 110.7 (*d*); 63.4 (*t*); 43.7 (*t*); 43.6 (*s*); 38.8 (*t*); 37.0 (*t*); 36.1 (*t*); 21.5 (*q*); 16.6 (*q*); 15.0 (*q*). EI-MS: 43 (20), 57 (13), 259 (15), 283 (68), 308 (28), 352 (10), 395 (100, M^+). Anal. calc. for $C_{25}H_{33}NO_3$ (395.54): C 75.91, H 8.41, N 3.54; found: C 76.19, H 8.36, N 3.50.

4-[1-Acetyl-4-(4-ethoxy-3-methylphenyl)piperidin-4-yl]-2-bromo-6-methylphenol (**42**). Br_2 (1.60 g, 10.0 mmol) was added dropwise at *ca.* −25° to a soln. of (*t*-Bu)NH_2 (1.46 g, 20.0 mmol) and 2,6-di(*tert*-butyl)-4-methylphenol (220 mg, 1.00 mmol) in PhMe (25 ml). After cooling to −78°, a soln. of **41** (3.67 g, 10.0 mmol) in (*t*-bu)NH_2 (5 ml) and PhMe (10 ml) was slowly added. The suspension was allowed to warm to 0° over a period of 4 h. Dilution with AcOEt (100 ml), washing with 2M aq. HCl soln. (3 × 100 ml) and sat. aq. NaCl (100 ml), drying ($MgSO_4$), evaporation, and FC (70 g of SiO_2; hexane/AcOEt 1:1) gave **42** (3.45 g, 77%). White solid. M.p. 173–175° (EtOH/Et_2O). IR ($CHCl_3$): 3523*w*, 3389*w* (br.), 3005*m*, 1627*s*, 1506*m*, 1478*m*, 1455*m*, 1249*s*, 1140*m*, 1046*w*, 994*w*. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 8.85 (br. *s*, 1H); 7.16 (*d*, *J* = 2.3, 1 H); 7.10–7.05 (*m*, 2 H); 7.05 (*d*, *J* = 2.3, 1 H); 6.81 (*d*, *J* = 8.5, 1 H); 3.97 (*q*, *J* = 7.0, 2 H); 3.55–3.45 (*m*, 1 H); 3.45–3.30 (*m*, 3 H); 2.40–2.15 (*m*, 4 H); 2.18 (*s*, 3 H); 2.10 (*s*, 3 H); 1.97 (*s*, 3 H); 1.31 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (100 MHz, $(CD_3)_2SO$): 167.9 (*s*); 154.5 (*s*); 149.5 (*s*); 140.0 (*s*); 137.5 (*s*); 128.6 (*d*); 128.2 (*d*); 128.1 (*d*); 126.6 (*s*); 125.4 (*s*); 125.0 (*d*); 110.93 (*d*); 110.87 (*s*); 62.9 (*t*); 42.90 (*t*); 42.84 (*s*); 37.9 (*t*); 35.7 (*t*); 35.0 (*t*); 21.2 (*q*); 17.3 (*q*); 16.2 (*q*); 14.7 (*q*). EI-MS: 43 (100), 56 (35), 165 (12), 281 (12), 333/335 (21/18), 445/447 (19/20, M^+). Anal. calc. for $C_{23}H_{28}BrNO_3$ (446.39): C 61.89, H 6.32, N 3.14, Br 17.90; found: C 61.77, H 6.44, N 3.10, Br 17.73.

1-Acetyl-4-(3-bromo-4-ethoxy-5-methylphenyl)-4-(4-ethoxy-3-methylphenyl)piperidine (**43**). A mixture of **42** (3.33 g, 7.46 mmol), EtI (5.82 g, 37.2 mmol), K_2CO_3 (3.09 g, 22.4 mmol), and 2,6-di(*tert*-butyl)-4-methylphenol (164 mg, 0.746 mmol) in DMF (15 ml) was stirred at 60° for 4 h. Filtration, evaporation, and FC (70 g of SiO_2; hexane/AcOEt 1:1) afforded **43** (3.39 g, 96%). White foam. M.p. 119–121° (PhMe/p.e.). IR ($CHCl_3$): 2984*m*, 1628*s*, 1506*m*, 1475*m*, 1455*m*, 1390*w*, 1252*s*, 1142*m*, 1032*m*, 993*w*, 903*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.20 (*d*, *J* = 2.4, 1 H); 7.00–6.95 (*m*, 2 H); 6.93 (*dm*, *J* = 2.4, 1 H); 6.73 (*dm*, *J* = 9.1, 1 H); 4.00 (*q*, *J* = 7.0, 2 H); 3.92 (*q*, *J* = 7.0, 2 H); 3.80–3.70 (*m*, 1 H); 3.55–3.40 (*m*, 3 H); 2.40–2.20 (*m*, 4 H); 2.25 (*s*, 3 H); 2.18 (*s*, 3 H); 2.07 (*s*, 3 H); 1.41 (*t*, *J* = 7.0, 3 H); 1.40 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 168.8 (*s*); 155.5 (*s*); 152.6 (*s*); 144.1 (*s*); 136.5 (*s*); 133.0 (*s*); 129.2 (*d*, 2 ×); 128.7 (*d*); 126.9 (*s*); 125.1 (*d*); 117.6 (*s*); 110.8 (*d*); 68.6 (*t*); 63.5 (*t*); 43.7 (*s*); 43.6 (*t*); 38.6 (*t*); 36.8 (*t*); 35.9 (*t*); 21.4 (*q*); 17.1 (*q*); 16.6 (*q*); 15.6 (*q*); 14.9 (*q*). EI-MS: 43 (29), 56 (25), 91 (100), 309 (3), 361/363 (5/4), 473/475 (8/7, M^+). Anal. calc. for $C_{25}H_{32}BrNO_3$ (474.44): C 63.29, H 6.80, N 2.95; found: C 63.38, H 6.84, N 3.01.

4-(3-Bromo-4-ethoxy-5-methylphenyl)-4-(4-ethoxy-3-methylphenyl)-1-ethylpiperidine (**44**). BH_3 · THF (1M in THF, 56 ml, 56 mmol) was added dropwise at r.t. to a soln. of **43** (5.36 g, 11.3 mmol) in THF (50 ml). The mixture was refluxed for 24 h, then quenched at 0° with MeOH (20 ml) and the solvent evaporated. The residue was taken up in 5% ethanolic H_2SO_4 soln. (50 ml), and the resulting soln. was refluxed for 3 h. Dilution with AcOEt (100 ml), washing with 2M aq. NaOH soln. (2 × 100 ml) and sat. aq. NaCl soln. (100 ml), drying ($MgSO_4$), evaporation, and FC (70 g SiO_2, CH_2Cl_2/acetone 1:1) afforded **44** (4.85 g, 93%). Colorless resin. IR ($CHCl_3$): 2979*m*, 2922*m*, 2823*w*, 1607*w*, 1505*s*, 1475*m*, 1388*m*, 1307*w*, 1252*s*, 1143*m*, 1032*m*, 904*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.22 (*d*, *J* = 2.3, 1 H); 7.00–6.95 (*m*, 2 H); 6.95 (*dm*, *J* = 2.4, 1 H); 6.71 (*d*, *J* = 9.1, 1 H); 3.99 (*q*, *J* = 7.0, 2 H); 3.93 (*q*, *J* = 7.0, 2 H); 2.55–2.35 (*m*, 8 H); 2.33 (*q*, *J* = 7.2, 2 H); 2.24 (*s*, 3 H); 2.18 (*s*, 3 H); 1.41 (*t*, *J* = 7.0, 3 H); 1.39 (*t*, *J* = 7.0, 3 H); 1.05 (*t*, *J* = 7.2, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 155.1 (*s*); 152.2 (*s*); 145.2 (br. *s*); 138.1 (br. *s*); 132.6 (*s*); 129.55 (*d*); 129.49 (*d*); 129.1 (*d*); 126.5 (*s*); 125.3 (*d*); 117.3 (*s*); 110.6 (*d*); 68.5 (*t*); 63.4 (*t*); 52.4 (*t*); 50.2 (*t*); 43.6 (*s*); 36.4 (*t*); 17.1 (*q*); 16.6 (*q*); 15.6 (*q*); 15.0 (*q*); 12.2 (*q*). EI-MS: 43 (18), 56 (20), 84 (100), 245 (38), 323/325 (50/49), 444/446 (10/9), 459/461 (10/9, M^+). HR-EI-MS: 459.1750 (M^+, $C_{25}H_{34}BrNO_2^+$; calc. 459.1768).

3,10-Dibutyl-7-{2-ethoxy-5-[4-(4-ethoxy-3-methylphenyl)-1-ethylpiperidin-4-yl]-3-methylphenyl}benzo[g]-pteridine-2,4(3H,10H)-dione (**46**). BuLi (1.6M in hexane, 3.12 ml, 4.98 mmol) was added at −78° to a soln. of TMEDA (579 mg, 4.98 mmol) in THF (10 ml). A soln. of **44** (459 mg, 0.997 mmol) in THF (5 ml) was added dropwise after 10 min, and, after 30 min, the mixture was treated with $(MeO)_3B$ (2.07 g, 19.9 mmol). The soln. was allowed to warm to r.t. and was stirred overnight. After quenching with sat. aq. NH_4Cl soln. (10 ml), the mixture was neutralized with sat. aq. $NaHCO_3$ soln. (20 ml) and diluted with Et_2O (50 ml). The org. layer was collected, dried ($MgSO_4$), and evaporated, yielding boronic acid **45**. This crude material was dissolved together with **10** (404 mg, 0.997 mmol) in PhMe (10 ml), EtOH (2.5 ml) and 0.5M aq. Na_2CO_3 soln. (8.0 ml, 4.0 mmol). The two-phase mixture was purged with Ar for 10 min, and, after addition of $[PdCl_2(PPh_3)_2]$ (35.0 mg, 49.8 mmol), was refluxed for 20 h. Washing with sat. aq. $NaHCO_3$ soln. (100 ml) and sat. aq. NaCl soln. (100 ml), drying ($MgSO_4$), evaporation, and filtration through a SiO_2 plug (CH_2Cl_2/acetone 10:1 → 1:1) gave an orange oil, which was purified by FC (50 g of SiO_2; hexane/AcOEt/Et_3N 100:50:3 → 100:50:10) to give **46** (373 mg, 53%). Orange foam. UV/VIS: 283 (4.77), 335 (3.95), 453 (4.05). Fluorescence: $\lambda_{max.\ em.}$ = 526 nm. IR ($CHCl_3$): 2963*m*,

1706*m*, 1655*s*, 1619*m*, 1590*m*, 1551*s*, 1505*m*, 1457*w*, 1385*w*, 1345*w*, 1251*m*, 1187*m*, 1143*w*, 1035*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.42 (*d*, *J* = 2.0, 1 H); 8.26 (*dd*, *J* = 9.0, 2.0, 1 H); 7.62 (*d*, *J* = 9.0, 1 H); 7.15, 7.11 (2 br. *d*, *J* = 2.1, 2 H); 7.05–7.00 (*m*, 2 H); 6.73 (*dm*, *J* = 9.2, 1 H); 4.80–4.70 (*m*, 2 H); 4.13 ('*t*', *J* = 7.5, 2 H); 3.99 (*q*, *J* = 7.0, 2 H); 3.51 (*q*, *J* = 7.0, 2 H); 2.65–2.40 (*m*, 8 H); 2.37 (*q*, *J* = 7.2, 2 H); 2.31 (*s*, 3 H); 2.18 (*s*, 3 H); 1.95–1.85 (*m*, 2 H); 1.80–1.70 (*m*, 2 H); 1.65–1.55 (*m*, 2 H); 1.50–1.40 (*m*, 2 H); 1.39 (*t*, *J* = 7.0, 3 H); 1.086 (*t*, *J* = 7.2, 3 H); 1.080 (*t*, *J* = 7.0, 3 H); 1.05 (*t*, *J* = 7.4, 3 H); 0.98 (*t*, *J* = 7.4, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 159.7 (*s*); 155.6 (*s*); 155.1 (*s*); 152.7 (*s*); 148.6 (*s*); 144.4 (br. *s*); 138.4 (*s*); 138.2 (br. *s*); 137.7 (*d*); 137.0 (*s*); 136.1 (*s*); 132.5 (*d*); 131.8 (*s*); 131.5 (*s*); 131.3 (*s*); 130.3 (*d*); 129.4 (*d*); 127.1 (*d*); 126.5 (*s*); 125.2 (*d*); 114.3 (*d*); 110.7 (*d*); 68.6 (*t*); 63.4 (*t*); 52.4 (*t*); 50.3 (*t*); 44.8 (*t*); 43.6 (*s*); 41.9 (*t*); 36.3 (*t*); 29.9 (*t*); 29.2 (*t*); 20.2 (*t*, 2×); 16.74 (*q*); 16.66 (*q*); 15.7 (*q*); 15.0 (*q*); 13.86 (*q*); 13.80 (*q*); 12.2 (*q*). FAB-MS: 706 (100, MH^+). HR-EI-MS: 705.4285 (M^+, $C_{43}H_{55}N_5O_4^+$; calc. 705.4248).

*4-[3-(3,10-Dibutyl-2,4(3*H*,10*H*)-dioxobenzo[*g*]pteridin-7-yl)-4-ethoxy-5-methylphenyl]-4-(4-ethoxy-3-methylphenyl)-1,1-diethylpiperidinium Chloride* (**47**). A soln. of **46** (1.41 g, 2.00 mmol) in EtI (20 ml) was stirred at r.t. for 24 h. Evaporation, FC (60 g of SiO_2; CH_2Cl_2/acetone 4:1 → 1:1), and ion exchange (20 g of *Dowex 1* × *8*, MeOH) gave an orange foam, which was dissolved in PhMe (10 ml) and precipitated by addition of Et_2O (10 ml). Filtration and drying (120°, 100 mbar, 3 h) gave **47** (1.22 g, 77%). Hygroscopic orange powder. M.p. 166–168° (dec.). UV/VIS: 283 (4.66), 334 (3.84), 453 (3.95). Fluorescence: $\lambda_{max.\ em.}$ = 526 nm. IR ($CHCl_3$): 3665*w*, 3351*w* (br.), 2962*m*, 2467*w*, 1706*w*, 1655*s*, 1620*m*, 1590*m*, 1552*s*, 1459*w*, 1345*w*, 1254*m*, 1188*m*, 1148*w*, 1034*w*. ^{1}H-NMR (400 MHz, CD_3OD): 8.31 (*d*, *J* = 2.0, 1 H); 8.24 (*dd*, *J* = 9.0, 2.0, 1 H); 7.98 (*d*, *J* = 9.0, 1 H); 7.36, 7.32 (2 br. *s*, 2 H); 7.25–7.20 (*m*, 2 H); 6.73 (*d*, *J* = 8.4, 1 H); 4.75–4.70 (*m*, 2 H); 3.98 (*q*, *J* = 7.0, 2 H); 3.96 ('*t*', *J* = 7.4, 2 H); 3.60–3.40 (*m*, 8 H); 3.49 (*q*, *J* = 7.0, 2 H); 2.95–2.75 (*m*, 4 H); 2.32 (*s*, 3 H); 2.16 (*s*, 3 H); 1.90–1.80 (*m*, 2 H); 1.70–1.50 (*m*, 4 H); 1.45–1.35 (*m*, 2 H); 1.36 (*t*, *J* = 7.0, 3 H); 1.32 (br. *t*, *J* = 7.3, 6 H); 1.05 (*t*, *J* = 7.0, 3 H); 1.03 (*t*, *J* = 7.3, 3 H); 0.96 (*t*, *J* = 7.4, 3 H). ^{13}C-NMR (75 MHz, CD_3OD, 40°): 161.5 (*s*); 157.9 (*s*); 157.2 (*s*); 154.8 (*s*); 150.3 (*s*); 143.3 (br. *s*); 139.0 (*s*); 138.58 (*s*); 138.48 (*d*); 137.3 (*s*); 136.7 (br. *s*); 133.9 (*s*); 133.6 (*s*); 133.3 (*s*); 132.9 (*d*); 130.8 (*d*); 129.8 (*d*); 128.6 (*s*); 127.5 (*d*); 126.1 (*d*); 117.1 (*d*); 112.7 (*d*); 69.8 (*t*); 64.8 (*t*); 56.9 (*t*); 55.9 (br. *t*); 53.9 (br. *t*); 46.2 (*t*); 43.7 (*s*); 42.8 (*t*); 30.9 (*t*); 30.7 (*t*); 30.4 (*t*); 21.2 (*t*); 21.1 (*t*); 16.8 (*q*); 16.6 (*q*); 15.9 (*q*); 15.3 (*q*); 14.2 (*q*, 2×); 7.6 (*q*, 2×). FAB-MS: 734 (100, $[M - Cl]^+$). Anal. calc. for $C_{45}H_{60}ClN_5O_4 \cdot H_2O$ (788.48): C 68.55, H 7.93, N 8.88; found: C 68.32, H 7.76, N 8.77.

*4-[3-(Chloromethyl)-4-ethoxy-5-methylphenyl]-4-{3-[3,10-dibutyl-2,4(3*H*,10*H*)-dioxobenzo[*g*]pteridin-7-yl]-4-ethoxy-5-methylphenyl}-1,1-diethylpiperidinium Chloride* (**48**). A slow stream of HCl gas was bubbled at r.t. through a soln. of **47** (1.17 g, 1.46 mmol) in AcOH (7 ml), conc. aq. HCl soln. (7 ml), and 37% aq. HCHO soln. (5.46 ml, 73.1 mmol). After 2 h, the soln. was poured into ice (50 g), diluted with CH_2Cl_2 (100 ml), and neutralized by careful addition of 2M aq. Na_2CO_3 soln. (150 ml). Removal of the org. layer, washing with sat. aq. NaCl soln. (100 ml), drying ($MgSO_4$), evaporation, and FC (20 g of SiO_2; CH_2Cl_2/acetone/MeOH 10:4:1 → 10:9:1) gave an orange foam, which was dissolved in PhMe (10 ml) and precipitated by addition of Et_2O (10 ml). Filtration and drying (120°, 100 mbar, 3 h) gave **48** (877 mg, 72%). Hygroscopic orange powder. M.p. 216–218°. UV/VIS: 283 (4.67), 334 (3.84), 453 (3.96). Fluorescence: $\lambda_{max.\ em.}$ = 526 nm. IR ($CHCl_3$): 3669*w*, 3347*w* (br.), 2962*m*, 2936*m*, 2458*w*, 1706*m*, 1655*s*, 1620*m*, 1590*m*, 1552*s*, 1459*m*, 1388*w*, 1345*w*, 1262*w*, 1187*m*, 1108*w*, 1031*w*. ^{1}H-NMR (400 MHz, CD_3OD): 8.35 (*d*, *J* = 1.7, 1 H); 8.27 (*dd*, *J* = 9.0, 1.7, 1 H); 8.01 (*d*, *J* = 9.0, 1 H); 7.41 (br. *s*, 1 H); 7.38 (br. *s*, 1 H); 7.36 (br. *s*, 1 H); 7.33 (br. *s*, 1 H); 4.75–4.70 (*m*, 2 H); 4.67 (*s*, 2 H); 3.97 ('*t*', *J* = 7.2, 2 H); 3.92 (*q*, *J* = 7.0, 2 H); 3.60–3.40 (*m*, 8 H); 3.50 (*q*, *J* = 7.0, 2 H); 2.95–2.80 (*m*, 4 H); 2.34 (*s*, 3 H); 2.27 (*s*, 3 H); 1.90–1.80 (*m*, 2 H); 1.70–1.55 (*m*, 4 H); 1.45–1.35 (*m*, 2 H); 1.39 (*t*, *J* = 7.0, 3 H); 1.35–1.30 (*m*, 6 H); 1.06 (*t*, *J* = 7.0, 3 H); 1.03 (*t*, *J* = 7.4, 3 H); 0.96 (*t*, *J* = 7.4, 3 H). ^{13}C-NMR (75 MHz, CD_3OD, 40°): 161.5 (*s*); 157.9 (*s*); 156.1 (*s*); 155.1 (*s*); 150.3 (*s*); 142.2 (br. *s*); 141.6 (br. *s*); 139.0 (*s*); 138.7 (*s*); 138.5 (*d*); 137.4 (*s*); 134.2 (*s*); 133.9 (*s*); 133.6 (*s*); 133.4 (*s*); 133.0 (*d* + *s*); 131.1 (*d*); 130.8 (*d*); 127.9 (*d*); 127.6 (*d*); 117.2 (*d*); 70.6 (*t*); 69.8 (*t*); 56.9 (*t*); 55.1 (br. *t*); 54.7 (br. *t*); 46.2 (*t*); 43.9 (*s*); 42.8 (*t*); 42.3 (*t*); 31.0 (*t*); 30.6 (*t*); 30.4 (*t*); 21.3 (*t*); 21.1 (*t*); 16.9 (*q*, 2×); 15.9 (*q*, 2×); 14.2 (*q*, 2×); 7.6 (*q*, 2×). FAB-MS: 782 (100, $[M - Cl]^+$). Anal. calc. for $C_{46}H_{61}Cl_2N_5O_4 \cdot H_2O$ (836.95): C 66.02, H 7.59, N 8.37, Cl 8.47; found: C 65.97, H 7.44, N 8.40, Cl 8.51.

*4-[3-(3,10-Dibutyl-2,4(3*H*,10*H*)-dioxobenzo[*g*]pteridin-7-yl)-4-ethoxy-5-methylphenyl]-1,1-diethyl-4-{4-ethoxy-3-methyl-5-[(4-methyl-3-thiazolio)methyl]phenyl}piperidinium Dichloride* (**7**). A soln. of **48** (500 mg, 0.336 mmol) in degassed 4-methylthiazole (5 ml) was heated for 2 h at 80°. Most of the excess 4-methylthiazole was then distilled off *in vacuo* at 80°, and the residue was purified by reversed-phase chromatography (40 g of SiO_2-C_{18}; MeOH/H_2O 1:1 → 2:1). The solvent was removed as an azeotrope with MeCN at 35° to give an orange oil, which was diluted with MeCN (5 ml) and acetone (5 ml), and precipitated with Et_2O (30 ml). Filtration and drying (10^{-6} mbar, 16 h, r.t.) yielded **7** (334 mg, 58%). Hygroscopic orange powder. M.p. 174–177°. UV/VIS: 284 (4.69), 334 (3.85), 453 (3.97). Fluorescence: $\lambda_{max.\ em.}$ = 526. IR ($CHCl_3$): 3687*w*, 3386*w*, 2961*m*, 1705*w*, 1655*m*, 1619*w*,

1590*m*, 1552*s*, 1460*w*, 1346*w*, 1187*w*, 1030*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 11.91 (br. *s*, 1 H); 8.32 (br. *d*, *J* = 9.1, 1 H); 8.19, 8.18 (2 br. *s*, 2 H); 7.75 (br. *s*, 1 H); 7.67 (*d*, *J* = 9.1, 1 H); 7.34 (br. *s*, 1 H); 7.25 (br. *s*, 1 H); 7.09 (br. *s*, 1 H); 5.95 (*s*, 2 H); 4.80–4.70 (*m*, 2 H); 4.11 ('*t*', *J* = 7.5, 2 H); 3.91 (*q*, *J* = 7.0, 2 H); 3.90–3.80 (*m*, 2 H); 3.65–3.50 (*m*, 6 H); 3.44 (*q*, *J* = 7.0, 2 H); 3.20–3.10 (*m*, 2 H); 2.67 (*s*, 3 H); 2.60–2.50 (*m*, 2 H); 2.35 (*s*, 3 H); 2.28 (*s*, 3 H); 2.00–1.85 (*m*, 2 H); 1.80–1.70 (*m*, 2 H); 1.65–1.55 (*m*, 2 H); 1.45–1.35 (*m*, 8 H); 1.40 (*q*, *J* = 7.0, 3 H); 1.10–1.00 (*m*, 6 H); 0.97 (*t*, *J* = 7.4, 3 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$, 40°): 160.8 (*d*); 159.2 (*s*); 154.7 (*s*); 154.1 (*s*); 152.9 (*s*); 148.9 (*s*); 145.8 (*s*); 141.2 (br. *s*); 140.6 (br. *s*); 137.9 (*s*); 136.08, 136.02 (*d* + *s*); 135.1 (*s*); 131.8 (*s*); 131.7 (*s*, 2×); 131.5 (*s*); 130.9 (*d*); 130.6 (*d*); 129.2 (*d*); 126.7 (*d*); 125.9 (*d*); 125.6 (*d*); 122.2 (*d*); 116.0 (*d*); 68.7 (*t*); 68.1 (*t*); 54.8 (*t*); 53.2 (br. *t*); 52.2 (*t*); 51.8 (br. *t*); 44.0 (*t*); 42.2 (*s*); 40.6 (*t*); 29.5 (*t*); 28.7 (*t*); 28.3 (*t*); 19.6 (*t*); 19.4 (*t*); 16.35 (*q*); 16.28 (*q*); 15.4 (*q*, 2×); 13.6 (*q*, 2×); 12.9 (*q*); 6.9 (*q*, 2×). FAB-MS: 423.0 (25, $[M - 2\,Cl]^{2+}$), 747 (37, $[M - C_4H_5NS - 2\,Cl]^+$), 845 (100, $[M - H - 2\,Cl]^+$), 881 (31, $[M - Cl]^+$). Anal. calc. for $C_{50}H_{66}Cl_2N_6O_4S \cdot 3\,H_2O$ (972.13): C 61.77, H 7.47, N 8.64; found: C 61.92, H 7.48, N 8.64.

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