Concave Reagents, 7[1]

# Concave Benzoic Acids

**Ulrich Lüning*[a], Carsten Wangnick[a], Karl Peters[b], and Hans Georg von Schnering[b]**

Chemisches Laboratorium der Universität[a],
Albertstraße 21, D-7800 Freiburg

Max-Planck-Institut für Festkörperforschung[b],
Heisenbergstraße 1, D-7000 Stuttgart 80

Received June 30, 1990

**Key Words:** Concave acid / Macrocycle / *m*-Terphenyl / Benzoic acids / Acidity

Based on *m*-terphenyl units, concave benzoic acids **11a** and **12a** were prepared via the 2,6-diarylbenzoic acid **7a**. Bromination of **7a** with NBS gave **9**, and cyclization of **9** with dithiols **10** led to the bimacrocyclic concave acids **11a** and **12a**. Their relative acidities were determined by photometric titrations in ethanol, and the three-dimensional structure of **11a** was determined by X-ray analysis.

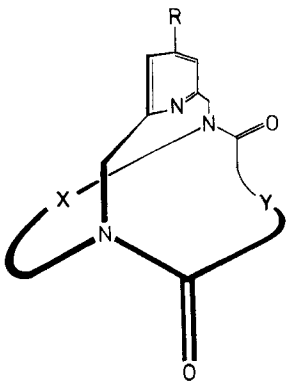
Concave Reagents have been designed[2a] to improve the selectivity of standard reagents in organic chemistry (acids and bases, redox reagents). A variety of concave bases have already been synthesized[2,3], and one area of application was the reprotonation reaction of nitronate anions via their conjugate acids[1,4]. Therefore, it seemed interesting to synthesize concave acids, too.

The already existing concave bases **1** – **3** are bimacrocyclic pyridines and 1,10-phenanthrolines with amide[2] or aryl[3] bridgeheads.

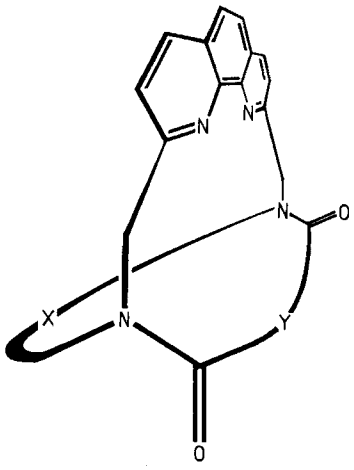
In analogous concave acids, a 2,6-disubstituted benzoic acid moiety should substitute the pyridine or 1,10-phenanthroline ring(s) present in the concave bases. Because amide bridgeheads lead to the formation of conformers[2], aryl bridgeheads are preferable. In the case of a direct connection between the benzoic acid moiety and the aryl groups, a *m*-terphenyl system has to be synthesized. Hart et al.[5] have recently found an attractive synthetic approach to *m*-terphenyl systems involving the addition of arylmagnesium halides to 1,3-dichloro-2-iodobenzene (**4**) (see Scheme 1).

In order to incorporate the carboxyl function into the *m*-terphenyl system, $CO_2$ was added to the intermediate *m*-terphenyl Grignard compound, but the desired products **7a**, **b** were not formed in acceptable yields. Therefore, the intermediate was quenched with iodine, and the iodides **6** were isolated. By lithiation with *n*-butyllithium and subsequent reaction with dry $CO_2$, these iodides **6** could then be transformed into the carboxylic acids **7**. By this method, two new 2,6-diarylbenzoic acids **7a** and **7b** were synthesized in 71 and 31% yield starting from 1,3-dichloro-2-iodobenzene (**4**) and 2-bromo-1,3-dimethylbenzene or 1-bromo-3,5-dimethylbenzene, respectively.

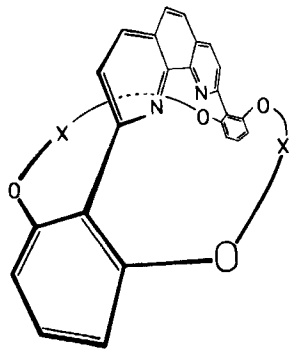
The functionalization of the tetramethyl-substituted acid **7a** was achieved by NBS bromination as described for the parent hydrocarbon (ref.[5b], no experimental data therein). Cyclization of the tetrabromide **9** with two equivalents of




**1**



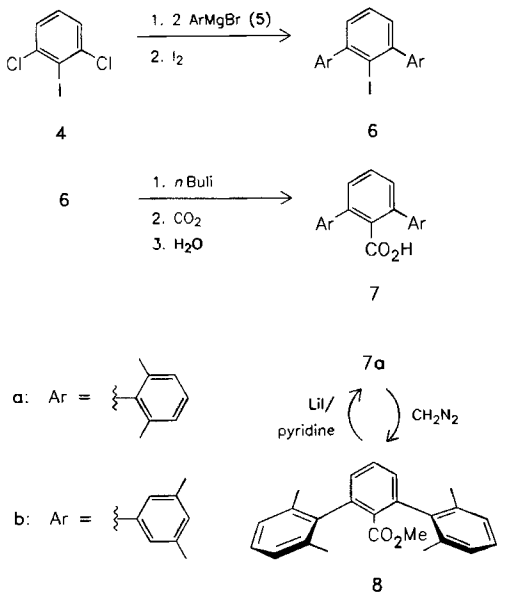

**2**



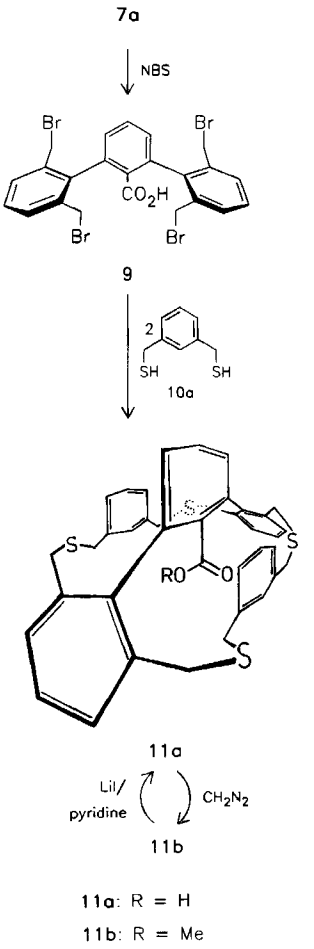

**3**

  0009–2940/91/0202–0397 $ 3.50+.25/0

Scheme 1




Scheme 2




the dithiol **10a** (see Scheme 2) led to the bimacrocyclic acid **11a** which was difficult to purify. Crystallization and chromatographic attempts failed.

Therefore, a purification method via a derivative was developed. Esterification with diazomethane, purification of the resulting methyl ester and saponification with LiI in pyridine[6] was first tested with the diaryl benzoic acid **7a** giving an excellent overall yield of 93%.

This method was then applied to the crude cyclization mixture, giving the bimacrocyclic concave acid **11a** in 13% yield based on 2,6-bis(2,6-dimethylphenyl)benzoic acid (**7a**) (see Scheme 2).

The three-dimensional structure of the bimacrocyclic acid **11a** was determined by an X-ray analysis (see Figure 1 and Table 1). The carboxyl function is embedded between the outer phenyl rings of the *m*-terphenyl system and the *m*-xylylene units. In comparison to Zimmerman's molecular tweezers[7] where the carboxyl function is embedded in a slot (comparable to the starting materials **7a, b**), the shielding in **11a** is two-dimensional. Based on the X-ray data, the accessibility of the carboxyl group was investigated by calculation of the solvent-accessible surface (Connolly routine[8]). The calculations show that the carboxyl oxygen atoms and the hydrogen atoms of the outer phenyl rings of the *m*-terphenyl system of **11a** approximately form a plane. Thus, the topology of **11a** is on the borderline between concave and convex. But the *m*-xylyene bridges are bent away from the carboxyl group in the solid state (see Figure 1). An exchange of these bridges by *p*-xylylene units should lead to a stiffer

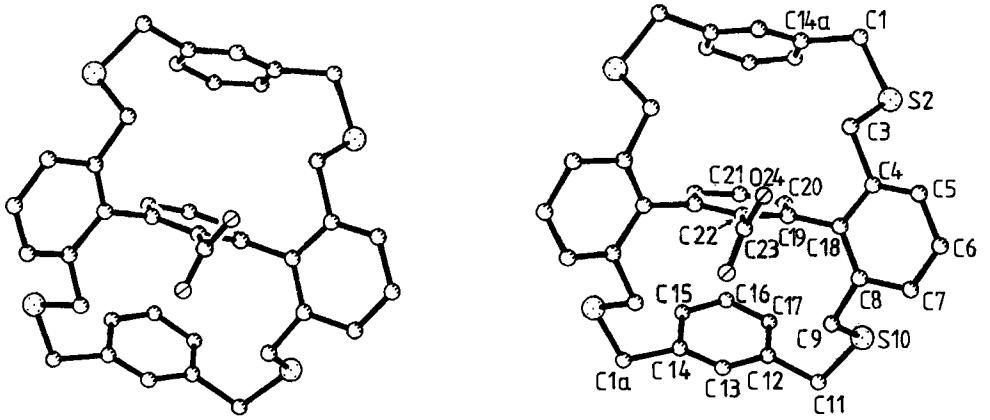



Figure 1. Stereo plot of the bimacrocyclic acid **11a** as determined by X-ray analysis

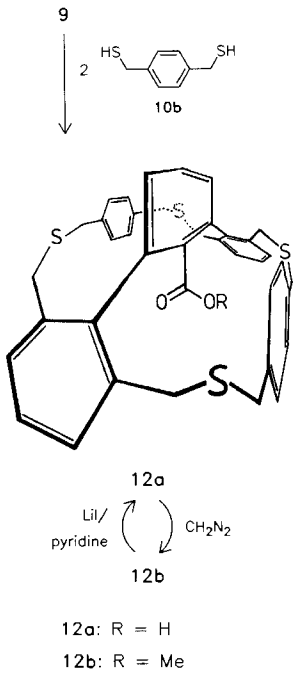
Table 1. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\times 10^{-1}$) [pm$^2$] of the crystal structure of **11a** (see Figure 1); equivalent isotropic $U$ defined as one third of the trace of the orthogonalized $U_{ij}$ tensor

| | x | y | z | U(eq) |
|---|---|---|---|---|
| S(2) | -2253(1) | 1555(1) | 6491(1) | 68(1) |
| S(10) | 543(1) | 1699(1) | 4450(1) | 61(1) |
| C(1) | -2635(1) | 1144(2) | 7525(2) | 70(1) |
| C(3) | -1720(1) | 2738(2) | 6864(2) | 61(1) |
| C(4) | -1297(1) | 3147(2) | 6108(1) | 51(1) |
| C(5) | -1582(1) | 3798(2) | 5437(2) | 62(1) |
| C(6) | -1209(1) | 4150(2) | 4721(2) | 67(1) |
| C(7) | -540(1) | 3863(2) | 4668(1) | 59(1) |
| C(8) | -233(1) | 3217(2) | 5329(1) | 48(1) |
| C(9) | 495(1) | 2886(2) | 5230(1) | 55(1) |
| C(11) | 1420(1) | 1275(2) | 4568(2) | 66(1) |
| C(12) | 1571(1) | 684(2) | 5427(2) | 54(1) |
| C(13) | 1999(1) | 1170(2) | 6044(2) | 57(1) |
| C(14) | 2157(1) | 613(2) | 6827(2) | 56(1) |
| C(15) | 1863(1) | -466(2) | 6992(2) | 62(1) |
| C(16) | 1438(1) | -963(2) | 6385(2) | 67(1) |
| C(17) | 1296(1) | -407(2) | 5605(2) | 64(1) |
| C(18) | -609(1) | 2860(2) | 6057(1) | 44(1) |
| C(19) | -290(1) | 2212(2) | 6793(1) | 42(1) |
| C(20) | -273(1) | 1000(2) | 6800(1) | 55(1) |
| C(21) | 0 | 415(2) | 7500 | 64(1) |
| C(22) | 0 | 2803(2) | 7500 | 41(1) |
| C(23) | 0 | 4111(3) | 7500 | 64(1) |
| O(24) | -541(1) | 4626(1) | 7659(1) | 85(1) |

molecule with a larger shielding of the carboxyl group because the mobility of the bridges should be diminished.

The incorporation of the *p*-xylylene bridges was accomplished by a synthetic sequence analogous to the one shown in Scheme 2. The tetrabromide **9** was bridged twice with 1,4-bis(mercaptomethyl)benzene (**10b**), and the resulting concave acid **12a** was purified via its methyl ester **12b** giving **12a** in 13% yield based on 2,6-bis(2,6-dimethylphenyl)benzoic acid (**7a**).

The exchange of the *m*-xylylene bridges (**11a**) by *p*-xylylene bridges (**12a**) in the bimacrocyclic benzoic acids **11a**




12a: R = H

12b: R = Me

and **12a** leads to differences in the relative acidities $\Delta pK_a$. The acidities of all new *m*-terphenyl carboxylic acids **7a**, **b**, **11a**, and **12a** were determined by photometric titration against *p*-nitrophenol in ethanol. The results are listed in Table 2.

Table 2. Relative acidities $\Delta pK_a$ of the *m*-terphenyl carboxylic acids **7a**, **b**, **11a**, and **12a** determined photometrically against *p*-nitrophenol in ethanol[a]

| Acid | $\Delta pK_a$[b] |
|---|---|
| *p*-nitrophenol | ≡ 0 |
| benzoic acid | ≤ −1.5 |
| **7a** | ca. 0 |
| **7b** | ≤ −1.7 |
| **11a** | −0.6 |
| **12a** | −0.1 |

[a] Analogous to the method described for the titration of thymol blue with bases (see ref. [2b]) the $\Delta pK_a$ acidities were determined by titration of a 100 μM solution of sodium *p*-nitrophenolate in ethanol with 25–70 mM solutions of the acids (solvents; ethanol for **7a**, **b**; chloroform for **11a**; acetone for **12a**). – [b] ± 0.1.

Only in the bis(3,5-dimethyl)-substituted *m*-terphenylcarboxylic acid **7b**, the acidity of the parent compound, benzoic acid, is conserved. When the substitution in the outer phenyl rings of the *m*-terphenyl system is tetra-*ortho* (**7a**, **11a**, and **12a**) the acidities are lowered by more than one order of magnitude. Furthermore, there is a distinct difference in acidity between the two bimacrocyclic benzoic acids **11a** and **12a**. The *p*-xylylene compound **12a** is three times less acidic than the *m*-xylylene compound **11a**.

Influences on the reactivity of the carboxylic groups in **11a** and **12a** can also be expected. Because the carboxyl group (and the carboxylate group, respectively) is shielded from all sides, reactions like nucleophilic attacks at the carboxyl function should be extremely retarded. This is confirmed by the difficulties encountered in the saponification of the ester **11b**[6]. Only LiI in pyridine is capable to cleave the ester **11b**. On the other hand, the carboxylate group should still show a considerable reactivity against electrophiles because the more basic electron pairs are oriented towards the solvent[9]. The esterification with diazomethane is a first example. Further investigations are being made.

We wish to thank Prof. Dr. *C. Rüchardt* for his generous support of this work. The financial help by the *Deutsche Forschungsgemeinschaft* and the *Fonds der Chemischen Industrie* is gratefully acknowledged.

## Experimental

*General Information:* See ref.[2–4]; lithium chloride was dried at >150°C/<0.1 Torr for 24 h.

*1,3-Bis(2,6-dimethylphenyl)-2-iodobenzene* (**6a**): A solution of 41.9 g (200 mmol) of 2,6-dimethylphenylmagnesium bromide (**5a**) was prepared from 37.0 g (200 mmol) of 2-bromo-1,3-dimethylbenzene[10] and 4.90 g (200 mmol) of magnesium in 200 ml of dry THF. To this solution was added over a period of 90 min a solution of 13.6 g (50 mmol) of 1,3-dichloro-2-iodobenzene[11] (**4**) in 200 ml

of dry THF, and the resulting mixture was refluxed for 5 h. After cooling to 0°C, a solution of 57.0 g (220 mmol) of iodine in 200 ml of dry THF was added to this mixture; stirring was then continued at 25°C for 15 h. After the destruction of excess iodine by the addition of a saturated $Na_2S_2O_5$ solution, THF was removed in vacuo. The aqueous residue was extracted with diethyl ether. The ethereal phase was dried with $MgSO_4$ and concentrated.

Volatile byproducts were distilled at 65°C/0.05 Torr. The brown residue was dissolved in cyclohexane and filtered through silica gel (6 × 4 cm) which was washed well. The solvent was evaporated and the residue recrystallized from ethanol to yield 16.9 g (82%) of **6a** as colorless crystals, m.p. 152°C. – IR (KBr): $\tilde{\nu}$ = 1575 $cm^{-1}$ (weak arom.), 1450, 1380, 1370 (arom.). – $^1H$ NMR (250 MHz, $CDCl_3$): δ = 2.01 (s, 12H), 7.1–7.3 (m, 8H), 7.50 (t, *J* = 7.4 Hz, 1H). – MS (EI, 70 eV): *m/z* (%) = 412 (100), 285 (16), 270 (23).

$C_{22}H_{21}I$ (412.32) Calcd. C 64.09 H 5.13
Found C 63.90 H 5.07

*2,6-Bis(2,6-dimethylphenyl)benzoic Acid* (**7a**): Under nitrogen, 31.0 g (731 mmol) of dry lithium chloride and 25 ml (62.5 mmol) of a 2.5 M solution of *n*-butyllithium in *n*-hexane (Janssen) were added to a solution of 25.1 g (60.9 mmol) of the iodide **6a** in 150 ml of dry cyclohexane. A white solid precipitated, and the mixture was stirred at 25°C for 15 h. The solvents were evaporated in vacuo to dryness. The lithium salt was dissolved in 180 ml of dry THF at −78°C (the lithium chloride was not completely dissolved) and stirred at −78°C for 15 min. In a nitrogen stream this mixture was poured onto 300 ml of dry THF and ca. 1 kg of dry $CO_2$ (obtained by condensation of gaseous $CO_2$ which was passed through conc. $H_2SO_4$). The mixture was warmed to 25°C with stirring for 8 h. After hydrolysis with 200 ml of 2 N HCl, THF was removed in vacuo, the aqueous residue extracted four times with 100 ml of ethyl acetate, and the organic extracts were dried with $Na_2SO_4$. Evaporation of the solvent yielded a yellow oil which was dissolved in ca. 100 ml of chloroform and filtered through silica gel (6 × 10 cm). When no more byproduct (hydrocarbon) was eluted by chloroform the solvent was changed to acetone, and the acid was eluted (ca. 2 l of acetone). Evaporation of the acetone yielded 16 g of a yellow solid which was recrystallized from ca. 1 l of dichloromethane to give 14.3 g (71%) of **7a** as colorless crystals, m.p. 210–212°C. – IR (KBr): $\tilde{\nu}$ = 3050–2540 $cm^{-1}$ (O–H), 1680 (C=O), 1575 (arom.). – $^1H$ NMR (250 MHz, $CDCl_3$): δ = 2.03 (s, 12H), 7.05 (d, *J* = 7.4 Hz, 4H), 7.1–7.2 (m, 4H), 7.54 (t, *J* = 7.4 Hz, 1H). – MS (EI, 70 eV): *m/z* (%) = 330 (100), 312 (89), 297 (94), 284 (60).

$C_{23}H_{22}O_2$ (330.43) Calcd. C 83.60 H 6.71
Found C 83.52 H 6.64

*Methyl 2,6-Bis(2,6-dimethylphenyl)benzoate* (**8**): To 330 mg (1.0 mmol) of the carboxylic acid **7a** in 20 ml of diethyl ether, a freshly prepared solution of diazomethane[12] in diethyl ether was condensed by distillation until the reaction mixture turned yellow. After 15 min of stirring at 25°C, the solvent was removed by distillation. Vacuum drying yielded analytically pure **8** as colorless crystals, m.p. 109°C. – IR (KBr): $\tilde{\nu}$ = 3050 $cm^{-1}$, 1720 (C=O). – $^1H$ NMR (250 MHz, $CDCl_3$): δ = 2.06 (s, 12H), 3.08 (s, 3H), 7.0–7.2 (m, 8H), 7.53 (t, *J* = 7.3 Hz, 1H). – MS (EI, 70 eV): *m/z* (%) = 344 (73), 312 (100), 297 (69).

$C_{24}H_{24}O_2$ (344.43) Calcd. C 83.69 H 7.02
Found C 83.53 H 6.99

*Saponification of* **8** *to* **7a**: 50 mg (0.15 mmol) of the ester **8** was heated to reflux for 120 h with 150 mg (1.12 mmol) of dry lithium iodide in 10 ml of dry pyridine. The reaction mixture was poured into 50 ml of icecold 6 N HCl, extracted four times with 50 ml of chloroform, washed three times with 30 ml of water, and the extracts were dried with $MgSO_4$. Evaporation of the solvent yielded 45 mg (93%) of TLC-pure **7a** (silica gel, dichloromethane, $R_f$ = 0.21).

*1,3-Bis(mercaptomethyl)benzene*[13] (**10a**): 23.0 g (87 mmol) of 1,3-bis(bromomethyl)benzene[14] was slowly added to a hot solution of 13.5 g (178 mmol) of thiourea in 130 ml of ethanol. After the exothermic reaction had ceased, the mixture was heated to reflux for 30 min, and the volume was reduced to 50%. Upon cooling, 25.2 g of colorless crystals precipitated. This isothiuronium salt was mixed with a solution of 104 g (1.85 mol) of KOH in 300 ml of water and heated to reflux for 5 h. While cooled with ice, the mixture was then acidified carefully with 9 M $H_2SO_4$ and extracted four times with 100 ml of diethyl ether. The combined organic phases were washed with brine and water and dried with $MgSO_4$. After evaporation of the solvent, **10a** was purified by distillation (110–114°C/0.05 Torr) to yield 8.65 g (58%). – $^1H$ NMR (250 MHz, $CDCl_3$): δ = 1.76 (t, *J* = 7.7 Hz, 2H), 3.69 (d, *J* = 7.7 Hz, 4H), 7.1–7.3 (m, 4H). – MS (EI, 70 eV): *m/z* (%) = 170 (54), 137 (100).

*2,6-Bis[2,6-bis(bromomethyl)phenyl]benzoic Acid* (**9**): Under nitrogen, 1.00 g (3.03 mmol) of the benzoic acid **7a** was dissolved in 50 ml of warm $CCl_4$ (p.a.), and 2.37 g (13.3 mmol) of NBS[15] and ca. 100 mg of benzoyl peroxide (containing 20% water, Merck) were added to the solution. After 5 min at reflux temperature, again ca. 100 mg of benzoyl peroxide was added and the mixture kept at reflux temperature for additional 15 min. The floating succinimide was filtered off while hot and extracted well with hot $CCl_4$. The filtrate was concentrated, and crystallization at 5°C yielded 1.70 g of a colorless compound which still contained succinimide. It could be removed by dissolving the mixture in diethyl ether and intensive extraction with water. After drying with $MgSO_4$ and evaporation of the solvent, 1.3 g (66%, impure) of a colorless powder remained which was used without additional treatment, m.p. 160–170°C (dec.). – IR (KBr): $\tilde{\nu}$ = 1680 $cm^{-1}$ (C=O), 590 (C–Br). – $^1H$ NMR (250 MHz, $CDCl_3$): δ = 4.08 (d, *J* = 10.5 Hz, ca. 4H), 4.22 (d, *J* = 10.5 Hz, ca. 4H), 7.3–7.8 (m, ca. 9H). – MS (EI, 70 eV): *m/z* (%) = 568, 566, 564, 562 (0.5, 2, 2, 0.5), 487, 485, 483 (11, 17, 10), 361, 359 (38, 38), 281 (97), 265 (100).

*3,11,19,27-Tetrathiaheptacyclo[15.15.7.1$^{5,9}$.1$^{21,25}$.1$^{34,38}$.0$^{13,19}$.0$^{29,33}$]-dotetraconta-1(32),5,7,9(42),13,15,17(39),21,23,25(41),29(33),30,34,36,38(40)-pentadecaene-40-carboxylic Acid* (**11a**): Under nitrogen and with vigorous stirring, a solution of 970 mg (1.50 mmol) of the tetrabromide **9** and 511 mg (3.00 mmol) of the dithiol **10a** in 160 ml of a 1:1 mixture of dry ethanol and dry toluene was added to a boiling solution of 1.35 g (24.1 mmol) of potassium hydroxide and 2.0 g (6.1 mmol) of $Cs_2CO_3$ (p.a., Fluka) in 150 ml of dry ethanol over a period of 9 h. After 12 h at 25°C, the solvents were distilled off the opaque, slightly yellow solution. The residue was diluted with 100 ml of 2 N HCl and extracted three times with 50 ml of chloroform. After drying of the extracts with $MgSO_4$, the solvent was evaporated and the oily residue (1.2 g) dissolved in 50 ml of chloroform. Into this solution, freshly synthesized diazomethane[12] in diethyl ether was condensed (ca. fivefold excess). The reaction mixture was stirred for 45 min and concentrated to dryness. Chromatography (silica gel, dichloromethane) of the oily product yielded 260 mg (26%) of the concave ester **11b** as a colorless crystalline product (analytical data see below). Under nitrogen, the ester **11b** was dissolved in 20 ml of dry pyridine, and 520 mg (3.90 mmol) of dry lithium iodide (Merck) was added to the solution. After refluxing for 120 h, the brown reaction mixture was hydrolyzed by addition of 50 ml of a 1:1 mixture of ice and conc. HCl and extracted three times with 20 ml of chloroform. The combined organic extracts were washed twice with 20 ml of water, dried with $Na_2SO_4$,

and concentrated to dryness. The crude product (ca. 540 mg) was dissolved in dichloromethane and purified by column chromatography (silica gel, 4 × 15 cm). After washing with 300 ml of dichloromethane, the carboxylic acid **11a** was eluted with acetone. The slightly brown product obtained by this procedure could be recrystallized from chloroform to yield 200 mg (20%) of analytically pure **11a**, m.p. 204–206°C. – IR (KBr): $\tilde{\nu}$ = 3400–2200 $cm^{-1}$ (OH), 1720, 1690 (C=O). – $^1H$ NMR (250 MHz, $CDCl_3$): δ = 2.83 (d, $J$ = 10.5 Hz, 4H), 3.44 (d, $J$ = 10.5 Hz, 4H), 3.45 (d, $J$ = 14.0 Hz, 4H), 3.64 (d, $J$ = 14.0 Hz, 4H), 6.64 (br. s, 2H), 6.74 (dd, $J$ = 7.0 Hz, $J$ = 8.0 Hz, 1H), 6.92 (d, $J$ = 7.7 Hz, 2H), 7.11 (br. d, $J$ = 7.4 Hz, 4H), 7.2–7.4 (m, 8H). – MS (EI, 70 eV): $m/z$ (%) = 663 (3), 644 (78), 311 (100), 295 (57), 137 (75), 105 (97).

$C_{39}H_{34}O_2S_4$ (663.0) Calcd. C 70.66 H 5.17
Found C 70.56 H 5.22

*X-ray Analysis of* **11a**[16] (see also Figure 1 and Table 1): Empirical formula: $C_{39}H_{34}O_2S_4$; molecular mass 663.0; $a$ = 1989.6(8), $b$ = 1152.0(4), $c$ = 1521.2(8) pm; $V$ = 3487(3) $10^6 \cdot pm^3$; $Z$ = 4, $d$(calcd.) = 1.261 $g \cdot cm^{-1}$; crystal system: orthorhombic, space group *Pbcn*. – Nicolet R3m/V diffractometer; Mo-$K_\alpha$ radiation; graphite monochromator; crystal size [mm]: 0.7 × 1.1 × 0.45; data collection mode: Wyckoff scan; Θ range [°]: 1.75–27.5; recip. latt. segment: $+h, +k, +l$; no. of refl. measd.: 4499; no. of unique refl.: 4022; no. of refl. with $F > 3\sigma(F)$: 3458; lin. abs. coeff.: 0.29 $mm^{-1}$; abs. correction: ψ scan. – Solution by direct phase determination; method of refinement: full matrix LSQ. Hydrogen positions were calculated and refined isotropically; parameter/$F_o$ ratio: 0.062; $R$ ($R_w$) = 0.045 (0.042), $w = 1/\sigma^2(F)$; largest difference peak: 0.26 e $Å^{-3}$; largest difference hole: −0.34 e $Å^{-3}$; program used: Nicolet SHELXTL PLUS.

*Methyl 3,11,19,27-Tetrathiaheptacyclo[15.15.7.1$^{5,9}$.1$^{21,25}$.1$^{34,38}$.0$^{13,39}$.0$^{29,33}$]dotetraconta-1(32),5,7,9(42),13,15,17(39),21,23,25(41),29(33),30,34,36,38(40)-pentadecaene-40-carboxylate* (**11b**): Synthesis see **11a**; analytical data: m.p. 201–207°C. – IR (KBr): $\tilde{\nu}$ = 1720 $cm^{-1}$ (C=O), 1600 (arom.), 1260 (C–O). – $^1H$ NMR (250 MHz, $CDCl_3$): δ = 2.86 (d, $J$ = 10.5 Hz, 4H), 2.88 (s, 3H), 3.45 (d, $J$ = 14.0 Hz, 4H), 3.46 (d, $J$ = 10.5 Hz, 4H), 3.59 (d, $J$ = 14.0 Hz, 4H), 6.65 (br. s, 2H), 6.75 (dd, $J$ = 7.0 Hz, $J$ = 8.0 Hz, 1H), 6.94 (d, $J$ = 7.7 Hz, 2H), 7.15 (d, $J$ = 7.7 Hz, 4H), 7.2–7.4 (m, 8H). – MS (EI, 70 eV): $m/z$ (%) = 677 (12), 676 (26), 644 (100), 311 (65), 137 (48), 105 (72).

$C_{40}H_{36}O_2S_4$ (676.99) Calcd. C 70.97 H 5.36
Found C 70.69 H 5.36

*3,10,18,25-Tetrathiaheptacyclo[14.14.7.2$^{5,8}$.2$^{20,23}$.1$^{32,36}$.0$^{12,37}$.0$^{27,31}$]dotetraconta-1(31),5,7,12,14,16(37),20,22,27,29,32,34,36(42),38,40-pentadecaene-42-carboxylic Acid* (**12a**): Under nitrogen and with intensive stirring, a solution of 4.08 g (6.3 mmol) of the tetrabromide **9** and 2.15 g (12.6 mmol) of the dithiol **10b**[17] in 800 ml of a 1:1 mixture of dry ethanol and dry toluene was added to a boiling solution of 17.7 g (316 mmol) of potassium hydroxide in 150 ml of dry ethanol over a period of 11 h. After 30 min at reflux and 12 h at 25°C, the solvents were distilled off the opaque, slightly yellow solution. The residue was diluted with 100 ml of 2 N HCl and extracted five times with 50 ml of chloroform. After drying of the extracts with $Na_2SO_4$, the solvent was evaporated, and the redbrown oily residue (ca. 4.8 g) was dissolved in 80 ml of chloroform. Into this solution, freshly synthesized diazomethane[12] in diethyl ether was condensed (ca. fivefold excess). The reaction mixture was stirred at 25°C for 1 h and concentrated to dryness. Chromatography (silica gel, dichloromethane, $R_f$ = 0.56) of the redbrown oily residue yielded 1.3 g of the concave ester **12b** as an almost colorless crystalline product. Recrystallization from dichloromethane/petroleum ether (boiling range 60–70°C) yielded 1.24 g (29%) of pure **12b** (analytical data see below). Under nitrogen, 295 mg (0.44 mmol) of the ester **12b** was dissolved in 30 ml of dry pyridine, and 900 mg (6.70 mmol) of dry lithium iodide (Merck) was added to the solution. After refluxing for 192 h, TLC (silica gel, dichloromethane, $R_f$ = 0) showed complete conversion. The brown reaction mixture was concentrated, and the residue was dissolved in 30 ml of chloroform and 30 ml of 2 N HCl. After fourfold extraction with 20 ml of chloroform, the combined organic extracts were washed three times with 6 N HCl, dried with $Na_2SO_4$, and concentrated to dryness. The yellow to brown crude residue (ca. 320 mg) was dissolved in dichloromethane and subjected to column chromatography (silica gel, 2 × 15 cm). The carboxylic acid **12a** was eluted with diethyl ether. The slightly yellow product obtained by this procedure ($R_f$ = 0.48, 320 mg) was recrystallized from diethyl ether to yield 200 mg (68%, based on **12b**) of analytically pure **12a**, m.p. 285–290°C (dec.). – IR (KBr): $\tilde{\nu}$ = 1715, 1695 $cm^{-1}$ (C=O). – $^1H$ NMR (250 MHz, [$D_6$]acetone): δ = 2.38 (d, $J$ = 9.9 Hz, 4H), 3.18 (d, $J$ = 9.9 Hz, 4H), 3.67 (d, $J$ = 13.0 Hz, 4H), 3.80 (d, $J$ = 13.0 Hz, 4H), 6.97 (s, 4H), 7.18 (dd, $J$ = 9 Hz, $J$ = 6 Hz, 2H), 7.2–7.3 (m, 8H), 7.45 (d, $J$ = 9 Hz, 2H), 7.61 (dd, $J$ = 9 Hz, $J$ = 7 Hz, 1H). – MS (EI, 70 eV): $m/z$ (%) = 663 (27), 662 (59), 644 (20), 311 (65), 104 (100).

$C_{39}H_{34}O_2S_4$ (662.96) Calcd. C 70.71 H 5.16
Found C 70.66 H 5.17

*Methyl 3,10,18,25-Tetrathiaheptacyclo[14.14.7.2$^{5,8}$.2$^{20,23}$.1$^{32,36}$.0$^{12,37}$.0$^{27,31}$]dotetraconta-1(31),5,7,12,14,16(37),20,22,27,29,32,34,36(42),38,40-pentadecaene-38-carboxylate* (**12b**): Synthesis see **12a**; analytical data: m.p. 228–230°C. – IR (KBr); $\tilde{\nu}$ = 1720 $cm^{-1}$ (C=O). – $^1H$ NMR (400 MHz, $CDCl_3$): δ = 2.28 (d, $J$ = 10.0 Hz, 4H), 2.75 (s, 3H), 3.11 (d, $J$ = 10.0 Hz, 4H), 3.67 (d, $J$ = 14.0 Hz, 4H), 3.75 (d, $J$ = 14.0 Hz, 4H), 6.89, (s, 4H), 7.19 (dd, $J$ = 9 Hz, $J$ = 8 Hz, 2H), 7.2–7.3 (m, 8H), 7.5–7.6 (m, 3H). – MS (EI, 70 eV): $m/z$ (%) = 677 (42), 676 (82), 644 (54), 311 (79), 104 (100).

$C_{40}H_{36}O_2S_4$ (676.99) Calcd. C 70.97 H 5.36
Found C 70.84 H 5.37

*1,3-Bis(3,5-dimethylphenyl)iodobenzene* (**6b**): A solution of 9.21 g (44.0 mmol) of 3,5-dimethylphenylmagnesium bromide (**5b**) was prepared from 8.14 g (44.0 mmol) of 1-bromo-3,5-dimethylbenzene[18] and 1.06 g (44.0 mmol) of magnesium in 60 ml of dry THF. A solution of 3.00 g (11.0 mmol) of 1,3-dichloro-2-iodobenzene[11] (**4**) in 50 ml of dry THF was added to the solution over a period of 2 h. After 15 h at 25°C, the mixture was heated to reflux for 3 h. Then at 0°C, a solution of 11.2 g (44.1 mol) of iodine in 50 ml of dry THF was added to this mixture; stirring was then continued at 25°C for 1 h. After the destruction of excess iodine by addition of a saturated $Na_2S_2O_5$ solution, THF was removed in vacuo. The aqueous residue was extracted with diethyl ether. The ethereal phase was dried with $MgSO_4$ and concentrated. Volatile byproducts were distilled off at 100°C/0.05 Torr. The brown residue was dissolved in cyclohexane and the solution filtered through silica gel (6 × 4 cm) which was washed well. The solvent was evaporated and the residue recrystallized from ethanol to yield 2.8 g (62%) of **6b** as colorless crystals, m.p. 113°C. – IR (KBr): $\tilde{\nu}$ = 1595 $cm^{-1}$ (arom.). – $^1H$ NMR (250 MHz, $CDCl_3$): δ = 2.37 (s, 12H), 6.98 (br. s, 4H), 7.03 (br. s, 2H), 7.20 [$m_c$ (d), $J \approx$ 7.5 Hz, 2H], 7.34 (dd, $J$ = 6.6 Hz, $J$ = 8.4 Hz, 1H). – MS (EI, 70 eV): $m/z$ (%) = 412 (100), 285 (53), 270 (93).

$C_{22}H_{21}I$ (412.3) Calcd. C 64.09 H 5.13
Found C 64.21 H 5.18

*2,6-Bis(3,5-dimethylphenyl)benzoic Acid* (**7b**): Under nitrogen, 7.5 ml (14 mmol) of a 2.5 M solution of *n*-butyllithium in *n*-hexane

(Janssen) was added to a solution of 2.5 g (6.1 mmol) of the iodide **6b** in 20 ml of dry petroleum ether (boiling range 30–50°C). After stirring at 25°C for 2 h, the solvents were evaporated in vacuo to dryness. 3.0 g (70 mmol) of dry LiCl was added to the lithium salt to aid the dissolution in 50 ml of dry THF at −78°C (the lithium chloride was not completely dissolved). In a nitrogen stream, this solution was poured into 100 ml of dry THF and ca. 300 ml of dry $CO_2$ (obtained by condensation of gaseous $CO_2$ which was passed through concd. $H_2SO_4$). After warming the reaction mixture to 25°C for ca. 4 h and allowing it to stand at 25°C for 15 h, 2.0 g (7.9 mmol) of iodine was added. After stirring at 25°C for 1 h, excess iodine was destroyed by the addition of 30 ml of a concd. $Na_2S_2O_5$ solution. The THF was distilled off in vacuo, and the aqueous residue was extracted with chloroform and dried with $MgSO_4$. Evaporation of the solvent yielded a yellow oil which was dissolved in dichloromethane and the solution filtered through silica gel. When no more byproduct could be detected by TLC, the solvent was changed to acetone, and the acid **7b** was obtained. Evaporation of the solvent yielded a yellow oil (1.5 g) which was dissolved in 30 ml of petroleum ether (boiling range 60–70°C). At −18°C, 1.0 g (50%) of **7b** could be obtained by crystallization, m.p. 163–165°C. – IR (KBr): $\tilde{\nu}$ = 3400–2300 $cm^{-1}$ (OH), 1690 (C=O), 1595 (arom). – $^1H$ NMR (250 MHz, $CDCl_3$): δ = 2.25 (s, 12H), 6.96 (br. s, 2H), 7.02 (br. s, 4H), 7.29 [$m_c$ (d), $J \approx$ 7.5 Hz, 2H], 7.45 (dd, $J$ = 6.7 Hz, $J$ = 8.6 Hz, 1H). – MS (EI, 70 eV): $m/z$ (%) = 330 (100), 313 (60).

$C_{23}H_{22}O_2$ (330.4) Calcd. C 83.60 H 6.71
Found C 83.48 H 6.79

CAS Registry Numbers

**4**: 19230-28-5 / **6a**: 129678-40-6 / **6b**: 129678-45-1 / **7a**: 124177-60-2 / **7b**: 129678-46-2 / **8**: 129678-41-7 / **9**: 129678-42-8 / **10a**: 41563-69-3 / **10b**: 105-09-9 / **11a**: 129707-46-6 / **11b**: 129707-47-7 / **12a**: 129678-43-9 / **12b**: 129678-44-0 / 2-bromo-1,3-dimethylbenzene: 576-22-7 / 1-bromo-3,5-dimethylbenzene: 556-96-7 / 2,6-bis-(2,6-dimethylphenyl)-1-lithiobenzene: 129678-47-3 / 2,6-bis(3,5-dimethylphenyl)-1-lithiobenzene: 129678-48-4 / 1,3-bis(bromomethyl)benzene: 626-15-3 / 1,3-bis(isothiouroniummethyl)benzene: 129678-49-5

[1] Concave Reagents, 6: U. Lüning, F. Schillinger, *Chem. Ber.* **123** (1990) 2073.
[2] [2a] U. Lüning, *Liebigs Ann. Chem.* **1987**, 949. – [2b] U. Lüning, M. Müller, *Liebigs Ann. Chem.* **1989**, 367. – [2c] U. Lüning, R. Baumstark, K. Peters, H. G. von Schnering, *Liebigs Ann. Chem.* **1990**, 129.
[3] U. Lüning, M. Müller, *Chem. Ber.* **123** (1990) 643.
[4] U. Lüning, R. Baumstark, M. Müller, C. Wangnick, F. Schillinger, *Chem. Ber.* **123** (1990) 221.
[5] [5a] C. F. Du, H. Hart, K. D. Ng, *J. Org. Chem.* **51** (1986) 3162. – [5b] T. K. Vinod, H. Hart, *J. Am. Chem. Soc.* **110** (1988) 6574. – [5c] T. K. Vinod, H. Hart, *J. Am. Chem. Soc.* **112** (1990) 3250, and references cited therein.
[6] Besides LiI in pyridine, three more saponification methods were tested unsuccessfully: aq. NaOH in dioxane, iodotrimethylsilane, and KO*t*Bu in DMSO.
[7] S. C. Zimmerman, W. Wu, *J. Am. Chem. Soc.* **111** (1989) 8054.
[8] QCPE program no. 429 by M. L. Connolly, used with Chem-X, developed and distributed by Chemical Design Ltd., Oxford England.
[9] [9a] For a discussion of the basicity of the *syn* and *anti* electron pairs of a carboxylate group see: J. Rebek, Jr., *Angew. Chem.* **102** (1990) 261, *Angew. Chem. Int. Ed. Engl.* **29** (1990) 245. – [9b] The stability of the *cis* and *trans* carboxyl groups is discussed in: L. Radom, W. A. Lathan, W. J. Hehre, J. A. Pople, *Aust. J. Chem.* **25** (1972) 1601.
[10] K.-M. E. Ng, T. C. McMorris, *Can. J. Chem.* **62** (1984) 1945.
[11] R. Bolton, J. B. P. Sandall, *J. Chem. Soc., Perkin Trans. 2*, **1977**, 278.
[12] T. J. De Boer, H. J. Backer, *Org. Synth. Coll. Vol.* **4** (1963) 250.
[13] Synthesis analogous to: R. H. Mitchell, V. Boekelheide, *J. Am. Chem. Soc.* **96** (1974) 1547. When the compound was prepared according to W. Autenrieht, F. Beuttel, *Chem. Ber.* **42** (1909) 4346 and 4357, the product contained always ethoxy groups ($^1H$ NMR).
[14] W. Wenner, *J. Org. Chem.* **17** (1952) 523.
[15] General procedure: Organikum, VEB Deutscher Verlag der Wissenschaften, 15th ed., p. 214, Berlin 1976.
[16] Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD-54685, the names of the authors, and the journal citation.
[17] M. Brink, *Synthesis* **1975**, 807.
[18] The synthesis was performed analogous to ref.[10], for analytical data see: H. A. Smith, C. A. Buehler, T. A. Magee, K. V. Nayak, D. M. Glenn, *J. Org. Chem.* **24** (1959) 1301.

[228/90]