Effect of Substituents on the Complexation of Aromatic and Quinoid Substrates with Molecular Tweezers and Clips

Frank-Gerrit Klärner,*[a] Jolanta Polkowska,[a] Jens Panitzky,[a] Uta P. Seelbach,[a] Ulrich Burkert,[a] Markus Kamieth,[a] Michael Baumann,[a] Arne E. Wigger,[a] Roland Boese,[b] and Dieter Bläser[b]

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Molecular tweezers and clips of type **1**–**3** substituted with OAc, OH, OCONHPh, OMe, OCH_2COOR and OCH_2-CONHR groups in the central spacer units have been synthesized by modification, by standard methods, either of the known diacetoxy-substituted derivatives **1b**, **2b** and **3b**, or of the correspondingly substituted bis-dienophiles **4b** and **5b**. The synthesis of the dimethoxy-diacetoxy-substituted tweezer **1d** could be accomplished through pressure-induced repetitive Diels–Alder reactions between the bis-dienophile **4b** and the newly prepared diene **6b** and subsequent DDQ oxidation. The thermodynamic parameters (K_a and ΔG) of complex formation between the new receptors and aromatic substrates such as DCNB **21**, TCNB **22**, TCNQ **24** and Kosower salt **25** and the maximum complexation-induced ^1H NMR shifts ($\Delta\delta_{max.}$) were determined by ^1H NMR titration experiments. It was found that the presence of substituents OH, OAc and OCONHPh in the central spacer units of the tweezers and clips **1**–**3** favours complex formation, whereas that of the substituents OMe, OCH_2COOR and OCH_2-CONHR disfavours it. This finding can be explained in terms of the size and different conformations of these groups in the tweezer and clip molecules as calculated by force-field (MMFF) techniques rather than of their influence on the electrostatic potential surfaces (EPSs) of the adjacent aromatic rings as calculated by quantum mechanical methods. The complementary natures of the negative EPSs inside the tweezer and clip cavities and the positive EPSs of the substrates forming complexes explained the high selectivity of these receptors toward electron-deficient substrates. The finding that the self-assembly of the $OCH_2COOCH_2CH_3$ side chain is only observed for the benzene-spaced tweezers **1i** and **1o** confirms earlier results obtained for the intermolecular complexation of these receptors. Accordingly, the benzene-spaced tweezers of type **1** selectively bind aliphatic substrates, whereas the naphthalene-spaced tweezers of type **2** and clips of type **3** preferentially complex aromatic substrates.

Introduction

The design of efficient synthetic receptors with the capability for selective substrate binding plays a key role in the construction of higher organized chemical systems with novel properties resembling the fascinating functions of biological systems.[1−6] Recently, we have described the synthesis and some supramolecular properties of the parent benzene- and naphthalene-spaced receptors **1a** and **2a** and a few substituted derivatives such as **1b**, **1c**, **1i**, **1o**, **2b** and **2c**.[7−11] These compounds belong to a family of molecules termed molecular tweezers[12−14] due to their belt-type concave−convex topography and their propensity to form complexes with electron-deficient aliphatic and aromatic substrates as well as organic cations by clipping the substrate between the tweezers' tips, similarly to the working principle of mechanical tweezers. Electron-rich arenes or anions, however, are not bound by **1a** or **2a**. This high selectivity toward electron-deficient substrates was correlated with markedly negative electrostatic potential surfaces (EPSs) calculated for the concave faces of **1a** and **2a** by quantum chemical methods.[15,16] When analogous calculations were performed for the substrates (bound to **1a** and **2a**) the complementary nature of their EPSs to those of **1a** and **2a** became evident, suggesting that the substrate-receptor binding in these cases is predominantly electrostatic in nature. This conclusion also explains the observation that the initially prepared tweezers **1e** and **2e**, each substituted with four electron-withdrawing ester groups at the terminal benzene rings, showed only a weak tendency to form complexes with substrates such as *p*-dicyanobenzene (DCNB) **21**. In the case of the benzene-spaced tweezer **1i**, self organisation by the aliphatic $OCH_2COOCH_2CH_3$ side chains at the central spacer unit was observed.[7] According to single-

[a] Institut für Organische Chemie, Universität Duisburg-Essen
45117 Essen, Germany
E-mail: frank.klaerner@uni-essen.de
[b] Institut für Anorganische Chemie, Universität Duisburg-Essen
45117 Essen, Germany
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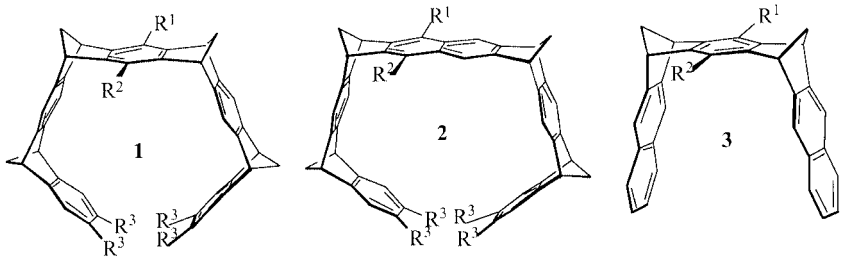
crystal structure analysis, one side chain is folded and its terminal methyl group is centred inside the cavity, whereas the other side chain has an extended conformation. In solution the exchange between the two side chains, one folded and the other one unfolded, seems to be fast on the NMR timescale, so that only one set of signals was observed for the two side chains. In order to study the effect of the receptor topography on the substrate specificity, the number of methylene bridges was reduced from four in the molecular tweezers **1** and **2** to two in the system **3**.[17,18] The dimethylene-bridged compounds **3** are called molecular clips, because they form complexes through the positioning of an aromatic substrate inside the receptor cavity with its plane of molecule almost parallel to the naphthalene side walls of **3**,[17] contrasting with the previously known geometries of the complexes with **2a** as receptor, in which the plane of the substrate is arranged nearly parallel to the central naphthalene spacer unit of the receptor.[11] Here we report the synthesis of the substituted tweezers **1d** and **2i**−**n** and of the clips **3f** and **3h**−**o**, together with their capabilities to form complexes with aromatic and quinoid substrates, as shown in Scheme 8. In particular, we were interested in the effect of the presence of substituents (such as OAc, OMe, OH, OCONHR and OCH_2CO_2R) in various receptor positions on the stabilities of the complexes. The branched hexacarboxylic acids **2m** and **3m** and the corresponding salts **2n** and **3**n were chosen with the aim of obtaining water soluble receptors.[19−21]

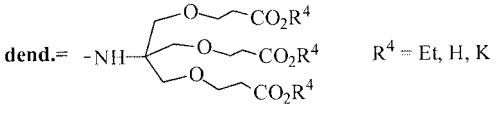
Synthesis of the Substituted Tweezers 1d and 2i−n and of the Clips 3f and 3h−n

The molecular tweezers **1** and **2** and the clips **3** can be synthesized by use of a molecular LEGO set consisting of the bis-dienophiles **4** and **5**[7,11,22,23] and the dienes **6**[24] and **10**[25−27] as molecular building blocks. The key steps in the synthesis of **1** and **2** are repetitive Diels−Alder reactions proceeding with high degrees of stereoselectivity on the *exo*-faces of the bis-dienophiles **4** and **5** and on the *endo*-faces of the diene **6**,[27−30] affording the bis-adducts **7** and **8**. Oxidative dehydrogenation of the cyclohexene moieties in **7** and **8** by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) produces the desired tweezers **1** and **2** (Scheme 2).

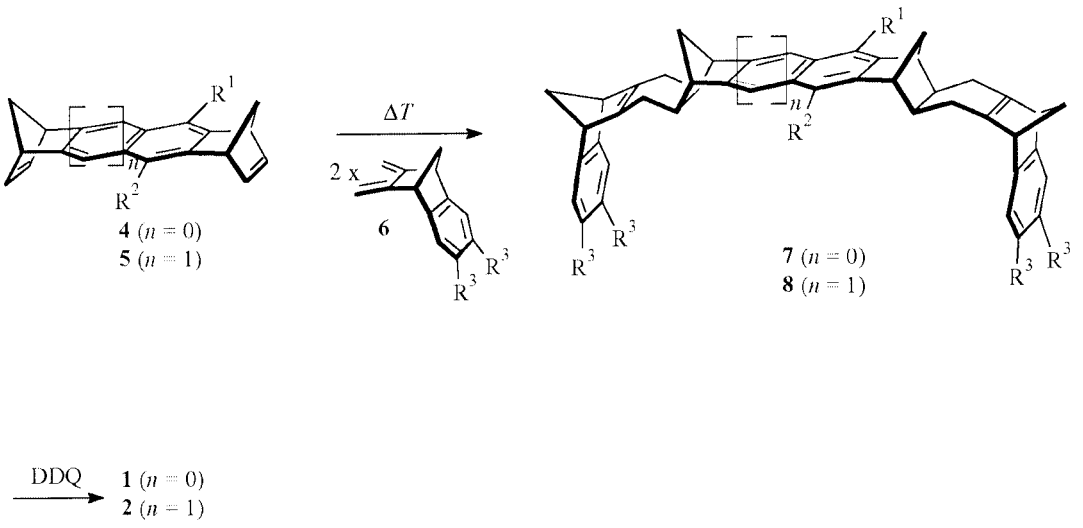
The molecular clips **3** can be prepared in a one-pot reaction starting from the bis-dienophile **4** and tetrabromoxylene **9**.[17] Repetitive Diels−Alder reactions between **4** and the dibromo-*o*-quinodimethane **10** (generated in situ by 1,4-Br_2 elimination from **9** by treatment with sodium iodide)



	R^1	R^2	R^3
a	H	H	H
b	OAc	OAc	H
c	OMe	OMe	H
d	OAc	OAc	OMe
e	OMe	OMe	CO_2Me
f	OH	OAc	H
g	OH	OH	H
h	OCONHPh	OCONHPh	H
i	OCH_2CO_2Et	OCH_2CO_2Et	H
j	OCH_2CO_2H	OCH_2CO_2H	H
k	OCH_2CO_2K	OCH_2CO_2K	H
l	OCH_2CO-dend.(R^4 = Et)	OCH_2CO-dend.(R^4 = Et)	H
m	OCH_2CO-dend.(R^4 = H)	OCH_2CO-dend.(R^4 = H)	H
n	OCH_2CO-dend.(R^4 = K)	OCH_2CO-dend.(R^4 = K)	H
o	OCH_2CO_2Et	OAc	H



Scheme 1. Substituted tweezers **1**, **2** and clips **3** synthesized to date

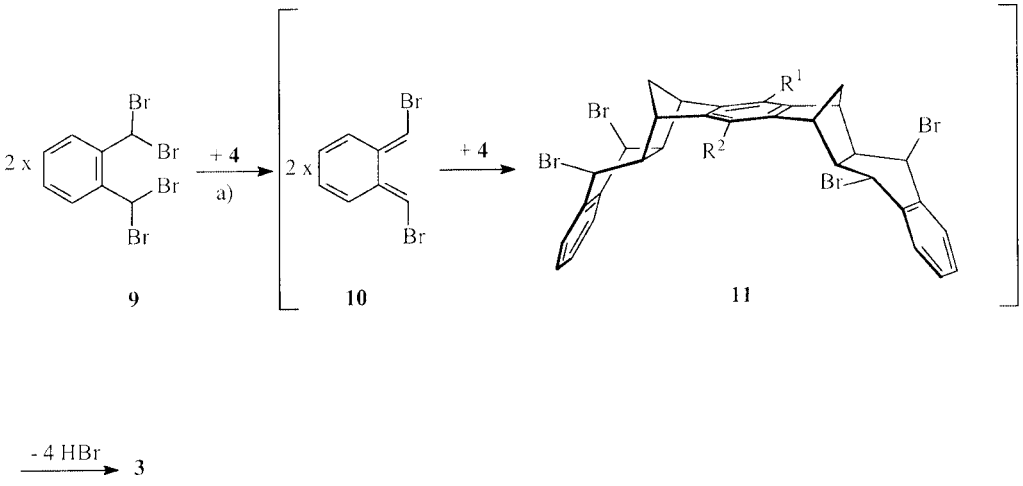


Scheme 2. General scheme for the synthesis of molecular tweezers **1** and **2**

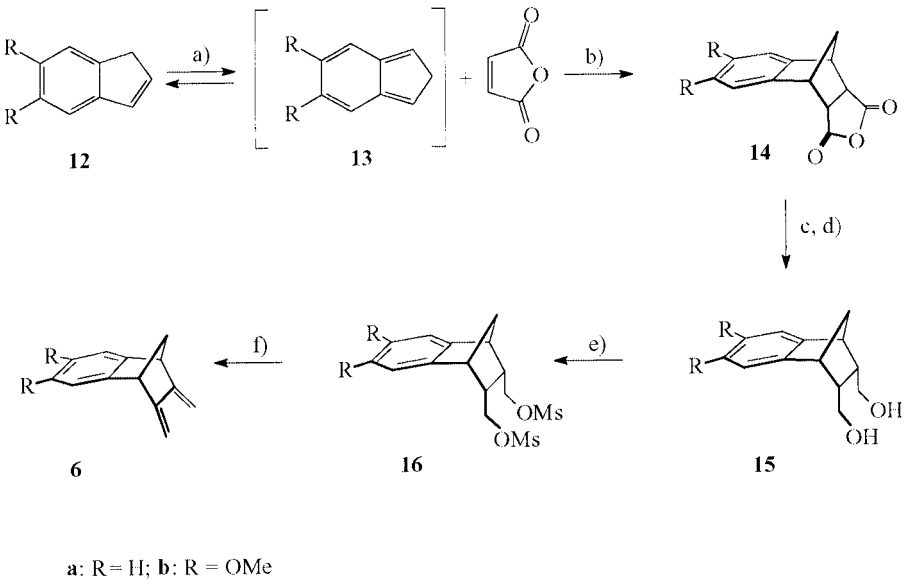
produced the primary bis-adduct **11**, which is not stable under the reaction conditions and eliminates four molecules of HBr to produce the clip **3**.

The described substituents in the molecular tweezers **1** and **2** and the clips **3** (Scheme 1) can be introduced either already in the starting materials **4**−**6** or by transformation of the substituents in **1**−**3**, as in, for example, transformation of the acetoxy groups into other functional groups.[10,11,17] Both routes were used to functionalize the tweezer and clip molecules. The diacetoxy-tetramethoxy-substituted tweezer **1d** was prepared through a reaction between the dimethoxy-substituted diene **6b** and the diacetoxy-substituted bis-dienophile **4b**. Diene **6b** could be synthesized analogously to the unsubstituted diene **6a** (Scheme 4).[24] At 200 °C, dimethoxyindene **12b** rearranges through a sigmatropic 1,5[H] shift to the isoindene **13b**, which can be trapped by Diels−Alder reaction with maleic anhydride (MA) to produce the cycloadduct **14b** in 42% yield.[31] Conversion of the anhydride **14b** into the diol **15b** by $LiAlH_4$ reduction, followed by mesylation of the OH groups in **15b** and basic elimination of the dimesylate **16b**, provided the diene **6b** in 56% yield over the last three steps.[24]

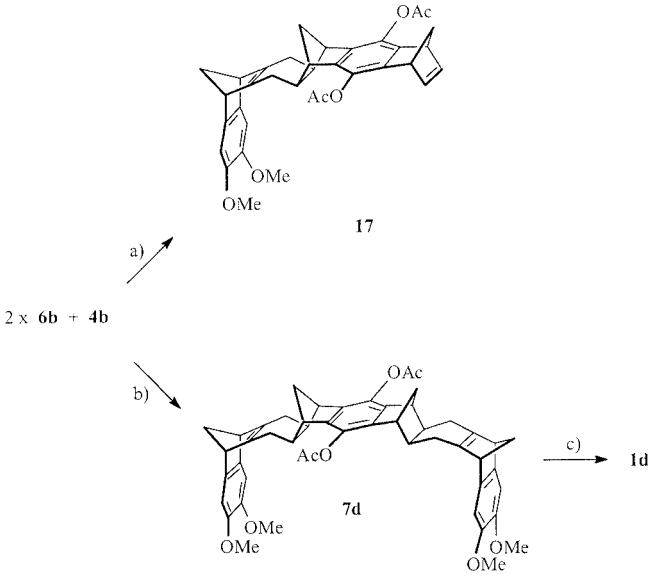
The behaviour of the dimethoxydiene **6b** in the Diels−Alder reaction with the bis-dienophile **4b** is significantly different to that of the parent diene **6a**. At 165 °C and atmospheric pressure, the reaction between **4b** and **6b** yields only the (1:1) Diels−Alder adduct **17**, whereas the corresponding reaction between **4b** and the parent diene **6a** under the same conditions gives the (2:1) Diels−Alder compound **7b** in 72% yield. There is no easy, straightforward explanation for the remote substituent effect on the Diels−Alder reactivity in diene **6b**. At high pressure (12 kbar), the Diels−Alder reaction between diene **6b** and dienophile **4b** was strongly accelerated, so that the time and temperature could be lowered to 24 h and 100 °C, respectively. The only product isolated from the high-pressure reaction, in 66% yield, was the desired (2:1) Diels−Alder adduct **7d**, which could be converted into **1d** by DDQ dehydrogenation in 14% yield.



Scheme 3. General scheme for the synthesis of molecular clips **3**; reaction conditions: a) NaI, $CaCO_3$, DMF, 55 °C, 100 mbar



Scheme 4. Synthesis of the diene **6b**; reaction conditions: a) 200 °C; b) 200 °C, 24 h, 42%; c) $LiAlH_4$, THF, reflux 4 h; d) H_2O, 84%; e) MsCl, pyridine, 22 °C, 12 h, 67%; f) KO*t*Bu, DMSO, 22 °C, 24 h, 99%

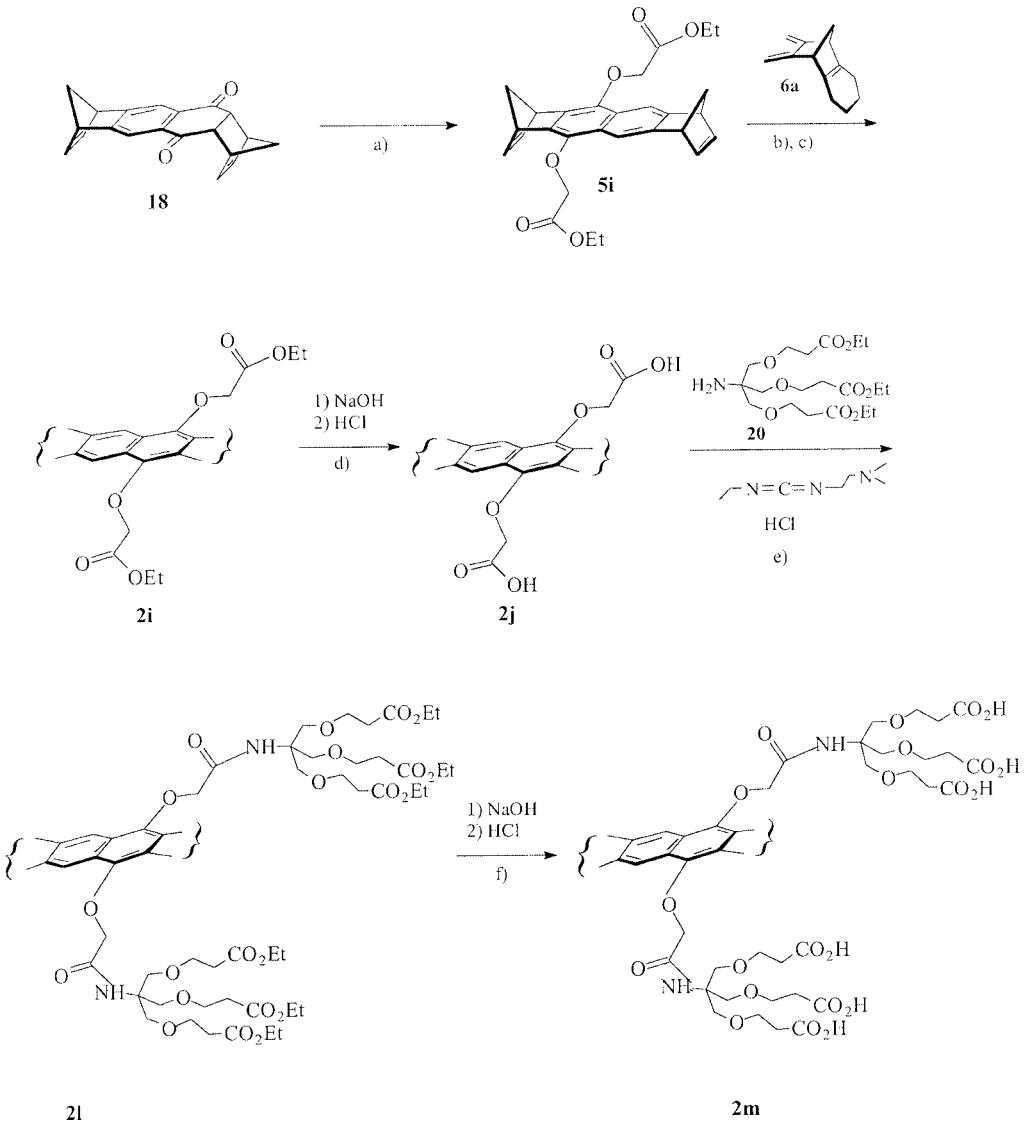


Scheme 5. Synthesis of the tweezer **1d**; reaction conditions: a) 165 °C, 1 bar, 6 d, Ph_2NH, NEt_3, toluene/MeCN, 56%, b) 100 °C, 12 kbar, 24 h, Ph_2NH, NEt_3, toluene/MeCN, 66%, c) DDQ, toluene, 120 °C, 1 h, 14%

As a precursor to the naphthalene-spaced tweezers **2i**−**n**, the bis-dienophile **5i** was prepared by enolization of the known diketone **18**[7,22,32] with DBU and subsequent nucleophilic substitution of ethyl bromoacetate with the resulting enolate (85% yield) (Scheme 6). A Diels−Alder reaction between **5i** and the diene **6a** and subsequent DDQ oxidation of the resulting bis-adduct **8i** gave the tweezer **2i**. Hydrolysis of the diester **2i** and amidation of the diacid **2j** with the amine **20** in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) [21] provided the branched hexaester **2l**, which could be hydrolysed to produce the hexaacid **2m**. Neutralization of **2m** with KOD produced the corresponding potassium salt **2n**.

The benzene-spaced diurethane **4h** and diester **4i** − potential precursors to the molecular tweezers **1h** and **1i** and to the clips **3h** and **3i** − could be obtained by keto−enol tautomerization of the known diketone **19**, affording the hydroquinone **4g**, and subsequent treatment of **4g** either with phenylisocyanate,[33] or with ethyl bromoacetate (Scheme 7). The diester **4i** could be prepared in a one-pot reaction starting from diketone **19** without the isolation of hydroquinone **4g**. To date, only the clips **3h** and **3i** (and not the tweezers **1h** and **1i**) have been prepared by treatment of **4h** and **4i** with *o*-1,1,2,2-tetrabromoxylene (**9**) under the conditions shown in Scheme 3 (yield of **3h**: 86%, **3i**: 75%). Starting from the diester **3i**, the clips **3j**−**n** could be prepared by the same methodology as used for the synthesis of the corresponding tweezers **2j**−**n** (yields of **3j**: 95%, **3k**: 92%, **3l**: 79%, **3m**: 65%, **3n**: 80%). The tweezer **1o**,[10] the clip **3o** and spacer unit **4o**, substituted with $R^1 = OCH_2COOCH_2CH_3$ and R^2 = OAc, were synthesized by treatment of the already known tweezers **1f** and **2f**, the clip **3f** and the spacer unit **4f** (R^1 = OH, R^2 = OAc) with ethyl bromoacetate as in the synthesis of the corresponding derivatives **1i**, **2i**, **3i** and **4i** ($R^1 = R^2 = OCH_2COOCH_3$).

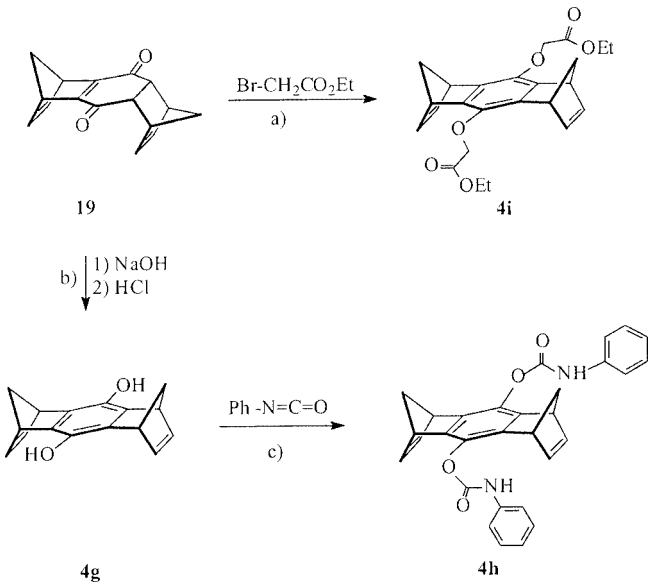
The structures of all new compounds have been characterized by their spectroscopic data, as described in the Exp. Sect. Whereas the parent tweezers **1a** and **2a**, the clip **3a** and their acetoxy- and methoxy-substituted derivatives **1b**, **1c**, **2b**, **2c**, **3b** and **3c** are only soluble in relatively non-polar organic solvents and not soluble in polar protic solvents such as methanol or water, the diacids **2j** and **3j** are soluble in methanol and methanol/water (1:2) and the hexaacids **2m** and **3m** in methanol and methanol/water (1:3). The potassium carboxylates **2n** and **3n** are soluble in water.



Scheme 6. Synthesis of the naphthalene-spaced bis-dienophile **5i** and the tweezers **2i**−**m**; reaction conditions: a) acetonitrile, DBU, $BrCH_2CO_2Et$, 0°C − room temp., 24 h, 85%, b) Et_3N, toluene, 6d, 160°C, 67%, c) DDQ, toluene, 120°C, 63%, d) EtOH, 4 h, 80°C, 95%, e) CH_2Cl_2, 0°C − room temp., 24 h, 88%, f) $MeOH/H_2O$ (4:1), 3 d, room temp., 76%

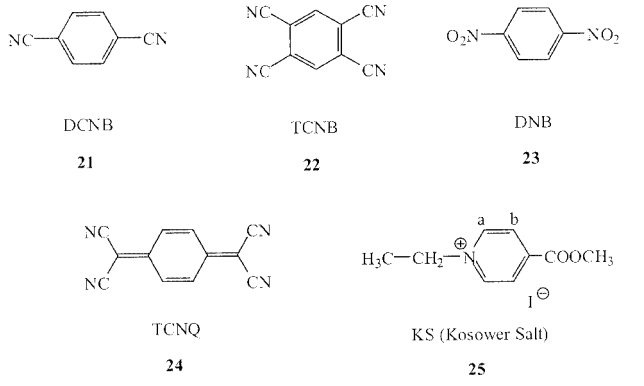
Thermodynamic Parameters of Complex Formation

The magnetic anisotropy of the receptor arene units makes ^1H NMR spectroscopy a very sensitive probe for investigation of the complexation of a substrate molecule inside the cavity of one of the receptor molecules **1**−**3**. The complex formation can easily be detected through the pronounced up-field shifts of the signals in the ^1H NMR spectrum of the substrate after addition of the receptor.[34] In all complexations reported here, the receptor-substrate association and dissociation are fast processes on the NMR timescale. Thus, the maximum complexation-induced ^1H NMR shifts ($\Delta\delta_{max.}$) of the substrate signals ($\Delta\delta_{max.} = \delta_0 - \delta_C$, δ_0, δ_C ^1H NMR shifts of free and complexed substrate) the association constants (K_a) and the free enthalpies of association (ΔG) could be determined by ^1H NMR titration experiments by measurement of the dependence of the complexation-induced ^1H NMR shifts ($\Delta\delta_{obsd.}$) on the receptor concentration ($[R]_0$) at constant substrate concentration ($[S]_0$ = const.), as described in the Exp. Sect. ($\Delta\delta_{obsd.} = \delta_0 - \delta_{obsd.}$, $\delta_{obsd.}$ is the substrate ^1H NMR shift observed in the presence of the receptor and hence the weighted average of δ_0 and δ_C).[35] The molecular tweezers **1** and **2** and the clips **3** bind a variety of electron-deficient neutral and cationic substrates inside their cavities. This report is focused on the influence of substituents (attached to various positions of **1**, **2** or **3**) on complexation with the aromatic and quinoid compounds **21**−**25** (Scheme 8) as representative examples of substrates. The maximum complexation-induced ^1H NMR shifts ($\Delta\delta_{max.}$) of the substrates, the association constants (K_a) and the free enthalpies of association (ΔG) determined for complex formation between the tweezers and clips **1a**−**d**, **2a**−**m** and **3b**−**i** and



Scheme 7. Synthesis of benzene-spaced dienophiles, reaction condition: a) KI, K_2CO_3, acetone, 24 h, reflux, 85%; b) EtOH, phenylhydrazine, 30 min, room temp., 95%; c) Et_3N, acetonitrile, 10 min, room temp., 94%

the substrates **21**−**25** are shown in Table 1−3. Since TCNB (**22**) and TCNQ (**24**) form relatively stable complexes with the tweezers **1** and **2**[11] and experimental analysis of these complex formations by ^{1}H NMR titration is difficult, we studied the less stable complexes with DCNB (**21**) and Kosower salt (**25**) to elucidate the substituent effects on complex stability. In the case of the dimethylene-bridged clips **3** the complexes with TCNB (**22**) and TCNQ (**24**) are less stable and could be used for this study.[17]



Scheme 8. The molecular structures of the substrate molecules used for complex formation with the tweezers **1** and **2** and the clips **3** as receptors

Comparison of the K_a and ΔG values found for complex formation by the benzene-spaced tweezers **1a**−**c** and the corresponding naphthalene-spaced analogues **2a**−**c** with DCNB (**21**) as substrate (Table 1 and 2) demonstrates (in agreement with earlier results obtained for the parent receptors **1a** and **2a**[11]) that the substituted naphthalene-spaced tweezers **2b** and **2c** are also better receptors than the corresponding benzene derivatives **1b** and **1c.** Aromatic substrates such as **21** fit into the larger cavity of the naphthalene-spaced system **2** better than they do into the smaller one of the benzene-spaced receptor **1**. According to single-crystal structure analyses, the cavities of **1a**[11] or **1k**[10] have to be substantially distorted during the complexation, whereas the shape and size of the cavity of **2a** is almost perfect for inclusion of an aromatic substrate.[11]

Table 1. Comparison of $\Delta\delta_{max.}$, K_a [M^{-1}] and ΔG [kcal/mol] for complex formation between the benzene-spaced tweezers **1a**−**d** as receptors and *p*-dicyanobenzene (DCNB, **21**) and *p*-dinitrobenzene (DNB, **23**) as substrates at 25 °C in $CDCl_3$

Receptor	Substrate					
	DCNB **21**			DNB **23**		
	$\Delta\delta_{max.}$	K_a	ΔG	$\Delta\delta_{max.}$	K_a	ΔG
1a	3.5	10	−1.4	3.5	17	−1.7
1b	2.2	40	−2.2	2.9	36	−2.1
1c	1.9	8	−1.2	2.7	6	−1.1
1d	2.3	21	−1.8		n.d.[a]	

[a] n.d. not determined

Table 2. Comparison of $\Delta\delta_{max.}$, K_a [M^{-1}] and ΔG [kcal/mol] for complex formation between the naphthalene-spaced tweezers **2a**−**m** as receptors and *p*-dicyanobenzene (DCNB, **21**) and Kosower salt (**25**) as substrates at 25 °C in $CDCl_3$

Receptor	Substrate					
	DCNB **21**			Kosower Salt **25**		
	$\Delta\delta_{max.}$	K_a	ΔG	$\Delta\delta_{max.}$	K_a	ΔG
2a	4.3	110	−2.8	4.1	1100	−4.1
2b	4.1	110	−2.8	4.1	3800	−4.9
2c	4.4	23	−1.9		n.d.	
2f	4.0	190	−3.1	4.2	1097	−4.1
2i	4.3	17	−1.7	3.5 (H^a)	354	−3.5
2j	4.0[a]	14	−1.6	3.9 (H^b)	311[a]	−3.4
2k	4.4[b]	177	−3.1	3.7 (H^a)	532[b]	−3.7
2l	3.9[b]	141	−2.9		n.d.	
	3.4	18	−1.7	3.4 (H^b)	100	−2.7

[a] In $CDCl_3$/[D_6]acetone (1:1). [b] In CD_3OD; n.d. not determined.

The data shown in Table 1 and 2 allow the conclusion that the tweezers **1b** and **2b** substituted with two acetoxy functions in the central spacer unit form complexes with DCNB (**21**), DNB (**23**), or the Kosower salt (**25**) that are as stable as − or even more stable than − those formed by the parent tweezers **1a** and **2a**,[11] whereas the presence of methoxy groups in these positions causes substantial weakening of the complexes of **1c** or **2c** with the substrates **21** or **23**. The diacetoxy-tetramethoxy-substituted tweezer **1d** forms a less stable complex than the diacetoxy-substituted tweezer **1b** with DCNB (**21**).

The enthalpies (ΔH [kcal/mol]) and the entropies of association (ΔS [cal/mol K]) were obtained from the temperature dependence of K_a, as determined by variable temperature ^{1}H NMR measurements: **DCNB@2a**: ΔH = −(2.6±0.1), ΔS = +(0.6±0.2), **DCNB@2b**: ΔH = −(1.9±0.2), ΔS = +(3.0±0.5), **DCNB@2c**: ΔH = −(1.6±0.1), ΔS = +(1.0±0.3).

Table 3. Comparison of $\Delta\delta_{max.}$, K_a [M^{-1}] and ΔG [kcal/mol] for complex formation between the benzene-spaced clips **3b**−**i** as receptors and 1,2,4,5-tetracyanobenzene (TCNB, **22**), tetracyanochinodimethane (TCNQ, **24**) and Kosower salt (**25**) as substrates at 25 °C in $CDCl_3$

Receptor	Substrate								
	TCNB (**22**)			TCNQ (**24**)			Kosower salt (**25**)		
	$\Delta\delta_{max.}$	K_a	ΔG	$\Delta\delta_{max.}$	K_a	ΔG	$\Delta\delta_{max.}$	K_a	ΔG
3b	3.4	140	−2.9	3.0	25	−1.9	2.4(H^b)	137	−2.9
3c		< 7[a]			n.d.			n.d.	
3f	3.4	490	−3.7	2.2	80	−2.6	3.0 (H^b)	670	−3.9
3g	3.6	2180	−4.6	2.6	137	−2.9	2.4 (H^b)	1080	−4.1
3h	3.8	558	−3.7	2.8	352	−3.5	3.0 (H^a)	265	−3.3
3i		< 5[a]			n.d.[b]			n.d.	

[a] Estimated value. [b] n.d.: not determined.

Evidently, the presence of methoxy groups substituted on the terminal benzene rings of the tweezer **1**, similarly to their presence on the central spacer unit of **1**, disfavours complex formation. In the case of the tweezer **2f**, substituted with a hydroxy and an acetoxy function in the central naphthalene spacer unit, the complex with DCNB (**21**) is more stable than the corresponding complex of the parent tweezer **2a**. The complexes of **2f** and **2a** with the Kosower salt (**25**) are of comparable stability. The OCH_2CO_2R substituents in the tweezers **2i**−**l** have the same effect as the OMe groups in **2c**, decreasing complex stability. The stabilities of the complexes between **2i** or **2j** as receptors and **21** or **25** as substrates are, however, again increased in methanol, evidently due to the solvophobic effect of the protic solvent.[6,18]

The substituents − the acetoxy, methoxy and hydroxy functions − in the central spacer units of the dimethylene-bridged clips **3b**, **3c**, **3f** and **3g** show the same effect on the stability of their complexes with TCNB (**22**), TCNQ (**24**) or Kosower salt (**25**) as already discussed for the complexes of the correspondingly substituted molecular tweezers **1b**, **1c**, **2b**, **2c** and **2f** with DCNB (**21**) and Kosower salt (**25**). No complexation could be experimentally observed within the limits of ^1H NMR detection for the alkoxy-substituted clips **3c** and **3i**−**n**, whereas the presence of hydroxy and phenylurethane functions in **3f**, **3g** and **3h** gives rise to an increase in the complex stability in relation to the acetoxy functions in **3b**.

Discussion

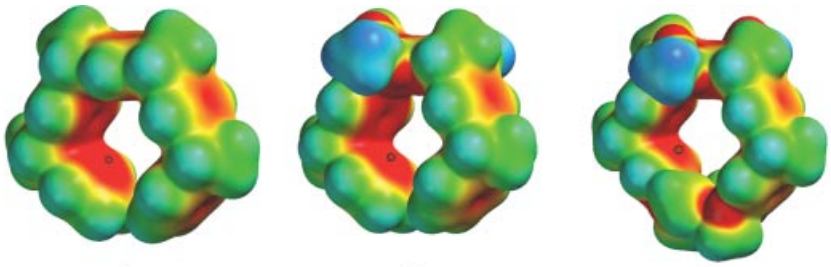
The systems studied here (Table 1−3) allow the following conclusions:

Relative to the parent systems, the presence of hydroxy and phenylurethane functions in the central spacer units of the tweezer **2f** and the clips **3f**, **3g** and **3h** increases complex stability, the complexes of the diacetoxy-substituted tweezers **1b**, **2b** and the clip **3b** are of either larger or similar stability, and the presence of methoxy substituents in the central spacer units of **1c**, **2c** and **3c**, as well as in the terminal benzene rings of **1d**, results in a decrease in the complex stability.

The alkoxy groups (OCH_2COOR or OCH_2CO-dend.) in **2i**−**n** and **3i**−**n** show the same (weakening) effect as the OCH_3 groups in **1c**, **2c** and **3c**. The complex between diacid **2j** and DCNB **21**, however, shows that the complex stability can be increased by use of a protic solvent such as methanol instead of chloroform. This can be explained by the solvophobic effect,[6] which favours noncovalent arene−arene interactions, the dominating binding interactions responsible for the complexation observed here.

The complex formation of the tweezers and clips and their high selectivity toward electron-deficient substrates have been explained in terms of the markedly negative electrostatic potential surfaces (EPSs)[15,16] calculated for the concave faces of **1a**, **2a** or **3a** by use of various quantum chemical methods such as the semiempirical AM1, ab initio or DFT methods.[36,37] The AM1 calculations gave results similar to those obtained by ab initio or DFT methods.

Methoxy and hydroxy groups are generally considered to be electron-donating substituents. Thus, the finding that methoxy groups do not enhance complex stability, but even decrease it, was contrary to expectations. First let us discuss the effect of the methoxy groups in tweezer **1d**. The molecular electrostatic potential, MEP, at the centre of the π surface of the dimethoxy-substituted benzene rings in **1d** is calculated by AM1 to be less negative than that on the π surfaces of the corresponding unsubstituted rings in **1a** or **1b** (Figure 1). According to the EPS calculations on **1a** and **1b**, the acetoxy substituents have almost no effect on the MEPs of the remote terminal benzene rings. The less negative MEP of **1d** (in relation to that of **1b**) therefore seems to be a reasonable explanation for the finding that **1d** forms a less stable complex than **1b** with DCNB **21**. To confirm this explanation and to explain the effects of the substituents in the central spacer units of the tweezers and clips we calculated the EPSs and MEPs of benzene and the dimethoxy, dihydroxy- and diacetoxy-substituted derivatives by AM1, DFT and ab initio methods (Table 4).[36] According to the calculations by all three methods, the absolute values of the negative MEPs decrease in the sequence: benzene (C_6H_6) > *p*-$C_6H_4(OMe)_2$ > *p*-$C_6H_4(OH)_2$ > *p*-$C_6H_4(OAc)_2$. The MEP of *o*-$C_6H_4(OMe)_2$ is calculated by DFT and AM1 to be either more or less negative than that of C_6H_6, and by ab initio methods to be almost the same. These data are in



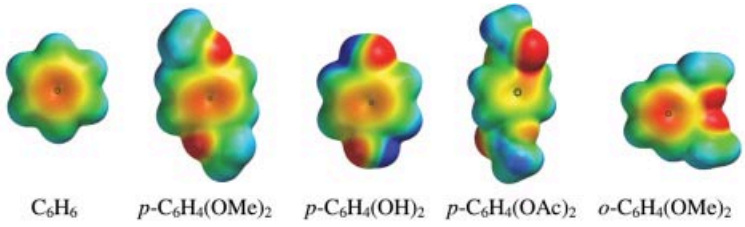
	1a	1b	1d
MEP:	– 33.4	– 33.9	– 28.7

Figure 1. The electrostatic potential surfaces (EPSs) of the benzene-spaced tweezers **1a**, **1b** and **1d** calculated by AM1 are depicted; the colour code ranges from −25 (red) to +25 kcal/mol (blue); molecular electrostatic potentials (MEPs in kcal/mol) are calculated at the marked positions above the centres of the terminal aromatic rings

agreement with EPS calculations performed by D.A. Dougherty et al.[38] for benzene and phenol by use of the same ab initio basis set (HF, 6−31 G**) and the AM1 method. The outcome, that the substitution of the benzene ring with OH or OMe groups does not result in more negative MEPs on the π surfaces of the ring, can be interpreted in terms of the σ-withdrawing and π-donating properties of these substituents. As far as the EPS of the ring is concerned, the σ and π effects of the OH and OMe group roughly cancel and so the MEPs of the methoxy- and hydroxy-substituted derivatives are similar to, or even a little less negative than, that of benzene. In the case of *p*-$C_6H_4(OAc)_2$ the σ effect is obviously dominating, most probably due to the withdrawing effect of the carbonyl group, and its MEP is therefore significantly less negative than that of benzene.

The EPS calculations shown in Table 4 cannot explain the experimental findings that the substitution of the tweezers and clips with hydroxy and acetoxy groups results in an increase in the complex stability whereas substitution with methoxy groups gives rise to a substantial decrease. To elucidate these apparent contradictions we calculated the conformations of the diacetoxy-, dimethoxy-, and dihydroxy-substituted tweezers **1b**, **1c**, **1g** and **2b**, **2c**, **2g**, the clips **3b**, **3c**, **3g** and the spacer units **4b**, **4c**, **4g** by force-field (MMFF) techniques.[36] These gas-phase calculations do not take the effects of solvents into consideration, but these are important for the formation of host−guest complexes. These calculations can therefore only give information about qualitative tendencies. The *anti*,*anti* conformations of **1b**−**4b**, in which both acetoxy groups point toward the methylene bridges of the central spacer units, are calculated to be the lowest-energy conformations, as shown for **3b** as a representative example in Figure 2 (the conformers of the other systems calculated by MMFF are shown in the Supporting Information to this article, Figure S1; for Supporting Information see also the footnote on the first page of this article). The corresponding *anti*,*syn* and *syn*,*syn* conformations of **3b** are calculated to be higher in energy by 1.3 and 3.8 kcal/mol, respectively. In the case of **3c**, the *syn*,*syn* conformation, in which both methoxy groups point toward the clip cavity, is calculated to be lower in energy than the *anti*,*syn* or *anti*,*anti* conformations by 1.7 and 3.7 kcal/mol, respectively. According to the calculations for **3g**, the OH groups are positioned almost parallel to the plane of the ring of the central spacer unit.

Table 4. The electrostatic potential surfaces (EPSs) of benzene and derivatives calculated for geometries optimized by DFT (B3LYP, 6−31G**) are depicted; the colour code ranges from −25 (red) to +25 kcal/mol (blue); the molecular electrostatic potentials (MEPs in kcal/mol) are calculated by DFT, HF (6−31G**, single-point calculations with the DFT-optimized geometries), and AM1 at the marked positions above the centres of the aromatic rings



	C_6H_6	*p*-$C_6H_4(OMe)_2$	*p*-$C_6H_4(OH)_2$	*p*-$C_6H_4(OAc)_2$	*o*-$C_6H_4(OMe)_2$
Method			MEP [kcal/mol]		
DFT	– 19.7	– 19.5	– 17.9	– 12.8	– 22.3
HF	– 22.9	– 21.3	– 18.8	– 14.8	– 22.7
AM1	– 24.3	– 21.3	– 17.8	– 18.1	– 22.8

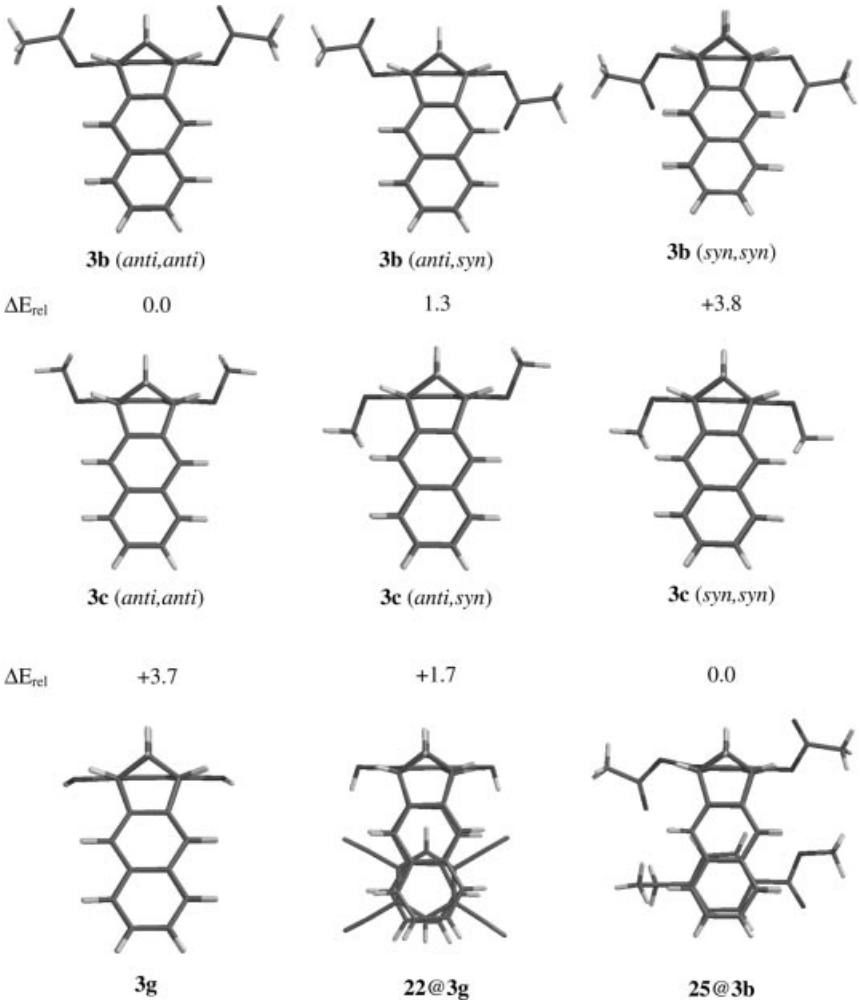


Figure 2. The relative energies ($\Delta E_{rel.}$, in kcal/mol) of the lowest-energy conformations of the diacetoxy, dimethoxy, and dihydroxy-substituted clips **3b**, **3c** and **3g** as calculated by force field (MMFF) techniques and single-crystal structure analyses of the complexes of TCNB (**22**) with **3g** and of Kosower salt (**25**) with **3b**[17]

The *syn*,*syn* conformation was experimentally observed in the single-crystal structure of the co-crystals of **1c**, TCNB **22**, and $CHCl_3$ (1:1:1), in which $CHCl_3$ is included in the cavity and **22** is positioned parallel to the naphthalene side walls outside the cavity of **1c**.[17] The sterically relatively large OMe substituents in the *syn*,*syn* conformation efficiently shield the cavities of the clips and tweezers, particularly that of the clip **3c**, and prevent the usual orientation of an aromatic substrate inside the clip cavity with its plane of molecule nearly parallel to the naphthalene side-walls and orthogonal to the central spacer unit. According to force-field calculations, either the substrate molecule has to be pushed into the cavity, which causes steric repulsion if the *syn*,*syn* conformation of the OMe groups is retained in the complex, or one or both OMe groups have to rotate into the *anti*,*syn* or *anti*,*anti* conformation during the complex formation. Both processes cost energy and disfavour complex formation. The conformational effect of the OMe groups on the substrate position were nicely demonstrated in the already published single-crystal structure of the solvent-free complex between **3c** as receptor and *p*-dinitrobenzene as substrate, which is stable only in the co-crystal and not in solution.[17]

Evidently, the presence of the OMe group in the *syn* position causes a substrate shift outside the cavity. The finding that the tweezers **1c** and **2c** form weak but detectable complexes in solution indicates that the steric effects of the OMe groups on these systems are smaller. The different binding properties of **1c** and **2c** on the one hand and **3c** on the other may be explained in terms of the different substrate alignments inside the cavities of the tweezers or clips (Figure 2−4).

In the case of the diacetoxy-substituted systems **1b**, **2b** and **3b**, the *anti*,*anti* conformation is calculated to be the most stable one. In this conformation there should be no steric hindrance to complex formation. The single-crystal structures of clip **3b** and of the co-crystals of **3b** and TCNB (**22**), in which the TCNB molecule is positioned outside the clip cavity,[17] however, show a *syn*,*anti* conformation of **3b** in both systems. The *syn*,*anti* conformation of **3b** is also observed in the single-crystal structures of the complexes KS **25**@**3b**[17] (Figure 2), DCNB **21**@**2b** (Figure 3) and

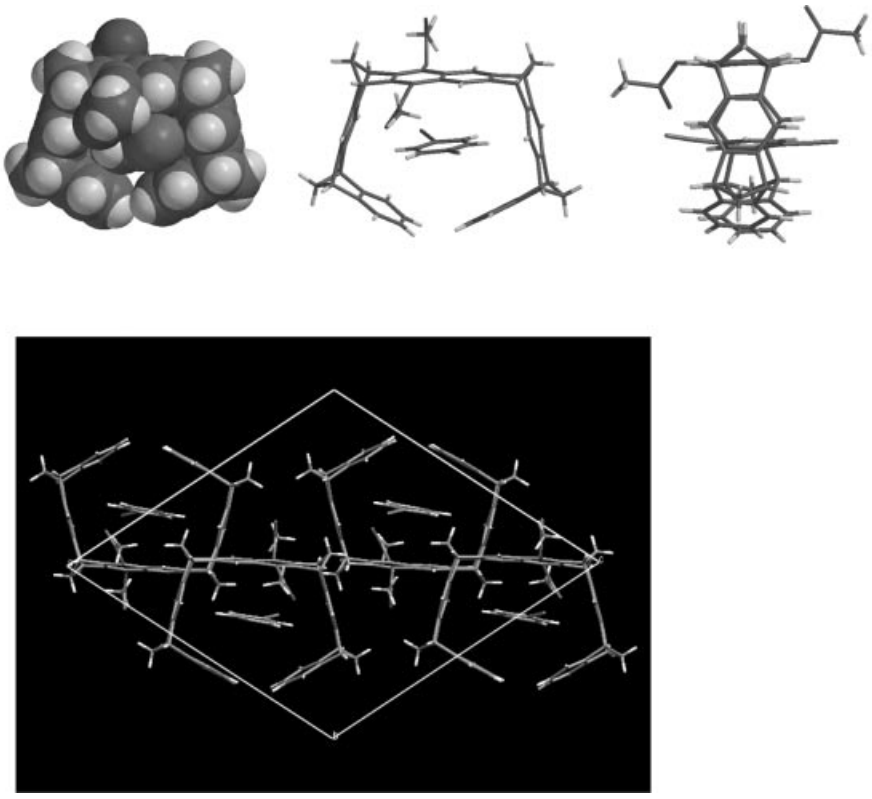


Figure 3. Single-crystal structure analysis of the complex DCNB **21**@**2b** (colourless plates); the packing of **21**@**2b** is shown with view along [010]; the smallest, intramolecular, non-bonded distances of the carbon atoms in the tweezer opening are both 3.92 Å

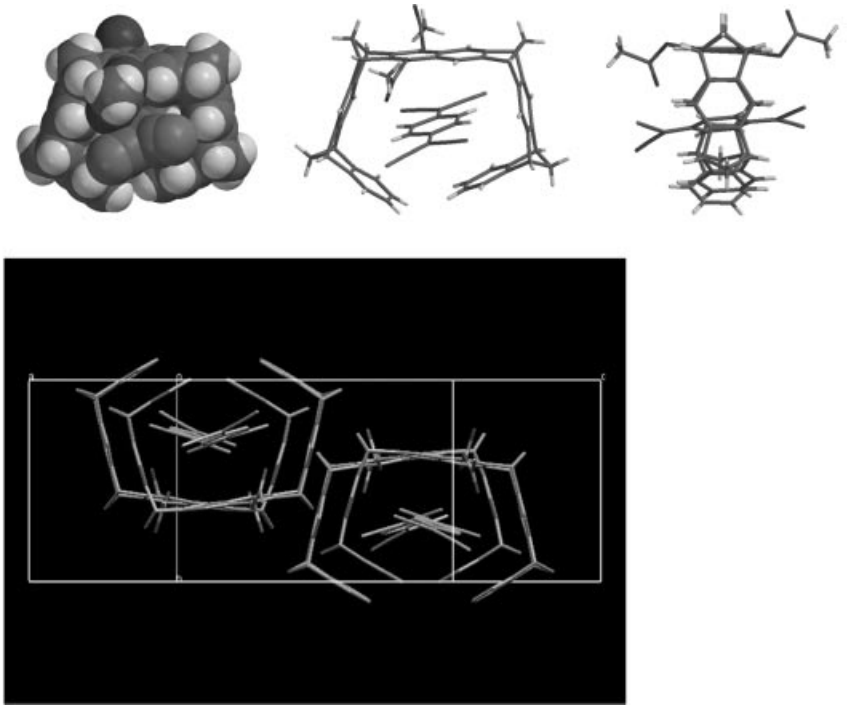


Figure 4. Single-crystal structure analysis of the complex TCNQ **24**@**2b** including $CHCl_3$ in the crystal lattice (dark green crystals); packing of **24**@**2b** with view along [201], the C_2 axis parallel to *b*, is situated between the molecules; the smallest, intramolecular, non-bonded distances of the carbon atoms in the tweezer opening are 4.03 and 3.99 Å, solvent molecules were omitted for clarity

TCNQ **24@2b** (Figure 4). Single crystals of the hitherto unknown complexes DCNB **21@2b** (colourless), and TCNQ **24@2b** (dark green) suitable for X-ray structure analysis were obtained by crystallization of (1:1) mixtures either of **21** and **2b** or of **25** and **2b** from chloroform/methanol (3:1). Inspection of the single-crystal structures of the complexes KS **25@3b**, DCNB **21@2b** and TCNQ **24@2b** allows the conclusion that the electrostatic interaction between the negatively charged carbonyl oxygen atom of the *syn*-configured acetoxy function and the positively charged substrate molecule is attractive and obviously overcompensates for the small energy difference between the *anti*,*anti* and *syn*,*anti* conformations of **3b**. This attractive interaction is nicely demonstrated in the crystal structure of the complex **25@3b** (Figure 2), in which the carbonyl oxygen atom of the *syn*-configured acetoxy group points toward the positively charged ring nitrogen atom of the Kosower salt. This structure is calculated by force field to be 10 kcal/mol lower in energy than the corresponding complex structure of the *anti*,*anti* conformer of **3b** (Supporting Information: Figure S1). The effect of the OH groups stabilizing the complexes of the tweezer **2f** and the clips **3f** and **3g** with various substrates (Table 2 and 3) can be explained in terms of the smaller steric demand of the OH function in relation to the more bulky OMe or OAc groups and the potential to form additional attractive O−H···N hydrogen bonds to substrates such as DCNB (**21**) or TCNB **22** (Figure 2). Finally, let us consider the potential for self-assembly of the $OCH_2COOCH_2CH_3$ side chains attached to the central spacer units of the tweezers **1i**, **1o** and **2i** and the clips **3i** and **3o**, which may also prevent the formation of intermolecular host-guest complexes. As already mentioned in the Introduction, the folding of one side chain inside the cavity of the benzene-spaced tweezer **1i** was detected by single-crystal structure analysis and from the pronounced up-field ^{1}H NMR shift of OCH_2CH_3 protons of the side chains in solution (Table 5).[7]

Table 5. Comparison of the ^{1}H NMR shifts of the methylene and methyl protons in the symmetrically substituted tweezers **1i**[7] and **2i**, the clip **3i**, the spacer units **4i** and **5i** ($R^1 = R^2 = OCH_2COOCH_2CH_3$) and in the unsymmetrically substituted tweezer **1o**, clip **3o** and spacer unit **4o**;[7] $R^1 = OCH_2COOCH_2CH_3$, R^2 = OAc) in $CDCl_3$

Compound	δ (CH_2)	δ (CH_3)
1i	3.37	−0.27
1o	2.66	−1.62
2i	4.31	1.35
3i	4.30	1.31
3o	4.37	1.36
4i	4.20	1.33
4o	4.24	1.29
5i	4.29	1.32

The equivalence of the side chains in the ^{1}H NMR spectrum of **1i** indicates either that both side chains are complexed by the arene units in a symmetrical arrangement or that only one side chain is complexed while the other one is free, similarly to the single-crystal structure analysis,[7] and that there is a rapid exchange between the complexed and the non-complexed side chain. Low-temperature ^{1}H NMR experiments have not allowed a decision between these two possibilities. The observations that the side chain CH_2 and CH_3 signals in the ^{1}H NMR spectrum of **1o** are shifted further upfield and that the chemical shifts of the corresponding signals of **1i** are roughly the average of those of the signals of **1o** and **4i**, allows a clear-cut decision in favour of the second possibility: rapid exchange between the complexed and non-complexed side chains in **1i**. The signals of the CH_2 and CH_3 protons in the ^{1}H NMR spectra of the naphthalene-spaced tweezer **2i** and the clips **3i** and **3o** are not significantly shifted in relation to those of the corresponding protons in the spacer units **4i**, **4o** and **5i**. This finding is good evidence that the side chains are not folded inside the cavities of these tweezers and clips. The structures of the benzene-spaced tweezer **1i** (with one side chain folded and the other one extended) and of the clip **3i** (with both side chains extended) (Figure 5) were calculated by force field techniques, by use of a Monte Carlo search of the conformer distribution,[36] to be the lowest-energy conformers, in agreement with the results obtained experimentally from the X-ray and ^{1}H NMR analysis.[7] The limitation of these force-field calculations performed for the gas phase can be shown in the structure of the naphthalene-spaced tweezer **2i**, which is calculated to have one folded side chain and the other one extended (Figure 5), similarly to **1i** but contrary to the ^{1}H NMR results. Inspection of space-filling models of the calculated folded structures of **1o** and **2o** (see Supporting Information: Figure S3) shows that the cavity of **2o** is too large to complex the terminal methyl group of the $OCH_2COOCH_2CH_3$ side chain efficiently whereas the size of the cavity of **1i** is optimal for the intramolecular complexation of the side chain methyl group through attractive CH-π interactions.

Conclusions

In summary, we have found that substituents such as OH, OAc and OCONHPh groups in the central spacer units of the tweezers and clips **1**−**3** favour complex formation with aromatic substrates (in relation to the parent tweezers and clips) whereas OMe groups in these positions disfavour it. This finding can be explained in terms of the different sizes and conformations of the substituents rather than by their influence on the electrostatic potential surfaces of the adjacent aromatic rings. The finding that the folding of the $OCH_2COOCH_2CH_3$ side chain is only observed for the benzene-spaced tweezers **1i** and **1o** indicates a high selectivity in the complex formation of the benzene-spaced tweezers with aliphatic substrates and confirms earlier results obtained for the intermolecular complexation of these receptors.[11] These results should now allow us to design more efficient and more selective receptors, such as water-soluble tweezers and clips for the complexation of bioactive substrate molecules. This work is currently in progress.

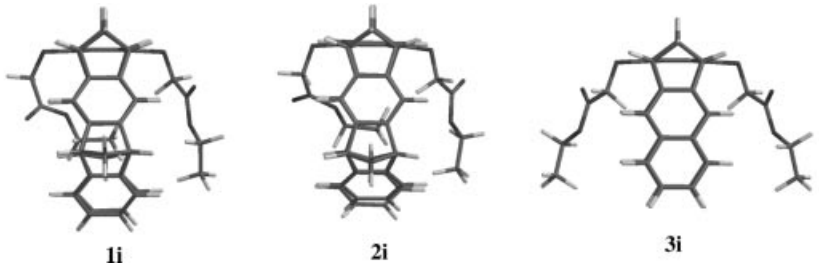
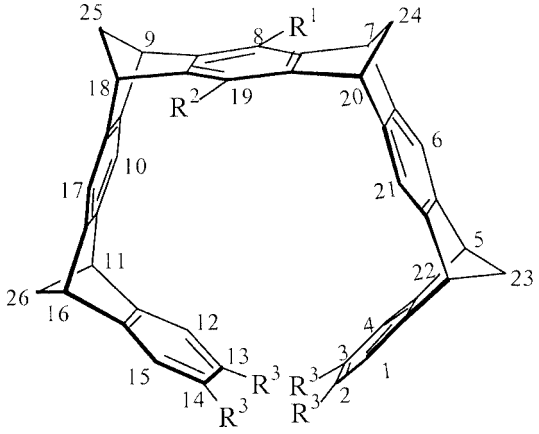


Figure 5. Lowest-energy structures of the tweezers **1i** and **2i** and of the clip **3i**, each substituted with $R^1 = R^2 = OCH_2COOCH_2CH_3$, as calculated by force field (MMFF) techniques by use of a search of the conformer distribution

Experimental Section

General Experimental Details: IR: Bio-Rad FTS 135. UV: J+M Tidas FG Cosytec RS 422. ^{1}H NMR, ^{13}C NMR, DEPT H,H-COSY, C,H-COSY, NOESY, HMQC, HMBC: Bruker AMX 300 and DRX 500. ^{1}H NMR titration experiments: Varian Gemini XL 200; the undeuterated proportion of the solvent was used as an internal standard. Positions of the protons of the methano bridges are indicated by the letters *i* (*innen*, towards the centre of the molecule) and *a* (*aussen*, away from the centre of the molecule). MS: Fison Instruments VG ProSpec 3000 (70 eV). All melting points are uncorrected. Column chromatography: silica gel 0.063−0.2 mm. All solvents were distilled prior to use. Ampoules were sealed in vacuo after three freeze (2-propanol/dry ice) and thaw cycles with argon as an inert gas.

Synthesis of the Benzene-Spaced Tweezers 1c, 1d and 1o



Synthesis of the Bis-adduct 7c: A solution of the bis-dienophile **4c**[22] (350 mg, 1.31 mmol), diene **6a** (920 mg, 5.5 mmol) and NEt_3 (0.1 mL) in anhydrous toluene (8.0 mL) was heated at 160 °C in a sealed ampoule for 6 days. The reaction mixture was cooled to room temperature. After removal of the solvent to about 2 mL, the crude product was purified by column chromatography (silica gel, cyclohexane/ethyl acetate, 10:1) to afford the bis-adduct **7c** as a colourless solid (590 mg, 0.98 mmol, 75%); m.p. 265 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.55 (m, 4 H, 24,25-H), 1.90 (dm, 4 H, 23,26-H), 2.10 (m, 12 H, 6a,9a,17a,20a,6,10,17,21-H), 3.10 (s, 4 H, 7,9,18,20-H), 3.55 (s, 4 H, 5,11,16,22-H), 3.73 (s, 6 H, $-OCH_3$), 6.80 (m, 4 H, 2,3,13,14-H), 7.15 (m, 4 H, 1,4,12,15-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 29.6 (CH_2, C-6,10,17,21), 40.1 (CH, C-6a,9a,17a,20a), 45.0 (CH_2, C-24,25), 49.2 (CH, C-7,9,18,20), 53.3 (CH, C-5,11,16,22), 61.2 ($C-OCH_3$), 67.0 (CH_2, C-23,26), 120.5 (CH, C-1,4,12,15), 123.8 (CH, C-2,3,13,14), 138.0 (C-7a,8a,18a,19a), 142.9 (C-8,C-19), 147.1 (C-5a,10a,16a,21a), 152.1 (C-4a,11a,15a,22a) ppm. IR (KBr): $\tilde{\nu}$ = 3040 ($CH_{arom.}$), 2966 (CH), 2927 (CH), 1482 (C=C), 1295 (C−O), 752 (CH=CH) cm^{-1}. MS (70 eV), *m/z* (%) = 602 (40) [M^+], 408 (80), 378 (45) [$M^+ - 194$], 214 (100) [$M^+ - 2 \times 194$].

Synthesis of Benzene Tweezer 1c: DDQ (400 mg, 1.76 mmol) was added to a solution of **7c** (100 mg, 0.166 mmol) in anhydrous toluene (7 mL). The intensively stirred mixture was immediately placed in an oil bath preheated to 120 °C and kept there for 90 min. The reaction mixture was cooled down to 60 °C. The excess of DDQ was converted into $DDQH_2$ by treatment with 1,4-cyclohexadiene (0.3 mL). After stirring for 20 min at 60 °C the mixture was filtered and the filtrate was concentrated in vacuo. Purification of the crude product by column chromatography (silica gel, cyclohexane/ethyl acetate, 5:1) gave tweezer **1c** as a colourless solid (49 mg, 0.09 mmol, 50%); m.p. >290 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.30 [dt, ^2J(24-H^a, 24-H^i) = 9, ^3J(24-H, 7-H) = 1.5 Hz, 2 H, 24,25-H^a], 2.35 (dt, 2 H, 24,25-H^i), 2.39 (dt, 2 H, 23-H^i, 26-H^a), 2.42 [dt, ^2J(23-H^a, 23-H^i) = 9, ^3J(23-H, 11-H) = 1.5 Hz, 2 H, 23-H^a, 26-H^i], 3.67 (s, 6 H, OCH_3), 4.05 (s, 4 H, 5,11,16,22-H), 4.24 (s, 4 H, 7,9,18,20-H), 6.75 (m, 4 H, 2,3,13,14-H), 7.09 (m, 4 H, 1,4,12,15-H), 7.23 (s, 4 H, 6,10,17,21-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 47.2 (CH, C-7,9,18,20), 50.3 (CH, C-5,11,16,22), 60.5 ($C-OCH_3$), 68.3 (CH_2, C-24,25), 68.7 (CH_2, C-23,26), 115.1 (CH, C-6,10,17,21), 120.4 (CH, C-1,4,12,15), 123.6 (CH, C-2,3,13,14), 138.6 (C-7a,8a,18a,19a), 144.4 (C-8,19), 146.3 (C-6a,9a,17a,20a), 147.4 (C-5a,10a,16a,21a), 149.48 (C-4a,11a,15a,22a) ppm. IR (KBr): $\tilde{\nu}$ = 2992 (CH), 2975 (CH_2), 2936 (CH_2), 1482 (C=C), 1279 (C−O), 1034 (CH) cm^{-1}. MS (70 eV): *m/z* (%) = 594 (100) [M^+], 579 (18) [$M^+ - CH_3$], 564 (8) [$M^+ - 2 \times CH_3$].

Synthesis of 14b: A solution of 3,4-dimethoxyindene (**12b**, 2.0 g, 11.4 mmol), maleic anhydride (11.1 g, 114 mmol) and hydroquinone (0.2 g, 1.8 mmol) in anhydrous toluene (10 mL), saturated with Ar, was heated at 200 °C in a sealed ampoule for 24 h. The solvent was removed in vacuo and the residue was purified by column chromatography (silica gel, cyclohexane/ethyl acetate, 5:1 to 2:1). The solvent was evaporated in vacuo, and the residue was washed with a small amount of diethyl ether and dried in vacuo to give **14b** (1.3 g, 4.74 mmol, 42%); m.p. 160 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.85 (dt, 1 H, 9-H^a), 2.05 (dt, 1 H, 9-H^i), 3.72 (m, 2 H, 5,8-H), 3.81 (m, 8 H, OCH_3, 5a,7a-H), 6.81 (s, 2 H, 1,4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 47.4 (CH_2, C-9), 48.9 (CH, C-5,8), 52.7 (CH, C-5a,7a), 56.0 (OCH_3), 106.7 (C-1,4), 133.4 (C-4a,8a), 148.6 (C-2,3), 207.8 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3088 (CH), 2955 (CH), 2800 (CH), 2840 (CH), 1854 (C=O), 1781 (C=O), 1223 (C−O) cm^{-1}. UV/Vis (MeOH): $\lambda_{max.}$ (log ε) =

230 (3.799), 284 nm (3.636). MS (70 eV) : *m/z* (%) = 274 (35) [M^+], 176 (100), 161 (25). $C_{15}H_{14}O_5$ (274.5): calcd. C 65.69, H 5.14, O 29.17; found C 65.84, H 5.52, O 28.64.

Synthesis of 15b: Lithium aluminium hydride (1.3 g, 34.3 mmol) was suspended in anhydrous tetrahydrofuran (40 mL) and the system was cooled to 0 °C. Under argon, a solution of **14b** (2.0 g, 7.3 mmol) in tetrahydrofuran (20 mL) was slowly added to the stirred suspension. After the addition was complete, the stirred mixture was heated at reflux for 4 h and then cooled to 0 °C. Water was added until the excess of lithium aluminium hydride had been hydrolysed, and aqueous sulfuric acid (10%) was added until all inorganic salts had dissolved. The mixture was extracted with diethyl ether (4 × 100 mL) and the combined organic layers were dried over anhydrous $MgSO_4$. After removal of the solvent **15b** was obtained as a colourless solid (1.62 g, 6.1 mmol, 84%); m.p. 115 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.70 (dt, 1 H, 9-H^a), 1.73 (dt, 1 H, 9-H^i), 2.62 (dd, 2 H, 5a,7a-H), 2.84 (t, 2 H, 5,8-H), 3.17 (t, 2 H, 6-H), 3.44 (dd, 2 H, 7-H), 3.81 (s, 6 H, OCH_3), 6.71 (s, 2 H, 1,4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 43.9 (CH_2, C-9), 47.7 (CH, C-5,8), 50.1 (CH, C-5a,7a), 56.2 (OCH_3), 63.1 (CH_2, C-6,7), 107.0 (CH, C-1,4), 136.7 (C-4a,8a), 147.1 (C-2,3) ppm. IR (KBr): $\tilde{\nu}$ = 3340 (OH), 2972 (CH), 2943 (CH), 2886 (CH), 2836 (CH), 1493 (C−O) cm^{-1}. UV/Vis (MeOH): $\lambda_{max.}$ (log ε) = 231 (3.757), 285 (3.643). MS (70 eV): MS (70 eV): *m/z* (%) = 264 (30) [M^+], 176 (100) [$M^+ - C_4H_2O_3$], 161 (25) [$M^+ - C_4H_2O_3 - CH_3$]

The Synthesis of 16b: A solution of **15b** (0.8 g, 3 mmol) in anhydrous pyridine (5 mL) was slowly added to a stirred solution of mesyl chloride (1.0 g, 8.7 mmol) in anhydrous pyridine (10 mL), cooled to 0 °C. The mixture was stirred overnight at room temperature, and was then acidified with aqueous HCl (15%) and extracted with dichloromethane (4 × 50 mL). The combined organic layers were washed with 50 mL of water and dried over anhydrous $MgSO_4$. After removal of the solvent, **16b** was obtained by recrystallization from methanol (0.84 g, 2.0 mmol, 67%); m.p. 137 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.73 (dt, 1 H, 9-H^a), 1.92 (dt, 1 H, 9-H^i), 2.82 (m, 2 H, 5,8-H), 2.97 (s, 6 H, SO_2CH_3), 3.41 (t, 2 H, 5a,7a-H), 3.49 (t, 2 H, 6-H), 3.69 (dd, 2 H, 7-H), 3.87 (s, 6 H, OCH_3), 6.87 (s, 6 H, 1,4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 38.2 (SO_2CH_3), 41.6 (CH_2, C-9), 46.1 (CH, C-5,8), 47.6 (CH, C-5a,7a), 57.0 (OCH_3), 69.7 (CH_2, C-6,7), 108.6 (CH, C-1,4), 136.0 (C-4a,8a), 148.5 (C-2,3) ppm. IR (KBr): $\tilde{\nu}$ = 3011 (CH), 2983 (CH), 2940 (CH), 2843 (CH), 1349 (SO_2), 1180 (C−O) cm^{-1}. UV/Vis (MeOH): $\lambda_{max.}$ (log ε) = 285 (3.684), 232 (3.749). MS (70 eV): *m/z* (%) = 420 (25) [M^+], 176 (100)], 161 (1), 83 (15).

Synthesis of 6b: KO*t*Bu (4.04 g, 36 mmol) was added under argon at room temperature to a stirred solution of **16b** (6.18 g, 14.7 mmol) in dimethyl sulfoxide (165 mL) and the system was stirred overnight. The mixture was poured into ice water (260 mL) and extracted with diethyl ether (4 × 200 mL). The combined organic layers were washed with 200 mL of saturated aqueous NaCl and dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, **6b** was obtained (3.32 g, 14.6 mmol, 99%); m.p. 62 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.90 (dt, 1 H, 9-H^a), 2.07 (dt, 1 H, 9-H^i), 3.75 (t, 2 H, 5,8-H), 3.82 (s, 6 H, OCH_3), 5.01 (s, 2 H, 6-H), 5.16 (s, 2 H, 7-H), 6.83 (s, 2 H, 1,4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 51.0 (CH_2, C-9), 51.4 (CH, C-5,8), 55.1 (OCH_3), 100.7 (CH_2, C-6,7), 104.8 (CH, C-1,4), 137.6 (C-5a,7a), 146.4 (C-4a,8a), 148.0 (C-2,3) ppm. IR (KBr): $\tilde{\nu}$ = 3075 (CH), 2973 (CH), 2933 (CH), 2865 (CH), 2831 (CH), 1300 (C−O) cm^{-1}. UV/Vis (MeOH): $\lambda_{max.}$ (log ε) = 244 (4.08), 300 (3.82). MS (70 eV) : *m/z* (%) = 228 (100) [M^+], 213 (15), 197 (10), 185 (20), 141 (10), 115 (15).

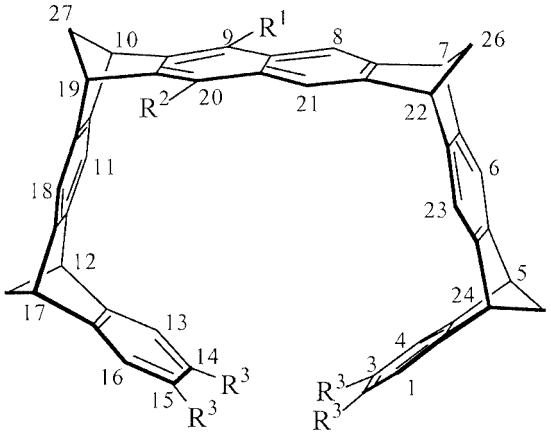
Synthesis of the Bis-adduct 7d: A solution of the bis-dienophile **4b**[23] (192 mg, 0.6 mmol), the diene **6b** (340 mg, 1.49 mmol), diphenylamine (40 mg, 3.4 mmol), triethylamine (0.12 mL, 8.6 mmol), anhydrous acetonitrile (0.8 mL) and anhydrous toluene (4 mL), degassed and saturated with argon, was heated for 24 h at 100 °C at 12 kbar in a sealed PFTE tube. After removal of the solvent, the residue was purified by column chromatography (silica gel, cyclohexane/ethyl acetate, 4:1). The eighth fraction (R_f = 0.1) contained **7d**. After removal of the solvent the residue was dried in vacuo to give **7d** (292 mg, 0.38 mmol, 66%); m.p. 150 °C. ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 1.74 (d, 2 H, 24,25-H^a), 1.89 (s, 6 H, OCOCH_3), 1.90 (m, 4 H, 6a,9a,17a,20a-H), 1.96 (d, 2 H, 24,25-H^i), 2.04 (m, 8 H, 6,10,17,21-H), 2.25 (m, 2 H, 23,26-H^a), 2.27 (m, 2 H, 23,26-H^i), 2.98 (m, 4 H, 7,9,18,20-H), 3.40 (m, 4 H, 5,11,16,22-H), 3.45 (s, 12 H, OCH_3), 6.76 (s, 4 H, 1,4,12,15-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 20.1 (OCOCH_3), 29.7 (CH, C-6,10,17,21), 38.9 (CH, C-6a,9a,17a,20a), 46.0 (CH_2, C-24,25), 50.5 (CH, C-7,9,18,20), 53.8 (CH, C-5,11,16,22), 56.5 (OCH_3), 67.7 (CH_2, C-23,26), 109.0 (CH, C-1,4,12,15), 135.8 (C-7a,8a,18a,19a) 139.7 (C-4a,5a,10a,11a,15a,16a,21a,22a), 144.5 (C-8,19), 146.6 (C-2,3,13,14), 147.1 (O$COCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 2967 (CH), 2933 (CH), 1478(C=C), 1211(C−O) cm^{-1}. UV/Vis (MeOH): $\lambda_{max.}$ (log ε) = 283 (2.92). MS (70 eV): *m/z* (%) = 778 (35) [M^+].

Synthesis of 17: A degassed solution of the bis-dienophile **4b** (139 mg, 0.43 mmol), the diene **6b** (100 mg, 0.43 mmol), diphenylamine (20 mg, 3.4 mmol) and triethylamine (0.1 mL, 7.2 mmol) in 3 mL of anhydrous toluene saturated with Ar was heated at 165 °C in a sealed ampoule for 6 days. The solvent was evaporated in vacuo and the residue was purified by column chromatography (silica gel, cyclohexane/ethyl acetate, 5:1). The second fraction (R_f = 0.3) contained **17**. After removal of the solvent the residue was dried in vacuo to give **17** (132 mg, 0.24 mmol, 56%); m.p. 171 °C. ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 1.80 (d, 1 H, 17-H^a), 1.81 (m, 2 H, 18-H), 1.92 (s, 6 H, OCOCH_3), 1.98 (d, 2 H, 19-H), 2.05 (m, 2 H, 6-H), 2.12 (d, 1 H, 17-H^i), 2.24 (d, 1 H, 7-H), 2.28 (d, 2 H, 15-H), 2.34 (m, 2 H, 6a,14a-H), 3.00 (t, 2 H, 9,12-H), 3.43 (t, 1 H, 14-H), 3.52 (s, 6 H, OCH_3), 3.84 (t, 2 H, 5,16-H), 6.12 (t, 2 H, 10,11-H), 6.81 (s, 2 H, 1,4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 20.2 (OCOCH_3), 29.8 (CH, C-5,16), 39.0 (CH_2, C-6,15), 46.2 (CH_2, C-18), 48.2 (CH, C-7,14), 50.4 (CH, C-6a,14a), 53.9 (CH_2, C-19), 56.6 (OCH_3), 67.8 (CH_2, C-17), 69.6 (CH, C-9,12), 109.0 (CH, C-1,4), 142.9 (C-7a,8a,12a,13a), 137.2 (C-4a,16a), 139.4 (C-5a,15a), 142.9 (CH, C-10,11), 144.6 (C-8,13), 146.9, 147.1 (C-2,3), 168.2 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 2960 (CH), 2926 (CH), 1754 (CH), 1654 (C=O), 1474 (C−O) cm^{-1}. UV/Vis (MeOH): $\lambda_{max.}$ (log ε) = 212 (4.0), 228 (4.5), 249 (4.7), 293 nm (4.0). MS (70 eV) : *m/z* (%) = 550 (70) [M^+], 176 (35).

Synthesis of the Benzene Tweezer 1d: A mixture of the bis-adduct **7d** (100 mg, 0.128 mmol) and DDQ (266 mg, 1.024 mmol) in anhydrous toluene (6 mL) was heated under argon at 120 °C for 1 h. The mixture was cooled to 70 °C and 1,4-cyclohexadiene (0.08 mL, 0.85 mmol) was added. The mixture was stirred for 10 min and then cooled to room temperature. The precipitate was filtered. The filtrate was evaporated to a volume of 1 mL and purified by column chromatography (silica gel, cyclohexane/ethyl acetate, 3:1). The first fraction (R_f = 0.1) contained the desired product, the solvent was removed, and the residue was dried in vacuo to give **1d** (14 mg, 0.018 mmol, 14%); m.p. 300 °C. ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 1.86 (s, 6 H, OCOCH_3), 2.24 (d, 2 H, 24, 25-H^a), 2.34 (dd, 4 H, 23,26-H), 2.48 (d, 2 H, 24,25-H^i), 3.32 (s, 12 H, OCH_3),

3.84 (s, 4 H, 5,11,16,22-H), 4.06 (s, 4 H, 7,9,18,20-H), 6.67 (s, 4 H, 1,4,12,15-H), 7.15 (s, 4 H, 6,10,17,21-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 20.2 ($OCO\mathit{C}H_3$), 49.6 (C-7,9,18,20), 51.7 (C-5,11,16,22), 56.4 ($O\mathit{C}H_3$), 69.8 (C-23,26), 72.0 (C-24,25), 109.5 (C-1,4,12,15), 116.9 (C-6,10,17,21), 138.1 (C-7a,8a,18a,19a), 141.8 (C-8,19), 143.1 (C-6a,9a,17a,20a), 146.4 (C-4a,5a,10a,11a,15a,16a, 21a,22a), 147.5 (C-2,3,13,14), 148.6 ($O\mathit{C}OCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 2966 (CH), 2934 (CH), 1483 (C=C), 1262 (C−O) cm^{-1}. UV/Vis (MeOH): $\lambda_{max.}$ (log ε) = 292 (4.05). MS (70 eV): *m*/*z* (%) = 770 (100) [M^+].

Synthesis of Naphthalene-Spaced Tweezers 2f, 2i−m:



Synthesis of the Bis-dienophile 5f: A solution of the diacetoxy-substituted **5b** (300 mg, 0.81 mmol), KOH (180 mg, 3.2 mmol) and 18-crown-6 (300 mg, 1.13 mmol) in 10 mL of anhydrous dioxane was stirred under Ar at room temperature for 3 h. The reaction mixture was poured into ice-water (40 mL). HCl (1 M, 10 mL) and CH_2Cl_2 (40 mL) were added to the reaction mixture. The aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with water and saturated aqueous $NaHCO_3$ and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography (silica gel, cyclohexane/ethyl acetate, 3:1) to afford **5f** as a colourless solid (230 mg, 0.69 mmol, 87%); m.p. > 300 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.44 (m, 4 H, 13,14-H^{i,a}), 2.44 (s, 3 H, $OCOC\mathit{H}_3$), 3.91 (m, 3 H, 1,4,10-H), 4.11 (s, 1 H, 7-H), 4.81 (s, 1 H, O*H*), 6.67 (m, 4 H, 2,3,8,9-H), 7.43 (s, 1 H, 5-H), 7.79 (s, 1 H, 12-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 20.8 ($OCO\mathit{C}H_3$), 45.6, 47.5, 49.8 (C-1,4,7,10), 65.9, 67.1 (C-13,14), 112.9, 113.5 (C-5,12), 122.5, 124.4 (C-5a,11a), 128.8, 134.01 (C-6,11), 138.6 (C-3), 141.7 (C-2,8,9), 148.4 (C-4a,12a), 149.4 (C-6a,10a), 169.7 (C=O) ppm. MS (70 eV): *m*/*z* (%) = 330 (25) [M^+], 288 (100) [M^+ − $COCH_3$]. HR-MS (70 eV) calcd. ($C_{22}H_{18}O_3$) 330.1256; found 330.1260.

Synthesis of the Naphthalene-Spaced Tweezer 2f: A solution of the tweezer **2b**[10] (100 mg, 0.14 mmol), KOH (33 mg, 0.58 mmol) and 18-crown-6 (85 mg, 0.32 mmol) in dioxane (2.5 mL) was stirred under Ar at room temperature for 1 hour. The reaction mixture was poured into ice-water (20 mL), and HCl (4 M, 5 mL) and CH_2Cl_2 (20 mL) were added. The aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with water and saturated aqueous $NaHCO_3$ and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography (silica gel, cyclohexane/ethyl acetate, 3:1) to afford the tweezer **2f** as a colourless solid (90 mg, 0.13 mmol, 94%); m.p. > 300 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.32 [t, ^3J(CH_2, $C\mathit{H}_3$) = 7 Hz, 6 H, $CO_2CH_2C\mathit{H}_3$], 2.12 (m, 1 H, 13-H^i), 2.19 (m, 1 H, 14-H^a), 2.22 (m, 1 H, 13-H^a), 2.32 (m, 1 H, 14-H^a), 3.95 [t, ^4J(1-H, 4-H) = 1.5 Hz, 2 H, 1,4-H], 4.25 [t, ^4J(7-H, 10-H) = 1.5 Hz, 2 H, 7,10-H], 4.29 [q, ^3J($C\mathit{H}_2$, CH_3) = 7 Hz, 4 H, $CO_2C\mathit{H}_2CH_3$], 4.6 [q, ^2J($OC\mathit{H}_2$) = 14 Hz, 4 H, $OC\mathit{H}_2$], 6.69 [dt, ^3J(2-H, 3-H) = 6 Hz, 2 H, 2,3-H], 6.71 [t, ^3J(8-H, 9-H) = 6 Hz, 2 H, 8,9-H], 7.86 (s, 2 H, 5,12-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 20.8 ($COO\mathit{C}H_3$), 46.4, 48.1, 50.6, 50.7 (CH, C-7,10,19,22), 51.0 (CH, C-5,12,17,24), 64.0 (CH_2, C-27), 64.9 (CH_2, C-26), 67.6 (CH_2, C-25,28), 112.8 (CH, C-8), 113.4 (CH, C-21), 116.1, 116.2, 116.3, 116.8 (CH, C-6,11,18,23), 121.5, 121.6, (CH, C-1,4,13,16), 122.7 (C-8a), 124.1, 124.2 (CH, C-2,3,14,15), 124.2 (C, C-20a), 128.5 (C, C-9a), 133.7 (C, C-9), 137.5 (C, C-19a), 141.9 (C, C-20), 145.7, 146.1, 146.7, 146.8 (C, C-5a,11a,17a,23a), 147.3, 147.7, 147.8, 148.0 (C, C-4a,6a,10a,18a,22a,24a), 148.3 (C-12a, C-16a), 150.5, 150.6 (C, C-7a,21a), 169.7 (−OO*C*CH$_3$) ppm. MS (70 eV): *m*/*z* (%) = 658 (27) [M^+], 616 [M^+ − $COCH_3$]. HR-MS (70 eV) calcd. ($C_{48}H_{34}O_3$) 658.2508; found 658.2520.

Synthesis of the Bis-dienophile 5i: A mixture of the diketone **18**[7,22,23] (2.0 g, 6.9 mmol) and anhydrous acetonitrile (20 mL) was stirred under Ar in an ultrasound bath for 30 min to dissolve **18**. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 2.3 mL, 1.52 mmol) was added dropwise to the solution of **18** in acetonitrile saturated with Ar. The mixture was stirred for 1 hour and cooled to 0 °C. Ethyl bromoacetate (3 mL, 3.47 mmol) was slowly added to the stirred mixture at 0 °C. The mixture was then stirred at room temperature for 3 h and again cooled to 0 °C. A second portion of DBU (4.6 mL, 3.04 mmol) was added and the stirred mixture was warmed to room temperature for 3 h and then cooled again to 0 °C. A second portion of ethyl bromoacetate (3 mL, 3.47 mmol) was added. During all these procedure the reaction mixture has to be kept rigorously oxygen-free, because the intermediately formed hydroquinone **5g** can easily be oxidized and is therefore highly air-sensitive. After the addition of the second portion of ethyl bromoacetate, the reaction mixture was stirred overnight at room temperature and hydrolysed with 2% aqueous HCl (50 mL). The separated organic layers were washed with HCl (2 M, 25 mL) and water (2 × 50 mL), and dried over anhydrous $MgSO_4$. After removal of the solvent, the crude product was purified by column chromatography (silica gel, cyclohexane/ethyl acetate, 5:1) to afford **5i** as a colourless solid (2.72 g, 5.9 mmol, 85%); m.p. 125 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.32 (t, 6 H, $CO_2CH_2C\mathit{H}_3$), 2.12 (m, 1 H, 13-H^i), 2.19 (m, 1 H, 14-H^a), 2.22 (m, 1 H, 13-H^a), 2.32 (m, 1 H, 14-H^a), 3.95 (t, 2 H, 1,4-H), 4.25 (t, 2 H, 7,10-H), 4.29 (q, 4 H, $CO_2C\mathit{H}_2CH_3$), 4.6 (q, 4 H, $OC\mathit{H}_2$), 6.69 (t, 2 H, 2,3-H), 6.71 (t, 2 H, 8,9-H), 7.86 (s, 2 H, 5,12-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 14.2 (CH_3, $CO_2CH_2\mathit{C}H_3$), 47.0 (CH, C-7,10), 49.8 (CH, C-1,4), 61.2 (CH_2, $CO_2\mathit{C}H_2CH_3$), 65.8 (CH_2, C-13), 67.2 (CH_2, C-14), 71.3 (CH_2, $O\mathit{C}H_2$), 114.1 (CH, C-5,12), 125. 4 (C, C-5a,11a), 136.3 (C, C-4a,12a), 141.9 (CH, C-8,9), 142.2 (CH, C-2,3), 144.8 (C, C-6,11), 149.0 (C, C-6a,10a), 169.4 (C=O) ppm. MS (70 eV): *m*/*z* (%) =460 (69) [M^+], 373 (100) [M^+ − $CH_2COOC_2H_5$]. HR-MS (70 eV) calcd. ($C_{28}H_{28}O_6$) 460.1886; found 460.1891.

Synthesis of the Bis-adduct 8i: A solution of the bis-dienophile **5i** (1.338 g, 3 mmol), diene **6a** (2.016 g, 12 mmol) and anhydrous triethylamine (1.85 mL) in anhydrous toluene (15 mL) was heated to 160 °C in a sealed ampoule for 6 days. The reaction mixture was cooled to room temperature. After removal of the solvent, the crude product was purified by column chromatography (silica gel,

cyclohexane/ethyl acetate, 20:1) to afford the bis-adduct **8i** as a colourless solid (1.6 g, 2 mmol, 67%); m.p. 125 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.31 [t, $^3J(CH_2, CH_3)$ = 7 Hz, 6 H, $CO_2CH_2CH_3$], 1.63 (m, 6 H, 6a,10a,18a,22a,26-H^a, 27-H^a), 2.07 (m, 2 H, 26-H^i, 27-H^i), 2.23 (m, 8 H, 6,11,18,23-H), 2.41 (m, 4 H, 25,28-H^{i,a}), 3.08 (s, 2 H, 7,22-H), 3.33 (s, 2 H, 10,19-H), 3.60 (s, 4 H, 5,12,17,24-), 4.29 [q, $^3J(CH_2, CH_3)$ = 4.5 Hz, 2 H, $CO_2CH_2CH_3$], 4.56 (s, 4 H, OCH_2), 6.79 (s, 4 H, 2,3,14,15-H), 7.10 [d, ^4J(1-H, 4-H) = 6 Hz, 4 H, 1,4,13,16-H], 7.75 (s, 2 H, 8-H, 21-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 14.2 (CH_3, $CO_2CH_2CH_3$), 29.6 (CH_2, C-6,11,18,23), 40.5 (CH, C-10a,18a), 40.7 (CH, C-6a,22a), 43.8 (CH_2, C-26), 44.1 (CH_2, C-27), 49.4 (CH, C-10,19), 52.5 (CH, C-7,22), 53.5 (CH, C-12,17), 53.5 (CH, C-5,24), 61.2 (CH_2, $CO_2CH_2CH_3$), 66.5 (CH_2, C-25), 66.6 (CH_2, C-28), 70.9 (CH_2, OCH_2), 112.4 (C, C-8,21), 120.6 (CH, C-13,16), 120.6 (CH, C-1,4), 123.9 (CH, C-14,15), 123.9 (CH, C-2,3), 126.5 (C, C-8a,20a), 135.2 (C, C-9a,19a), 143.1 (C, C-9,20), 147.2 (C, C-7a,21a), 147.3 (C, C-11a,17a), 147.4 (C, C-5a,23a), 151.9 (C, C-12a,16a), 152.0 (C, C-4a,24a), 169.5 (C=O) ppm. MS (70 eV): *m*/*z* (%) = 795 (100) [$M^+ - H$], 709 (6) [$M^+ - CH_2COOC_2H_5$]. HR-MS (70 eV) calcd. ($C_{54}H_{52}O_6$) 796.3764; found 796.3780.

Synthesis of the Naphthalene-Tweezer 2i: DDQ (3.2 g, 14.7 mmol) was added to a solution of **8i** (1.338 g, 1.68 mmol) in anhydrous toluene (85 mL). The intensively stirred mixture was immediately placed in an oil bath preheated to 120 °C and kept there for 3 h. The reaction mixture was cooled down to 60 °C. The excess of DDQ was converted into $DDQH_2$ by treatment with 1,4-cyclohexadiene (0.3 mL). After stirring for 20 min at 60 °C the mixture was filtered and the filtrate was concentrated in vacuo. Purification of the crude product by column chromatography (silica gel, cyclohexane/ethyl acetate, 5:1) gave tweezer **2i** as a colourless solid (0.8 g, 1 mmol, 63%); m.p. 145 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.35 [t, 6 H, $^3J(CH_2, CH_3)$ = 7 Hz, $CO_2CH_2CH_3$], 2.43 (m, 7 H, 25,26,27,28-H^{i,a}), 2.50 (dm, 1 H, 26-H^i), 4.04 (d, 4 H, 5,12,17,24-H), 4.16 (s, 2 H, 7,22-H), 4.31 (dq, 4 H, $CO_2CH_2CH_3$), 4.43 (s, 4 H, OCH_2), 4.47 (s, 2 H, 10,19-H), 6.75 (m, 4 H, 2,3,14,15-H), 7.03 (m, 4 H, 1,4,13,16-H),7.05 (m, 4 H, 6,11,18,23-H), 7.67 (s, 2 H, 8,21-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 14.2 (CH_3, $CO_2CH_2CH_3$), 47.6 (CH, C-10,19), 50.7 (CH, C-7,22) 51.1 (CH, C-5,12,17,24), 61.2 (CH_2, $CO_2CH_2CH_3$), 63.7 (CH_2, C-26), 65.0 (CH_2, C-27), 67.6 (CH_2, C-25), 67.6 (CH_2, C-28), 71.0 (CH_2, OCH_2), 114.0 (C, C-8,21), 116.2 (CH, C-11,18), 116.3 (CH, C-6,23), 121.5 (CH, C-13,16), 121.7 (CH, C-1,4), 124.0 (CH, C-14,15), 124.1 (CH, C-2,3), 125.8 (C, C-8a,20a), 135.6 (C, C-9a,19a), 144.5 (C, C-11a,17a), 146.3 (C, C-9,20), 146.9 (C, C-5*a*,23*a*), 147.6 (C, C-10a,18*a*), 147.9 (C, C-6a,22a), 148.2 (C, C-7a,21a), 150.5 (C, C-12a,16a), 150.8 (C, C-4a,24a), 169.7 (C=O) ppm. MS (70 eV): *m*/*z* (%) = 788 (100) [M^+], 701 (46) [$M^+ - CH_2COOC_2H_5$], 614 (36) [$M^+ - 2 \times CH_2COOC_2H_5$]. HR-MS (70 eV) calcd. ($C_{54}H_{44}O_6$) 788.3138; found 788.3146.

Synthesis of the Naphthalene Tweezer 2j: A solution of NaOH (91.98 mg, 2.3 mmol) in water (10 mL) was added to a stirred suspension of the diester **2i** (500 mg, 0.63 mmol) in 50 mL of ethanol. The reaction mixture was stirred for 4 h at 80 °C, and then poured into ice-water (40 mL). HCl (1 M, 10 mL) was added to the mixture, and the precipitate was filtered and dried in vacuo. The dicarboxylic acid **2j** was isolated as a colourless solid (440 mg, 0.6 mmol, 95%); m.p. ≥ 350 °C. ^{1}H NMR (500 MHz, CD_3OD, 25 °C): δ = 2.37 (m, 8 H, 25,26,27,28-H^{a,i}), 4.06 (s, 2 H, 12,17-H), 4.12 (s, 2 H, 5,24-H), 4.19 (s, 2 H, 7,22-H), 4.44 (s, 4 H, OCH_2), 4.50 (s, 2 H, 10,19-H), 6.65 (m, 2 H, 14,15-H), 6.71 (m, 2 H, 2,3-H), 7.01 (m, 2 H, 13,16-H), 7.07 (m, 2 H, 1,4-H), 7.17 (s, 2 H, 8,21-H), 7.25 (s, 2 H, 6,23-H), 7.74 (s, 2 H, 11,18-H) ppm. ^{13}C NMR (126 MHz, CD_3OD, 25 °C): δ = 52.2 (CH, C-7,10,19,22), 52.4 (CH, C-12,17), 52.5 (CH, C-5,24), 66.4 (CH_2, C-26), 67.5 (CH_2, C-27), 68.8 (CH_2, C-25), 69.1 (CH_2, C-28), 71.7 (CH_2, OCH_2), 114.7 (C, C-8,21), 117.1 (CH, C-6,11,18,23), 122.3 (CH, C-13,16), 122.4 (CH, C-1,4), 125.6 (CH, C-14,15), 125.8 (CH, C-2,3), 127.1 (C, C-8a,20a), 137.2 (C, C-9a,19a), 145.6 (C, C-11a,17a), 147.6 (C, C-9,20), 148.1 (C, C-5a,23a), 149.4 (C, C-10a,18a), 149.6 (C, C-6a,22a), 149.9 (C, C-7a,21a), 151.9 (C, C-12a,16a), 152.0 (C, C-4a,24a), 17.14 (C=O) ppm. ^{1}H NMR (500 MHz, $CDCl_3$/[D_6]acetone, 1:1, 25 °C): δ = 2.34 (m, 8 H, 25,26,27,28-H^{a,i}), 3.98 (s, 2 H, 12,17-H), 4.01 (s, 2 H, 5,24-H), 4.11 (s, 2 H, 7,22-H), 4.40 (s, 4 H, OCH_2), 4.45 (s, 2 H, 10,19-H), 6.63 (m, 4 H, 2,3,14,15-H), 6.94 (m, 4 H, 1,4,13,16-H), 7.02 (s, 2 H, 8,21-H), 7.09 (s, 2 H, 6,23-H), 7.58 (s, 2 H, 11,18-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$/[D_6]acetone, 1:1, 25 °C): δ = 47.6 (CH, C-10,19), 50.7 (CH, C-7,22) 51.1 (CH, C-5,12,17,24), 63.6 (CH_2, C-26), 64.9 (CH_2, C-27), 67.5 (CH_2, C-25,28), 70.4 (CH_2, OCH_2), 113.9 (CH, C-8,21), 116.3 (CH, C-6,23), 116.4 (CH, C-11,18), 121.6 (CH, C-13,16), 121.6 (CH, C-1,4), 124.2 (CH, C-14,15), 124.3 (CH, C-2,3), 125.7 (C, C-8a,20a), 135.8 (C, C-9a,19a), 144.1 (C, C-11a,17a), 146.3 (C, C-9,20), 146.9 (C, C-5a,23a), 147.8 (C, C-10a,18a), 148.2 (C, C-6a,22a), 148.3 (C, C-7a,21a), 150.6 (C, C-12a,16a), 150.8 (C, C-4a,24a), 170.5 (C=O) ppm. MS (70 eV): *m*/*z* (%) = 732 (16) [M^+], 614 (100) [$M^+ - C_2H_3O_2$].

Synthesis of the Dipotassium Salt 2k: An aqueous solution of KOH (5.86 mg, 0.1 M) in 10 mL of H_2O was added to a solution of the diester **2i** (115.5 mg, 0.15 mmol) in ethanol (10 mL). The reaction mixture was stirred under reflux for 4 h. After removal of the solvent, the colourless solid consisted of the dipotassium dicarboxylate **2k**, which was dried in vacuo (100 mg, 0.12 mmol, 85%); m.p. ≥ 350 °C. ^{1}H NMR (500 MHz, CD_3OD, 25 °C): δ = 2.32 (dm, 2 H, 25,26-H^i), 2.41 (m, 6 H, 25,26,27,28-H^{a,i}), 4.07 (s, 2 H, 12,17-H), 4.12 (s, 2 H, 5,24-H), 4.18 (m, 6 H, 7,22-H, OCH_2), 4.52 (s, 2 H, 10,19-H), 6.67 (m, 2 H, 14,15-H), 6.72 (m, 2 H, 2,3-H), 7.02 (m, 2 H, 13,16-H), 7.07 (m, 2 H, 1,4-H), 7.16 (s, 2 H, 8,21-H), 7.32 (s, 2 H, 6,23-H), 7.79 (s, 2 H, 11,18-H) ppm. ^{13}C NMR (126 MHz, CD_3OD, 25 °C): δ = 49.9 (CH, C-7,22), 52.3 (CH, C-10,19), 52.5 (CH, C-12,17), 52.5 (CH, C-5,24), 66.3 (CH_2, C-26), 67.4 (CH_2, C-27), 68.8 (CH_2, C-25), 69.2 (CH_2, C-28), 74.5 (CH_2, OCH_2), 114.9 (CH, C-8,21), 117.0 (CH, C-6,23), 117.2 (CH, C-11,18), 122.2 (CH, C-13,16), 122.3 (CH, C-1,4), 125.6 (CH, C-14,15), 125.7 (CH, C-2,3), 127.4 (C, C-8a,20a), 137.1 (C, C-10a,19a), 145.6 (C, C-11a,17a), 147.9 (C, C-9,20), 148.3 (C, C-5a,23a), 149.0 (C, C-9a,18a), 149.3 (C, C-6a,22a), 149.6 (C, C-7a,21a), 152.0 (C, C-4a,12a,16a,24a), 177.1 (C=O) ppm.

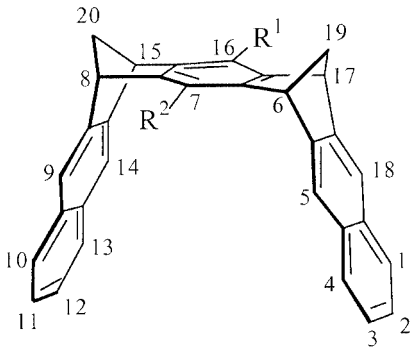
Synthesis of the Naphthalene Tweezer 2l: Hydroxybenzotriazole BtOH (86.2 mg, 0.64 mmol) was added at 0 °C to a stirred solution of the diacid **2j** (233 mg, 0.32 mmol) in anhydrous CH_2Cl_2 (50 mL) saturated with Ar. After 10 min, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC, 134.2, 0.7 mmol) was added and the reaction mixture was stirred until the EDC had completely dissolved. The amine **20** (281 mg, 0.67 mmol) was added to the stirred solution. The mixture was stirred at room temperature overnight and washed twice with saturated $NaHCO_3$, citric acid (20%), brine and water. The combined aqueous layers were extracted with dichloromethane (3 × 50 mL) and dried over $MgSO_4$. The solvents were evaporated from the combined organic layers in vacuo and the crude product was purified by column chromatography (Al_2O_3, MeOH/CH_2Cl_2) to afford **2l** (430 mg, 0.12 mmol, 88%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.3 [t, 18 H, $^3J(CH_2, CH_3)$ = 7 Hz, $CO_2CH_2CH_3$], 2.4 (m, 20 H, 25,26,27,28-H^{a,i}, OCH_2CH_2), 3.5 (s, 12 H, OCH_2CH_2), 3.8 (m, 12 H, $CO_2CH_2CH_3$), 3.9 (m, 12 H,

CCH_2), 4.05 (m, 4 H, 5,12,17,24-H), 4.14 (m, 4 H, 7,10,19,22-H), 4.3 (m, 4 H, OCH_2), 6.8 (m, 4 H, 2,3,14,15-H), 7.15 (m, 4 H, 1,4,13,16-H), 7.23 (s, 2 H, 8,21-H), 7.4 (m, 4 H, 6,11,18,23-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 14.2 (CH_3, $CO_2CH_2CH_3$), 47.5 (CH, C-7,22), 50.8 (CH, C-10,19), 51.1 (CH, C-12,17), 51.2 (CH, C-5,24), 60.5 (CH_2, OCH_2CH_2), 65.6 (CH_2, CCH_2), 65.9 (C, CCH_2), 69.2 (CH_2, C-26), 66.7 (CH_2, OCH_2CH_2), 69.3 (CH_2, C-27), 69.3 (CH_2, C-25), 69.4 (CH_2, C-28), 72.9 (CH_2, OCH_2), 113.6 (CH, C-8,21), 117.6 (CH, C-6,23), 117.7 (CH, C-11,18), 121.7 (CH, C-13,16), 121.8 (CH, C-1,4), 124.1 (CH, C-14,15), 125.8 (CH, C-2,3), 128.8 (C, C-8a,20a), 136.1 (C, C-9a,19a), 146.0 (C, C-11a,17a), 146.7 (C, C-9,20), 147.9 (C, C-5a,23a), 148.4 (C, C-10a,18a), 148.6 (C, C-6a,22a), 150.5 (C, C-7a,21a), 150.7 (C, C-4a,12a,16a,24a), 169.2 (C=O, $CO_2CH_2CH_3$), 171.3 (C=O, OCH_2CO) ppm.

Synthesis of the Naphthalene Tweezer 2m: A mixture of the ester **2l** (211.2 mg, 0.14 mmol) in 12.5 mL of methanol/water mixture (4:1) and NaOH (72.0 mg, 1.8 mmol) was stirred at room temperature for 3 d and then neutralized with HCl (1 M) until a pH value of 2 was reached. The mixture was extracted three times with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over $MgSO_4$. Evaporation of the solvent gave the acid **2m** (145 mg, 0.1 mmol, 76%). ^{1}H NMR (500 MHz, CD_3OD, 25 °C): δ = 2.34 (m, 20 H, 25,26,27,28-H^{a,i}, OCH_2CH_2), 3.4 (m, 12 H, OCH_2CH_2), 3.85 (m, 12 H, CCH_2), 4.05 (m, 4 H, 5,12,17,24-H), 4.2 (m, 4 H, 7,10,19,22-H), 4.35 (m, 4 H, OCH_2), 6.78 (m, 4 H, 2,3,14,15-H), 7.15 (m, 4 H, 1,4,13,16-H), 7.23 (s, 2 H, 8,21-H), 7.4 (m, 4 H, 6,11,18,23-H) ppm. ^{13}C NMR (126 MHz, CD_3OD, 25 °C): δ = 47.5 (CH, C-7,22), 50.8 (CH, C-10,19), 51.1 (CH, C-12,17), 51.2 (CH, C-5,24), 60.5 (CH_2, OCH_2CH_2), 65.6 (CH_2, OCH_2CH_2), 65.9 (C, CCH_2), 69.2 (CH_2, C-26), 66.7 (CH_2, CCH_2), 69.3 (CH_2, C-27), 69.3 (CH_2, C-25), 69.4 (CH_2, C-28), 72.9 (CH_2, OCH_2), 113.6 (CH, C-8,21), 117.6 (CH, C-6,23), 117.7 (CH, C-11,18), 121.7 (CH, C-13,16), 121.8 (CH, C-1,4), 124.1 (CH, C-14,15), 125.8 (CH, C-2,3), 128.8 (C, C-8a,20a), 136.1 (C, C-9a,19a), 146.0 (C, C-11a,17a), 146.7 (C, C-9,20), 147.9 (C, C-5a,23a), 148.4 (C, C-10a,18a), 148.6 (C, C-6a,22a), 150.5 (C, C-7a,21a), 150.7 (C, C-4a,12a,16a,24a), 169.2 (C=O, COOH), 171.3 (C=O, OCH_2CO) ppm.

Synthesis of the Dipotassium Salt 2n: A solution of potassium hydroxide (100 mg, 1.8 mmol) in D_2O (2 mL) was evaporated in vacuo and the residue, consisting of KOD, was added to a solution of the acid **2m** (25.0 mg, 0.02 mmol) in CD_3OD (5 mL). The reaction mixture was stirred for 1 h at room temperature. Evaporation of the solvent in vacuo gave **2n** (20 mg, 0.016 mmol). ^{1}H NMR (500 MHz, CD_3OD, 25 °C): δ = 2.31 (m, 20 H, 25,26,27,28-H^{a,i}, OCH_2CH_2), 3.42 (m, 12 H, OCH_2CH_2), 3.83 (m, 12 H, CCH_2), 4.05 (m, 4 H, 5,12,17,24-H), 4.23 (m, 4 H, 7,10,19,22-H), 4.38 (m, 4 H, OCH_2), 6.81 (m, 4 H, 2,3,14,15-H), 7.20 (m, 4 H, 1,4,13,16-H), 7.24 (s, 2 H, 8,21-H), 7.43 (m, 4 H, 6,11,18,23-H) ppm. ^{13}C NMR (126 MHz, CD_3OD, 25 °C): δ = 47.5 (CH, C-7,22), 50.8 (CH, C-10,19), 51.1 (CH, C-12,17), 51.2 (CH, C-5,24), 60.5 (CH_2, OCH_2CH_2), 65.6 (CH_2, OCH_2CH_2), 65.9 (C, CCH_2), 69.2 (CH_2, C-26), 66.7 (CH_2, CCH_2), 69.3 (CH_2, C-27), 69.3 (CH_2, C-25), 69.4 (CH_2, C-28), 72.9 (CH_2, OCH_2), 113.6 (CH, C-8,21), 117.6 (CH, C-6,23), 117.7 (CH, C-11,18), 121.7 (CH, C-13,16), 121.8 (CH, C-1,4), 124.1 (CH, C-14,15), 125.8 (CH, C-2,3), 128.8 (C, C-8a,20a), 136.1 (C, C-9a,19a), 146.0 (C, C-11a,17a), 146.7 (C, C-9,20), 147.9 (C, C-5a,23a), 148.4 (C, C-10a,18a), 148.6 (C, C-6a,22a), 150.5 (C, C-7a,21a), 150.7 (C, C-4a,12a,16a,24a), 169.2 (C=O, COOH), 171.3 (C=O, OCH_2CO) ppm.

Synthesis of the Clips 3h−o



Synthesis of the Bis-dienophile 4 h: A mixture of phenylisocyanate (2.25 g, 18.9 mmol, 2.03 mL) and Et_3N (4 drops) was slowly added to a solution of the hydroquinone **4g** (1.5 g, 6.3 mmol) in acetonitrile (100 mL). After 10 min the colourless precipitate containing **4h** was filtered and dried in vacuo (2.9 g, 6.1 mmol, 94%); m.p. 258 °C. ^{1}H NMR (500 MHz, [D$_7$]DMF, 25 °C): δ = 2.2 (m, 4 H, 11,12-H^{i,a}), 3.96 (s, 4 H, 1,4,6,9-H), 6.8 (s, 4 H, 2,3,7,8-H), 7.1 (m, 2 H, *p*-C_6H_5), 7.4 (m, 4 H, *o*-C_6H_5), 7.7 (m, 4 H, *m*-C_6H_5) ppm. ^{13}C (126 MHz, [D$_7$]DMF, 25 °C): δ = 48.2 (CH, C-1,4,6,9), 70.3 (CH_2, C-11,12), 119.2 (CH, *p*-C_6H_5), 123.6 (CH, *o*-$C_6H_5$6), 129.6 (CH, *m*-C_6H_5), 138.3 (C, C-5,10), 140.0 (C, NH*C*), 143.1 (C, C-4a,5a,9a,10a), 143.5 (CH, C-2,3,7,8), 152.6 (C=O) ppm. MS (70 eV): *m*/*z* (%) = 238 (100) [M$^+$ − 2 × PhNHCO]. MS (ESI, MeOH): *m*/*z* = 499.52 [M + Na].

Synthesis of the Clip 3h: A mixture of phenylisocyanate (89.66 mg, 0.7 mmol, 83.6 μL) and Et_3N (2 drops) was added to a solution of the clip **3g** (150 mg, 0.34 mmol) in acetonitrile (100 mL). The reaction mixture was stirred for 4 h at room temperature and neutralized with aqueous H_2SO_4 (20%) until a pH value of 4 was reached. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$. After evaporation of the solvent in vacuo the residue consisted of the desired product **3h** (200 mg, 0.29 mmol, 86%); m.p. 263 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.4 [d, ^2J(19-H^a, 20-H^a) = 8 Hz, 2 H, 19,20-H^a], 2.7 [d, ^2J(19-H^i, 20-H^i) = 8 Hz, 2 H, 19,20-H^i], 4.45 (s, 4 H, 6,8,15,17-H), 7.15 (m, 2 H, *p*-C_6H_5), 7.25 (m, 8 H, 2,3,11,12-H, *o*-C_6H_5), 7.4 (m, 4 H, 5,9,14,18-H), 7.55 (m, 8 H, 1,4,10,13-H, *m*-C_6H_5) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 47.9 (CH, C-6,8,15,17), 65.0 (CH_2, C-19,20), 118.7 (CH, *o*-C_6H_5), 120.1 (CH, C-5,9,14,18), 124.1 (CH, *p*-C_6H_5), 125.3 (CH, C-2,3,11,12), 127.6 (CH, C-1,4,10,13), 129.3 (CH, *m*-C_6H_5), 132.1 (C, C-4a,9a,13a,18a), 137.0 (C, NH*C*), 137.5 (C, C-5a,8a,14a,17a), 141.3 (C, C-7,16), 146.0 (C, C-6a,7a,15a,16a), 150.8 (C=O) ppm. MS (70 eV): *m*/*z* (%) = 438 [M$^+$ − 2 × PhNHCO]. MS (ESI, MeOH): *m*/*z* = 699.24 [M + Na].

Synthesis of the Bis-dienophile 4i: Anhydrous K_2CO_3 (5.8 g, 0.042 mmol) and a small amount of KI were suspended in a solution of ketone **19** (2.5 g, 0.01 mmol) and ethyl bromoacetate (4.38 g, 0.026 mmol) in anhydrous acetone (300 mL), and the stirred mixture was heated under reflux for 24 h. After cooling to room temperature the reaction mixture was filtered and the filtrate was concentrated in vacuo. The crude product was purified by chromatography column (silica gel, cyclohexane/ethyl acetate, 3:1) to afford **4i** (3.7 g, 85%); m.p. 110 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.33 [t, ^3J(CH_2, CH_3) = 7 Hz, 6 H, $CO_2CH_2CH_3$], 2.17 (m, 4 H, 11,12-H^{a,i}), 4.05 (m, 4 H, 1,4,6,9-H), 4.20 (q, 4 H, $CO_2CH_2CH_3$), 4.50 (s, 4 H, OCH_2), 6.73 (m, 4 H, 2,3,7,8-H) ppm.

^{13}C (126 MHz, $CDCl_3$, 25 °C): δ = 14.2 (CH_3, $CO_2CH_2CH_3$), 47.6 (CH, C-1,4,6,9), 61.1(CH_2, C-11,12), 67.0 (CH_2, $CO_2CH_2CH_3$), 70.8 (CH_2, OCH_2), 143.0 (C, C-4a,5a,9a,10a), 143.1 (C, C-5,10), 145.1 (CH, C-2,3,7,8), 169.5 (C=O) ppm. IR (KBr): ṽ = 2967 (CH), 2935 (CH), 1725 (C=O) cm^{-1}. MS (70 eV): *m*/*z* (%) = 410 (100) [M^+], 323 (38) [$M^+ - CH_2COOC_2H_5$], 307 (32) [$M^+ - OCH_2COOC_2H_5$], 234 (19) [$M^+ - 2 \times H - 2 \times CH_2COOC_2H_5$], 218 (14) [$M^+ - 2 \times H - 2 \times OCH_2COOC_2H_5$]. HR-MS (70 eV) calcd. ($C_{24}H_{26}O_6$) 410.1729; found 410.1731.

Synthesis of the Clip 3i: A mixture of **4i** (2 g, 4.9 mmol), 1,1,2,2-tetrabromo-*o*-xylene (20 g, 47.8 mmol), anhydrous NaI (46.8 g, 0.3 mol), anhydrous $CaCO_3$ (10 g, 0.1 mol) and anhydrous dimethylformamide (150 mL) was stirred at 55 °C for 6 h in vacuo (100 mbar). The reaction mixture was poured into ice (500 g) and the brown mixture was decolourized by addition of aqueous $NaHSO_3$. The mixture was extracted with dichloromethane (3 × 150 mL), and the combined organic layers were filtered, washed with saturated aqueous $NaHCO_3$ and water, and then dried over $MgSO_4$. After evaporation of the solvent in vacuo the crude product was purified by column chromatography (silica gel, cyclohexane/ethyl acetate, 3:1) to afford **3i** (2 g, 75%); m.p. 82 °C. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.31 [t, $^3J(CH_2, CH_3)$ = 7 Hz, 6 H, $CO_2CH_2CH_3$], 2.37 [d, ^2J(19-H^i, 20-H^i) = 8 Hz, 2 H, 19,20-H^i], 2.48 [d, ^2J(19-H^a, 20-H^a) = 8 Hz, 2 H, 19,20-H^a], 4.30 (q, 4 H, $CO_2CH_2CH_3$), 4.42 (s, 4 H, 6, 8,15,17-H), 4.52 (s, 4 H, OCH_2), 7.19 (m, 4 H, 2,3,11,12-H), 7.45 (m, 4 H, 5,9,14,18-H), 7.50 (m, 4 H, 1,4,10,13-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 14.77 (CH_3, $CO_2CH_2CH_3$), 48.05 (CH, C-6,8,15,17), 61.71 (CH_2, $CO_2CH_2CH_3$), 64.61 (CH_2, C-19,20), 70.93 (CH_2, OCH_2), 120.04 (CH, C-5,9,14,18), 125.70 (CH, C-2,3,11,12), 128.00 (CH, C-1,4,10,13), 132.46 (C, C-4a,9a,13a,18a), 140.51 (C, C-6a,7a,15a,16a), 147.26 (C, C-5a,8a,14a,17a), 169.85 (C=O) ppm. IR (KBr): ṽ = 2932 (CH), 2850 (CH), 1758 (C=O), 1287 (C−O), 1203 (C−O), 1181 (C−O) cm^{-1}. MS (70 eV): *m*/*z* (%) = 610 (100%) [M^+], 523 (73%) [$M^+ - CH_2COOEt$], 436 (31) [$M^+ - 2CH_2COOEt$]. HR-MS (70 eV) calcd. ($C_{40}H_{34}O_6$) 610.2302; found 610.2304.

Synthesis of the Clip 3j: An aqueous solution of NaOH (2 mL, 10%) was slowly added to a suspension of **3i** (1.0 g; 1.6 mmol) in ethanol (25 mL). The reaction mixture was stirred under reflux for 4 h, then poured into ice, and neutralized with 1 M HCl to a pH value of 4. The precipitate, consisting of **3j**, was filtered and dried in vacuo (860 mg, 1.55 mmol, 95%); m.p. 197 °C. ^1H NMR (500 MHz, CD_3OD, 25 °C): δ = 2.42 [d, ^2J(19-H^i, 20-H^i) = 8 Hz, 2 H, 19,20-H^i], 2.52 (d, 2 H, 19,20-H^a), 4.52 (s, 4 H, 6,8,15,17-H), 4.58 (s, 4 H, OCH_2), 7.19 (m, 4 H, 2,3,11,12-H), 7.50 (m, 4 H, 5,9,14,18-H), 7.55 (m, 4 H, 1,4,10,13-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 46.69 (CH, C-6,8,15,17), 63.37 (CH_2, C-19,20), 68.81 (CH_2, OCH_2), 118.78 (CH, C-5,9,14,18), 124.51 (CH, C-2,3,11,12), 126.73 (CH, C-1,4,10,13), 131.08 (C, C-5a,9a,14a,17a), 139.16 (C, C-6a,7a,15a,16a), 143.17 (C, C-7,16), 145.27 (C, C-4a,9a,13a,18a), 172.12 (C=O). MS (70 eV): *m*/*z* (%) = 554 (100) [M^+], 495 (66) [$M^+ - CH_2COOH$]. HR-MS (70 eV) calcd. ($C_{36}H_{26}O_6$) 554.1729; found 554.1625.

Synthesis of the Dipotassium Salt 3k: An aqueous solution of KOH (2 mL, 10%) was slowly added to a suspension of **3i** (250 mg; 0.41 mmol) in ethanol (25 mL). The reaction mixture was stirred under reflux for 4 h. The precipitate, consisting of **3k**, was filtered and dried in vacuo (240 mg, 0.4 mmol, 92%). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.42 [d, ^2J(19-H^i, 20-H^i) = 8 Hz, 2 H, 19,20-H^i], 2.52 (d, 2 H, 19,20-H^a), 4.52 (s, 4 H, 6,8,15,17-H), 4.58 (s, 4 H, OCH_2), 7.19 (m, 4 H, 2,3,11,12-H), 7.50 (m, 4 H, 5,9,14,18-H), 7.55 (m, 4 H, 1,4,10,13-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 46.69 (CH, C-6,8,15,17), 63.37 (CH_2, C-19,20), 68.81 (CH_2, OCH_2), 118.78 (CH, C-5,9,14,18), 124.51 (CH, C-2,3,11,12), 126.73 (CH, C-1,4,10,13), 131.08 (C, C-5a,8a,14a,17a), 139. 16 (C, C-6a,7a,15a,16a), 143.17 (C, C-7,16), 145.27 (C, C-4a,9a,13a,18a), 172.12 (C=O).

Synthesis of the Clip 3l: Hydroxybenzotriazole (243 mg, 1.8 mmol) was added at 0 °C to a solution of the diacid **3j** (500 mg, 0.9 mmol) in anhydrous CH_2Cl_2 (50 mL), saturated with Ar. After 10 min, EDC (380 mg, 2 mmol) was added and the reaction mixture was stirred until the EDC had completely dissolved. After that, the amine **20** (760 mg, 1.8 mmol) was added. The reaction mixture was stirred overnight at room temperature and then washed twice with saturated aqueous $NaHCO_3$, citric acid (20%) and brine. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, evaporated in vacuo and purified by column chromatography (Al_2O_3, CH_2Cl_2/MeOH, 95:5) to obtain **3l** (643 mg, 79%). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.2 [t, $^3J(CH_2, CH_3)$ = 7 Hz, 18 H, $CO_2CH_2CH_3$], 2.6 (m, 16 H, 19,20-H^{i,a}, OCH_2CH_2), 3.8 (t, 12 H, OCH_2CH_2), 3.9 (s, 12 H, CCH_2), 4.06 (q, 12 H, $CO_2CH_2CH_3$), 4.24 (s, 4 H, 6,8,15,17-H), 4.51 (s, 4 H, OCH_2), 7.24 (m, 4 H, 2,3,11,12-H), 7.50 (m, 4 H, 5,9,14,18-H), 7.55 (m, 4 H, 1,4,10,13-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 14.2 (CH_3, $CO_2CH_2CH_3$), 35 (CH_2, OCH_2CH_2), 47.1 (CH, C-6,8,15,17), 60.4 (CH_2, $CO_2CH_2CH_3$), 63.3 (CH_2, C-19,20), 66.2 (CH_2, CCH_2), 67.1 (CH_2, OCH_2CH_2), 69.4 (CH_2, OCH_2), 72.2 (C, CCH_2), 120.1 (CH, C-5,9,14,18), 125.1 (CH, C-2,3,11,12), 128 (CH, C-1,4,10,13), 132 (C, C-4a,9a,13a,18a), 140 (C, C-6a,7a,15a,16a), 144 (C, C-7,16), 147 (C, C-5a,8a,14a,17a), 169 (C=O), 172 (C=O, $COOC_2H_5$) ppm.

Synthesis of the Clip 3m: A mixture of ester **3l** (259 mg, 22.4 mmol) in 12.5 mL of methanol/water mixture (4:1) and NaOH (53.7 mg, 1.3 mmol) was stirred at room temperature for 2 d, then neutralized with 1 M HCl until a pH value of 2 was reached, and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$. Evaporation of the solvent gave acid **3m** (222 mg, 0.22 mmol, 65%). ^1H NMR (500 MHz, CD_3OD, 25 °C): δ = 2.55 (m, 16 H, 19,20-H^{i,a}, OCH_2CH_2), 3.75 (t, 12 H, OCH_2CH_2), 3.9 (s, 12 H, CCH_2), 4.3 (m, 4 H, 6,8,15,17-H), 4.6 (s, 4 H, OCH_2), 7.21 (m, 4 H, 2,3,11,12-H), 7.50 (m, 4 H, 5,9,14,18-H), 7.55 (m, 4 H, 1,4,10,13-H) ppm. ^{13}C NMR (126 MHz, CD_3OD, 25 °C): δ = 35.65 (CH_2, OCH_2CH_2), 47.2 (CH, C-6,8,15,17), 63.3 (CH_2, C-19,20), 66.4 (CH_2, CCH_2), 68.12 (CH_2, OCH_2CH_2), 68.14 (CH_2, OCH_2), 70.3 (C, CCH_2), 120.1 (CH, C-5,9,14,18), 126.4 (CH, C-2,3,11,12), 128.7 (CH, C-1,4,10,13), 133.6 (C, C-4a,9a,13a,18a), 140 (C, C-6a,7a,15a,16a), 144 (C, C-7,16), 147 (C, C-5a,8a,14a,17a), 169 (C=O), 173.6 (C=O, COOH) ppm.

Synthesis of the Dipotassium Salt 3n: A solution of potassium hydroxide (100 mg, 1.8 mmol) in D_2O (2 mL), was evaporated in vacuo and the residue, consisting of KOD, was added to a solution of the acid **3m** (24.2 mg, 0.02 mmol) in CD_3OD (5 mL). The reaction mixture was stirred for 1 h at room temperature. Evaporation of the solvent in vacuo gave **3n** (21 mg, 0.014 mmol). ^1H NMR (500 MHz, CD_3OD, 25 °C): δ = 2.5 (m, 16 H, 19,20-H^{a,i}, OCH_2CH_2), 3.6 (t, 12 H, OCH_2CH_2), 3.9 (s, 12 H, CCH_2), 4.24 (s, 4 H, 6,8,15,17-H), 4.51 (s, 4 H, OCH_2), 7.24 (m, 4 H, 2,3,11,12-H), 7.50 (m, 4 H, 5,9,14,18-H), 7.55 (m, 4 H, 1,4,10,13-H) ppm. ^{13}C NMR (126 MHz, CD_3OD, 25 °C): δ = 35.2 (CH_2, OCH_2CH_2), 47.2 (CH, C-6,8,15,17), 63.3 (CH_2, C-19,20), 66.4 (CH_2, CCH_2), 67.3 (CH_2, OCH_2CH_2), 69.4 (CH_2, OCH_2), 72.2 (C, CCH_2), 120.1 (CH, C-5,9,14,18), 125.1 (CH, C-2,3,11,12), 128 (CH, C-1,4,10,13), 132 (C, C-4a,9a,13a,18a), 140 (C, C-6a,7a,15a,16a), 144 (C, C-

7,16), 147 (C, C-5a,8a,14a,17a), 169 (C=O), 172.3 (C=O, *C*OOH) ppm.

Synthesis of the Bis-dienophile 4o: A mixture of **4b** (200 mg, 0.96 mmol) 18-crown-6 (500 mg, 1.89 mmol) and KOH (230 mg, 4.04 mmol) in 1,4-dioxane (15 mL) was stirred under Ar at room temperature for 2 h. After that, ethyl bromoacetate (1.3 g, 7.78 mmol) was added and the mixture was stirred then for another 30 min. The solvent was then removed in vacuo, and the oily product was purified by column chromatography (silica gel, cyclohexane/ethyl acetate, 4:1) to afford the bis-dienophile **4o** (270 mg, 0.74 mmol, 77%) as a colourless solid; m.p. 118−121 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.29 (t, 3 H, $CO_2CH_2CH_3$), 2.20 (m, 4 H, 11,12-H), 2.32 (s, 3 H, $COCH_3$), 3.76 (m, 2 H, 1,9-H), 4.10 (m, 2 H, 4,6-H), 4.24 (m, 2 H, $CO_2CH_2CH_3$), 4.49 (s, 2 H, OCH_2), 6.71 (m, 2 H, 2,8-H), 6.72 (m, 2 H, 3,7-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 14.21 (CH_3, $CO_2CH_2CH_3$), 20.76 (CH_3, $COCH_3$), 47.54, 47.74 (CH, C-1,4,6,9), 61.11 (CH_2, $CO_2CH_2CH_3$), 68.83 (CH_2, C-11,12), 70.68 (CH_2, OCH_2), 136.39 (C, C-5), 141.11, 142.23 (C, C-4a,5a,9a,10a), 142.92, 143.09 (CH, C-2,3,7,8), 146.07 (C, C-10), 169.24, 169.40 (C, C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3124 (CH), 3068 (CH), 2934 (CH), 1757 (C=O), 1218 (C−O) cm^{-1}. MS (70 eV): *m/z* (%) = 366 (100%) [M$^+$].

Synthesis of the Clip 3o: A mixture of **3b** (500 mg, 0.96 mmol), 18-crown-6 (500 mg, 1.89 mmol) and KOH (230 mg, 4.04 mmol) in 1,4-dioxane (15 mL) was stirred under Ar at room temperature for 2 h. After that, ethyl bromoacetate (1.3 g, 7.78 mmol) was added and the mixture was then stirred for another 30 min. The solvent was then removed in vacuo, and the oily product was purified by column chromatography (silica gel, cyclohexane/ethyl acetate, 4:1) to afford the clip **3o** (498 mg, 0.88 mmol, 92%) as a colourless solid; m.p. 178 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.36 (t, 3 H, $CO_2CH_2CH_3$), 2.43 [d, ^2J(19-H^i, 19-H^a) = 8 Hz, 2 H, 19,20-H^i], 2.47 (s, 3 H, $COCH_3$), 2.60 (d, 2 H, 19,20-H^a), 4.26 (m, 2 H, 6,8-H), 4.37 (q, 2 H, $CO_2CH_2CH_3$), 4.53 (s, 2 H, OCH_2), 4.62 (m, 2 H, 15,17-H), 7.26 (m, 4 H, 2,3,11,12-H), 7.51/7.53 (s, 4 H, 5,9,14,18-H), 7.57 (m, 4 H, 1,4,10,13-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 14.32 (CH_3, $CO_2CH_2CH_3$), 20.83 (CH_3, $COCH_3$), 47.79, 47.88 (CH, C-6,8,15,17), 61.28 (CH_2, $CO_2CH_2CH_3$), 64.48 (CH_2, C-19,20), 70.51 (CH_2, OCH_2), 119.51, 120.19 (CH, C-5,9,14,18), 125.22, 126.1 (CH, C-2,3,11,12), 127.56, 127.65 (CH, C-1,4,10,13), 132.07, 132.10 (C, C-4a,9a,13a,18a), 135.79 (C, C-7), 139.94, 140.75 (C, C-6a,7a,15a,16a), 146.14, 146.46 (C, C-5a,8a,14a,17a), 146.85 (C, C-16), 168.76, 169.43 (C, C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3052 (CH), 3002 (CH), 2968 (CH), 2866 (CH), 1764 (C=O), 1760 (C=O), 1205 (C−O), 1178 (C−O) cm^{-1}. MS (70 eV): *m/z* (%) = 566 (100%) [M$^+$], 524 (55) [M$^+$ − CH_2CO],437 (71) [M$^+$ − CH_2CO, -$CH_2CO_2CH_2CH_3$], 43 (12) [CH_3CO^+]. HR-MS (70 eV) calcd. ($C_{38}H_{30}O_5$) 566.2090; found 566.2030.

Determination of Association Constants (K_a), the Gibbs Enthalpies of Association (Δ*G*), and the Maximum Complexation-Induced ^{1}H NMR shifts ($\Delta\delta_{max.}$) by ^{1}H NMR Titration Experiments: Receptor R and substrate S are in equilibrium with the 1:1 complex RS (R + S ⇄ RS). The association constant K_a is then defined by Equation (1). $[R]_0$ and $[S]_0$ are the starting concentrations of the receptor and the substrate, respectively.

$$K_a = \frac{[RS]}{[R]\cdot[S]} = \frac{[RS]}{\left([R]_0 - [RS]\right)\cdot\left([S]_0 - [RS]\right)} \quad (1)$$

The observed chemical shift ($\delta_{obsd.}$) of the substrate in the ^{1}H NMR spectrum is an averaged value between free (δ_0) and complexed substrate (δ_{RS}), assuming that the exchange is fast on the NMR timescale (2). Combination of Equations (1) and (2) and the use of the differences in chemical shift ($\Delta\delta = \delta_0 - \delta_{obsd.}$; $\Delta\delta_{max.} = \delta_0 - \delta_{RS}$) gives Equation (3).

$$\delta_{obs} = \frac{[S]}{[S]+[RS]}\cdot\delta_0 + \frac{[RS]}{[S]+[RS]}\cdot\delta_{RS} \quad (2)$$

$$\Delta\delta = \frac{\Delta\delta_{max.}}{[G]_0}\left(\frac{[W]_0}{2} + \frac{([G]_0 + K_d)}{2} - \frac{1}{2}\sqrt{[W]_0^2 + 2[W]_0\,(K_d - [G]_0) + (K_d - [G]_0)^2}\right) \quad (3)$$

In the titration experiments, the total substrate concentration $[S]_0$ was kept constant, whereas the total receptor concentration $[R]_0$ was varied. This was achieved by dissolving a defined amount of the receptor R in 0.6 mL of a solution containing the substrate concentration $[S]_0$. Δδ was determined from the chemical shift of the pure substrate and the chemical shift of the substrate measured in the ^{1}H NMR spectrum (500 MHz, 25 °C) of this mixture. Successive addition of further solution containing $[S]_0$ results in a dilution of the concentration $[R]_0$ in the mixture while $[S]_0$ is kept constant. Measurement of the dependence of the chemical shift of the substrate on the concentration $[R]_0$ afforded the data pairs Δδ and $[R]_0$. Fitting of these data to the (1:1) binding isotherm by iterative methods[34] delivered the parameters K_a and $\Delta\delta_{max.}$.

In the case of substrates possessing more than one kind of non-equivalent protons the determination of the association constants K_a sometimes gives different values of K_a. This may result from increasing errors caused by decreasing $\Delta\delta_{max.}$ values. To minimize such errors the association constants K_a were determined for that proton of the substrate S displaying the largest value for $\Delta\delta_{max.}$. The $\Delta\delta_{max.}$ values of the other substrate protons are calculated by the use of Equation (5).

$$[RS] = [S]_0\frac{\Delta\delta_1}{\Delta\delta_{1,max}} = [S]_0\frac{\Delta\delta_2}{\Delta\delta_{2,max}} = [S]_0\frac{\Delta\delta_n}{\Delta\delta_{n,max}} \quad (4)$$

$$\Rightarrow \Delta\delta_{n,max} = \Delta\delta_n\frac{\Delta\delta_1}{\Delta\delta_{1,max}} \quad (5)$$

From the corresponding relationship between the concentrations of the receptor $[R]_0$ and the complex [RS] the maximum complexation-induced shifts ($\Delta\delta_{R,\,max.}$) for the protons of the receptor R can be calculated by the use of Equation (6).

$$[RS] = [S]_0\frac{\Delta\delta_1^S}{\Delta\delta_{1,max}^S} = [R]_0\frac{\Delta\delta_1^R}{\Delta\delta_{1,max}^R}$$

$$\Rightarrow \Delta\delta_{1,max}^R = \frac{[R]_0}{[S]_0}\,\Delta\delta_1^R\,\frac{\Delta\delta_{1,max}^S}{\Delta\delta_1^S} \quad (6)$$

Crystal Structure Determinations of 21@2b: $C_{50}H_{36}O_4{\cdot}C_8H_4N_2$, crystal dimensions 0.24 × 0.08 × 0.05 mm^3, measured with a Siemens SMART-CCD diffractometer with Mo-K_α-radiation. T = 203(2)K. Cell dimensions a = 19.1741(14), b = 12.3870(9), c = 19.3916(14) Å, β = 113.5550(10)°, V = 4221.9(5) Å^3, monoclinic crystal system, Z = 4, $d_{calcd.}$ = 1.304 gcm^{-3}, μ = 0.082 mm^{-1},

space group $P2_1/n$, data collection of 52888 intensities, 10464 independent ($R_{merg.}$ = 0.0705, 1.93° > Θ > 28.3°), 4340 observed [$F_o \geq 4\sigma(F)$], absorption correction with Siemens SADABS program: $R_{merg.}$ before/after: 0.0416/0.0374, max./min. transmission 1.00/0.89; structure solution with direct methods (SHELXS) and refinement on F^2 (SHELXTL rel. 5.01) (577 parameters), the hydrogen atom positions were calculated and refined as riding groups with the 1.2 fold of the corresponding C atoms. $R1$ = 0.0411, $wR2$ (all data) = 0.0867, $w^{-1} = \sigma^2(F_o^2) + (0.0416 \cdot P)^2$, where P = [max. F_o^2) + $(2F_c^2)$]/3, maximum residual electron density 0.245 e·Å^{-3}.

24@2b: $C_{50}H_{36}O_4 \cdot C_{12}H_4N_4 \cdot CHCl_3$, crystal dimensions 0.43 × 0.41 × 0.37 mm^3, measured on a Siemens SMART-CCD diffractometer with Mo-K_α radiation. T = 203(2) K. Cell dimensions a = 19.870(3), b = 10.8438(14), c = 24.554(3) Å, β = 91.791(2)°, V = 5288.1(12) Å^3, monoclinic crystal system, Z = 4, $d_{calcd.}$ = 1.362 gcm^{-3}, μ = 0.0304 mm^{-1}, space group $P2/c$, data collection of 51425 intensities, 13840 independent ($R_{merg.}$ = 0.0314, 1.98° > Θ > 28.39°), 9418 observed [$F_o \geq 4\sigma(F)$], absorption correction with Siemens SADABS program: $R_{merg.}$ before/after: 0.0985/0.0338, max./min. transmission 1.00/0.87; structure solution with direct methods (SHELXS) and refinement on F^2 (SHELXTL rel. 5.01) (694 parameters), the hydrogen atom positions were calculated and refined as riding groups with the 1.2 fold of the corresponding C atoms. $R1$ = 0.0735, $wR2$ (all data) = 0.2317, $w^{-1} = \sigma^2(F_o^2) + (0.1396 \cdot P)^2 + 1.61 \cdot P$, where P = [max. F_o^2) + $(2F_c^2)$]/3, maximum residual electron density 0.657 e·Å^{-3}. Trichloromethane atoms C(71) and Cl(5) were disordered and refined over two sites with occupancies 0.5 together with the riding hydrogen atom.

CCDC-222268 (for 2**1**@2**b**) and -222267 (for **24**@2**b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

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