On the Formation of 2-Sulfonylbenzo[*a*]heptalene-1,3-diols as Precursors for the Synthesis of Colchicinoids

by **Khaled Abou-Hadeed** and **Hans-Jürgen Hansen***

Organisch-chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich

Dedicated to *Duilio Arigoni* on the occasion of his 75th birthday

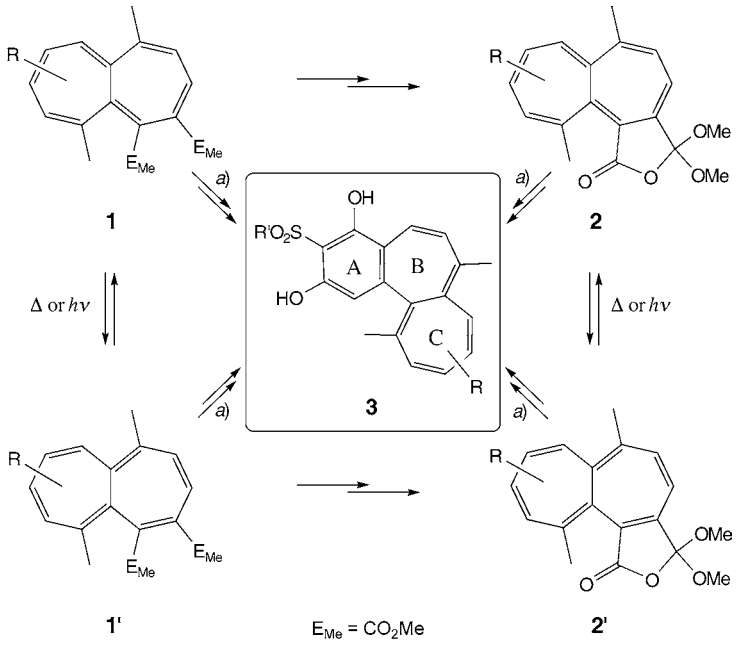
The benzo[*a*]heptalene formation from 4-[(R-sulfonyl)acetyl]heptalene-5-carboxylates **15** and 5-[(R-sulfonyl)acetyl]heptalene-4-carboxylates **16** (R = Ph or morpholino) in the presence of $R'SO_2CH_2Li$ and BuLi has been investigated (*Scheme 6*). Only the sulfonyl moiety linked to the C=O group at C(4) of the heptalene skeleton is found at C(3) of the formed benzo[*a*]heptalene-2,4-diols **3** in accordance with the general mechanism of their formation (*Scheme 3*). Intermediates that might rearrange to corresponding 2-sulfonylbenzo[*a*]heptalene-1,3-diols lose HO^- under the reaction conditions to yield the corresponding cyclopenta[*d*]heptalenones of type **11** (*Schemes 6* and *7*). However, the presence of an additional Me group at C(α) of the lithioalkyl sulfones suppresses the loss of HO^-, and 4-methyl-2-sulfonylbenzo[*a*]heptalene-1,3-diols of type **4c** have been isolated and characterized for the first time (*Schemes 8* and *10*). A number of X-ray crystal-structure analyses of starting materials and of the new benzo[*a*]heptalenes have been performed. Finally, benzo[*a*]heptalene **4c** has been transformed into its 1,2,3-trimethoxy derivative **23**, a benzo[*a*]heptalene with the colchicinoid substitution pattern at ring A (*Scheme 11*).

1. Introduction. – The formation of 3-sulfonylbenzo[*a*]heptalene-2,4-diols (**3**) in a 'one-pot' reaction from heptalene-4,5- or -1,2-dicarboxylates (**1** and **1′**, respectively; *Scheme 1*) [1][2] or their corresponding pseudo-esters **2** and **2′** [3] and lithiomethyl sulfones in the presence of BuLi is attractive in a sense that it principally opens a new entrance to the synthesis of colchicinoids[1]), where the aromatic ring A is constructed at the heptalene rings B and C. The OH groups of **3** can easily be methylated, and the sulfonyl substituent may subsequently be removed reductively, followed by introduction of a third MeO residue after oxidation of C(3) [5]. These procedures demonstrate that benzo-anellation of heptalenedicarboxylates is, indeed, suitable for the construction of ring A of prospective colchicinoids. A disadvantage of the synthesis, however, is that it leads exclusively to benzo[*a*]heptalenes of type **3** with the wrong *C*(2,3,4)-substitution pattern at ring A compared with biologically active colchicines from nature, which all show *O*-substituents at C(1,2,3) [6]. A central question is, therefore, whether the benzo-annelation of **1** and **1′** (or their pseudo-forms **2** and **2′**) can be influenced or modified in a way that 2-sulfonylbenzo[*a*]heptalene-1,3-diols of type **4** are formed instead of their isomers **3** (*Scheme 2*).

All observations we have made so far indicate that the crucial intermediates of the new annelation reaction represent 1*H*-cyclopenta[*a*]heptalene-1,3-diolates of type **5**,

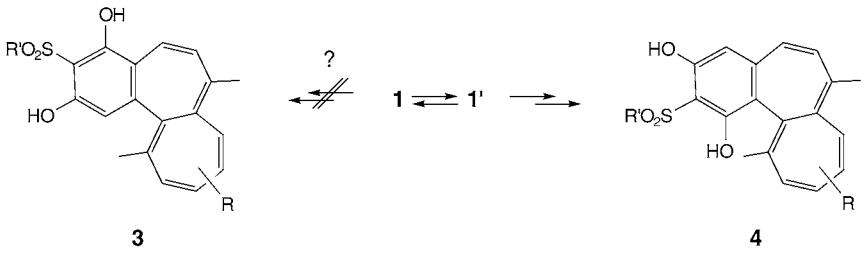
[1]) For other syntheses of colchicines and their derivatives, based on ring-B or -C construction, see the literature cited in [4].

Scheme 1



a) 1. $R'SO_2CH_2Li$, $-78°$; 2. BuLi, -78 to $20°$.

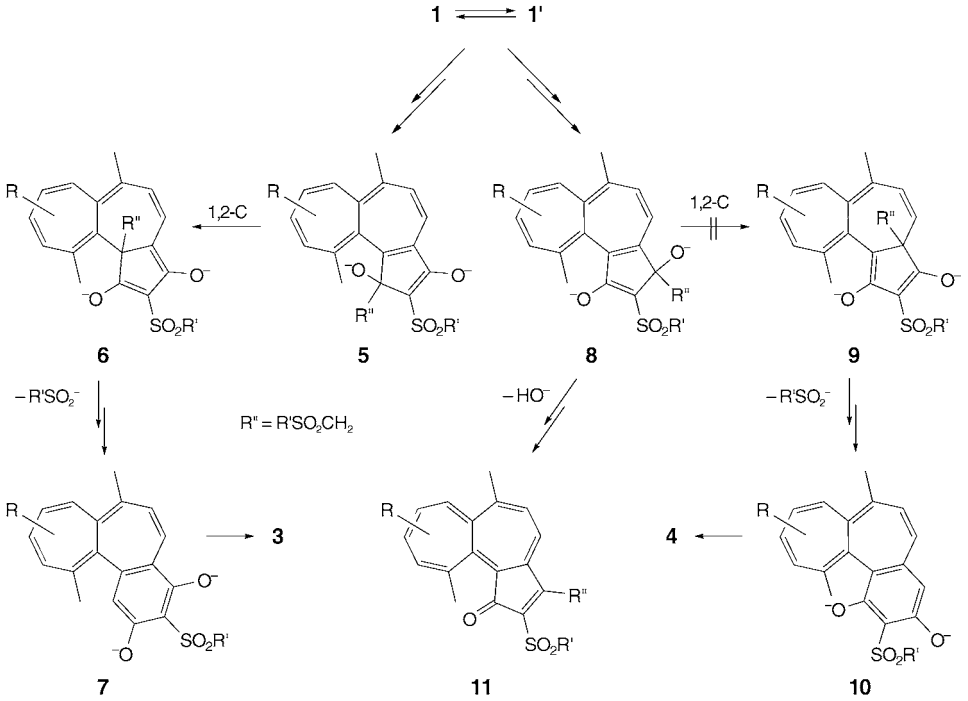
Scheme 2



which undergo a 1,2-C shift[2]) of the $R'SO_2CH_2$ residue (R″) that leads to the formation of the better resonance-stabilized compounds **6** (*Scheme 3*) [2][3]. The latter then lose under the influence of BuLi, in a not yet fully understood reaction, $R'SO_2^-$, accompanied by ring enlargement to the corresponding 3-sulfonylated benzo[*a*]heptalene-2,4-diolates **7** [3]. Besides **5**, the isomeric compounds **8** must also be present in the reaction mixtures, but do not undergo the 1,2-C shift that would result in the formation of **10** and the desired **4**. It seems that the bisanions **8**, in place of rearranging to **9**, lose

[2]) The postulated 1,2-C shift may also be regarded as a sigmatropic [1*s*,5*s*]-C rearrangement of a 5,5-disubstituted cyclopentadiene (*cf.* [7] and refs. cit. therein).

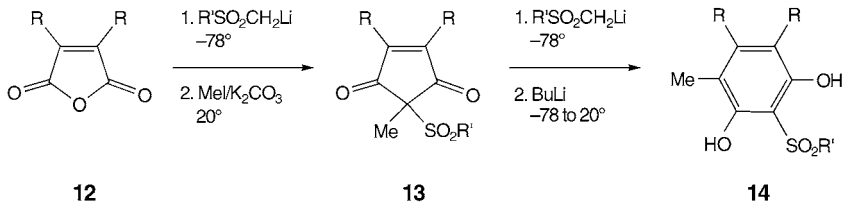
Scheme 3



more rapidly HO^- to yield finally compounds of type **11**, which we have found in all reactions together with **3** [1–3].

The benzo-ring-forming reaction of vicinal heptalenedicarboxylates is of general applicability and can also be performed with 1,2-disubstituted maleic anhydrides **12** in a two-step process, leading *via* **13** to the corresponding 2-sulfonylated 6-methylresorcinols **14** (*Scheme 4*) [8]. These results suggest that α-sulfonylethyl groups undergo the decisive 1,2-C shift in compounds of type **5** (*Scheme 3*), followed by loss of $R'SO_2^-$ under concomitant ring enlargement. Moreover, by interplay of an α-sulfonylethyl and a sulfonylmethyl substituent under strongly basic conditions, it is the former to undergo the 1,2-shift since only the latter possesses a second H-atom necessary for the formation of the crucial sulfonylated intermediates of type **5** (or **8**) ready for the rearrangement of

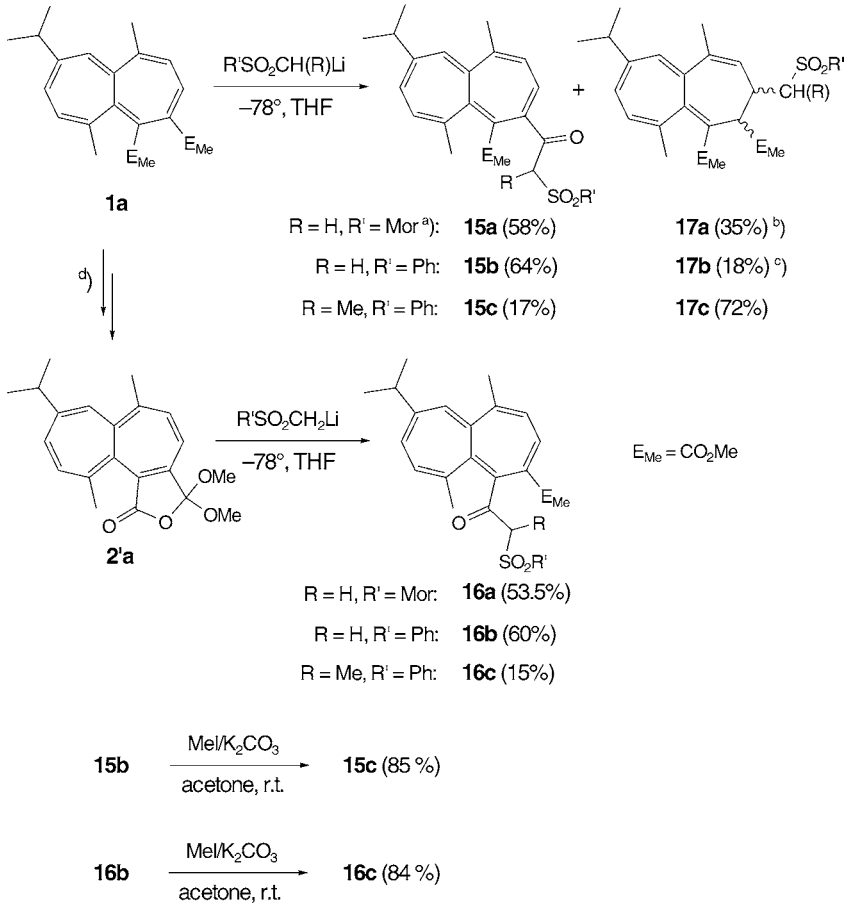
Scheme 4



the sulfonylated alkyl substituent at this position. In the following part, we will describe a number of experiments that are based on these considerations.

2. Results and Discussion. – 2.1. *Chemical Transformations.* The mechanistic pathway for the formation of the 3-sulfonylbenzo[*a*]heptalene-2,4-diols **3**, as shown in *Scheme 3*, requires an $R'SO_2CH_2$ group linked to the C=O group at C(5) in the very first intermediates (see below), to become part of the benzo moiety *via* steps **5** → **6** → **7**. We, therefore, synthesized a number of 4-[(R′-sulfonyl)acetyl]heptalene-5-carboxylates **15** and 5-[(R′-sulfonyl)acetyl]heptalene-4-carboxylates **16** (R′ = Ph or morpholino) as model compounds for benzo[*a*]heptalenediol formation to corroborate the general mechanistic validity of *Scheme 3*. We chose **1a** and its easily accessible pseudoester **2′a** as starting materials (*Scheme 5*). Alkylation of **1a** with lithiomethyl morpholino, lithiomethyl phenyl, or α-lithioethyl phenyl sulfone at −78° in THF led

Scheme 5



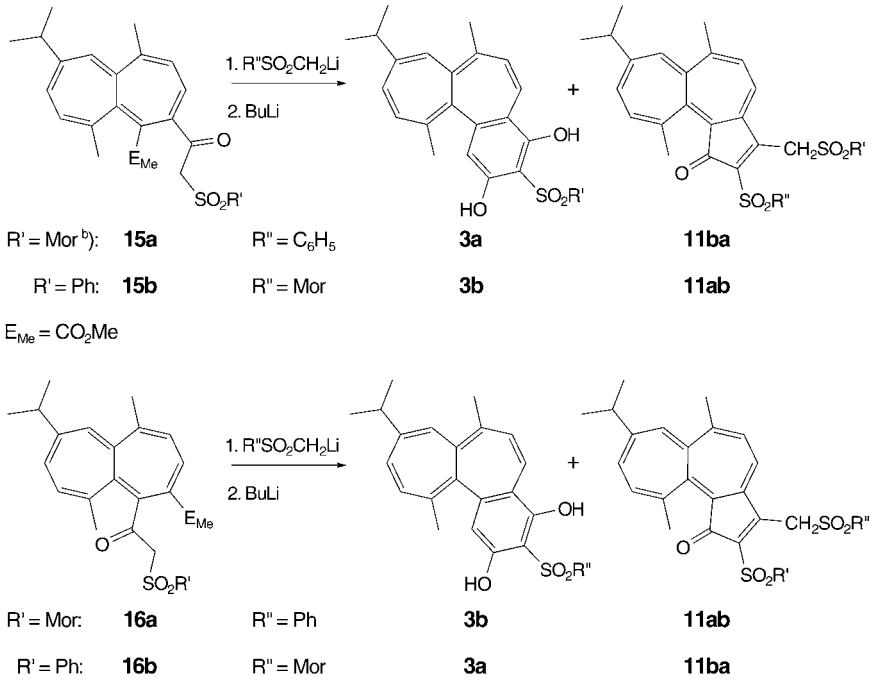
a) Mor = morpholino. b) See [1]. c) The reaction was performed at −20°. d) For details see [3] and *Exper. Part.*

selectively to the 4-[(R′-sulfonyl)acetyl]heptalene-5-carboxylates **15a**–**c** and to stereoisomeric mixtures of the corresponding *Michael* adducts **17a**–**c** as side products. Nevertheless, the two product types could easily be separated by column chromatography on silica gel, with **15** as the faster-running product type[3]). The same procedure, applied to the pseudo-ester **2′a**, gave mostly the inversely substituted heptalene-4-carboxylates **16a**–**16c**. ^{1}H-NMR Spectroscopy indicated in all cases the sole presence of the displayed 4,5-dicarbonyl forms **15** and **16**, respectively. Moreover, the structures of **15c**, **16a**, **16b**, and **17c** were further corroborated by X-ray crystallography (see *Exper. Part*).

It should be noted that the α-Me substituted forms **15c** and **16c** could also be prepared in excellent yields by smooth methylation of **15b** and **16b**, respectively, with MeI in acetone at room temperature in the presence of 1 equiv. of powdered K_2CO_3 (*Scheme 5*).

All benzo[*a*]heptalene syntheses were performed in the same way under standard 'one-pot' conditions (*Table 1* and *Scheme 6*). The results were unambiguous. In the case of **15a** and **15b**, it was, in accordance with *Scheme 3*, the $R'SO_2CH_2$ group of the

Scheme 6[a])



[a]) For details see *Table 1*. [b]) Mor = morpholino.

[3]) In recent experiments, we found that the Mg compound of methyl phenyl sulfone adds almost exclusively at the ester C=O group at C(4) of heptalene-4,5-dicarboxylates [9].

reactants that were built into the benzo ring of **3a** and **3b**, respectively, whereas, in turn, in the case of **16a** and **16b**, the added $R''SO_2CH_2Li$ reagent (as a C_1 synthon) was built into **3b** and **3a**, respectively.

Table 1. *Benzo[*a*]heptalene Formation with (Sufonylacetyl)heptalenes* **15** *and* **16** (for structures, see *Schemes 6* and *8*). Mor stands for morpholino.

Starting material	Reagent[a])	Products (yield [%])	
15a	$LiCH_2SO_2Ph$	**3a** (26)[b])	**11ba** (20–30)[b])
15b	$LiCH_2SO_2$(Mor)	**3b** (23)[b])	**11ab** (25)[b])
15b	$LiCH(Me)SO_2Ph$	**3c** (28)	**17b**[c])
15c	$LiCH_2SO_2Ph$	**4c** (19)	**11bc**[c])
16a	$LiCH_2SO_2Ph$	**3b** (37)	**11ab**[d])
16b	$LiCH_2SO_2$(Mor)	**3a** (35)	**11ba**[d])
16b	$LiCH(Me)SO_2Ph$	**4c** (29)	**11bc**[c])
16c	$LiCH_2SO_2Ph$	**3c** (24)	**17b**[c])

[a]) All transformations were performed as follows: the lithiated sulfone (4 equiv.) was added at $-40°$ to **15** or **16** (1 equiv.) in anh. THF. The temp. was raised to $-5°$ within 3 h. Then, BuLi in hexane (4 equiv., *ca.* 2M soln.) was added. Afterwards, the temp. was raised to 20°, and stirring was continued for 3 h (lithiomethyl sulfones) or 15 h (1-lithioethyl sulfone), followed by workup. [b]) The yields of **3** and **11** were determined by independent experiments. [c]) Compound not detected; see footnote in *Scheme 8*). [d]) Compounds **11ab** and **11ba**, resp., were detected by TLC, but not isolated. Qualitatively, their amounts were comparable with those formed from **15a** and **15b**, resp.

In separate experiments, we isolated as second main products and in comparable amounts to the benzo[*a*]heptalene-2,4-diols the cyclopenta[*d*]heptalen-1(1*H*)-ones **11** (*cf. Scheme 6* and *Table 1*) in full accordance with the mechanistic guidelines of *Scheme 3*[4]). Compounds **11ab** and **11ba** with exchanged positions of the morpholino and Ph substituents at C(2) and CH_2–C(3), respectively, could be easily distinguished by ^{1}H-NMR. The coupling constant of the *AB* system of the CH_2 group at C(3), which exhibits a strong reciprocal ^{1}H-NOE effect with H–C(4), is larger in the case of **11ab** ($J_{AB} = 12.7–12.8$ Hz) than in the case of **11ba** ($J_{AB} = 12.4–12.5$ Hz) [1][2]. More convincing regarding the structure of the side chain at C(3) are the ^{13}C-NMR shifts of the CH_2 C-atom. Its signal appears in the presence of a $PhSO_2$ group above 50 ppm (**11ab** ($CDCl_3$): 52.96 ppm), but below this value in the presence of a morpholinosulfonyl group (**11ba** ($CDCl_3$): 45.01 ppm), respectively [1][2]. The unequivocal assignment of the structure of **11ab** and **11ba** supports our observation that neither a (phenylsulfonyl)methyl nor a (morpholinosulfonyl)methyl group at C(3) of the intermediate **8** does undergo the required 1,2-C shift to **9** (*Scheme 3*). The formation of an enolate ion **18** (*Scheme 7*) with extended conjugation by loss of HO^- from C(3) under the strongly basic condition used for the formation of the benzo[*a*]heptalene-2,4-diolates **7** seems to be more favorable than the formation of diolates of type **9**. Indeed,

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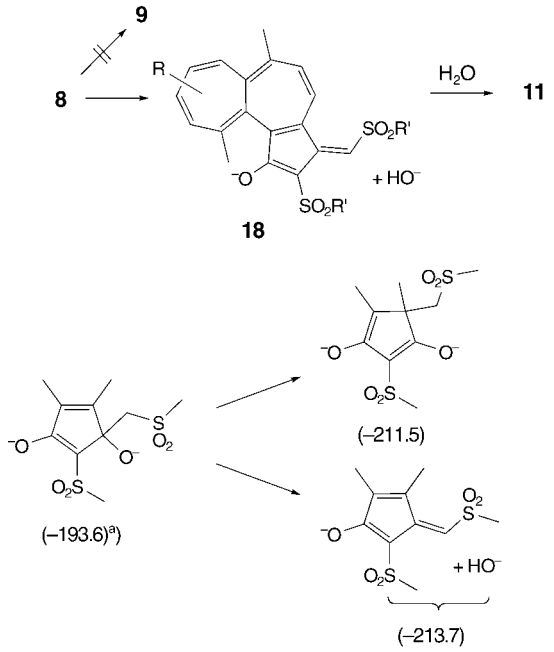
[4]) We showed that the compounds of type **11** are truly the final products under the original, strongly basic reaction conditions, *i.e.*, they are not the result of the loss of H_2O from the corresponding 3-OH-substituted cyclopenta[*d*]heptalen-1-ones (see, *e.g.*, **19c** in *Scheme 9*) under the workup conditions. It should also be noted that **3** and **11** are formed at the same temperature range (-5 to 20°) under strongly basic conditions (*cf. Table 1*).

Scheme 7



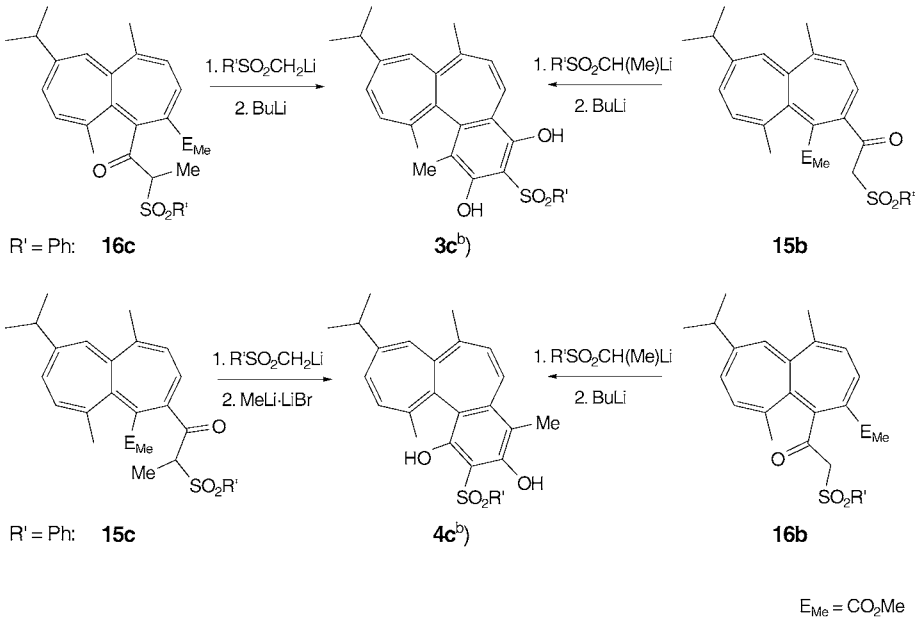
a) AM1-Calculated ΔH_f° values [kcal · mol^{-1}].

AM1 calculations of simplified model structures were in agreement with these assumptions.

Of much greater interest for us was, therefore, the benzo[*a*]heptalene-forming reaction with **15c** and **16c** carrying α-methylated 4- and 5-[(phenylsulfonyl)acetyl] groups. When **16c** was treated in the usual manner with lithiomethyl phenyl sulfone, then compound **3c**, carrying an additional Me group at C(1), was obtained in (nonoptimized) 24% yield (*Scheme 8* and *Table 1*). Product **3c** was obtained in nearly the same yield, when **15b** was reacted with α-lithioethyl phenyl sulfone. The structure of **3c** was fully established by X-ray crystal-structure analysis (*Fig. 1*; see also *Chapt. 2.2*). These results gave us confidence that **15c**, with its 4-[(phenylsulfonyl)acetyl] substituent, carrying an additional α-Me group, would undergo the transformation into a 4-methyl-benzo[*a*]heptalene-1,3-diol, provided that the postulated loss of HO^- from the crucial intermediates of type **8** (*Schemes 3* and *7*) was hindered (or at least retarded) in favor of the 1,2-C shift to **9** due to the α-Me substituent at the C-atom at C(3).

Indeed, the reaction of **2′a** with 2 equiv. of α-lithioethyl phenyl sulfone gave, as the main product after crystallization, one pure stereoisomer of the 3-hydroxycyclopenta[*d*]heptalen-1-one **19c** (*Scheme 9*), which cannot react further and whose structure was unambiguously determined by X-ray crystal-structure analysis (*Fig. 2*; see also *Chapt. 2.2*). The formation of the correct cyclopenta[*d*]heptalenone, *i.e.*, with the 1-(phenylsulfonyl)ethyl moiety at C(3), was in agreement with AM1 calculations of

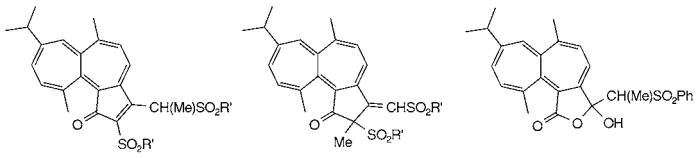
Scheme 8[a])



R' = Ph: **16c** **3c**[b]) **15b**

R' = Ph: **15c** **4c**[b]) **16b**

[a]) For exper. details see *Table 1*. [b]) We found no indication for the presence of **17b** or **11bc** in amounts $>1\%$. However, when **15c** was treated with KOH in MeOH at r.t., compound **24** was obtained in 41% yield.



11bc **17b** **24**

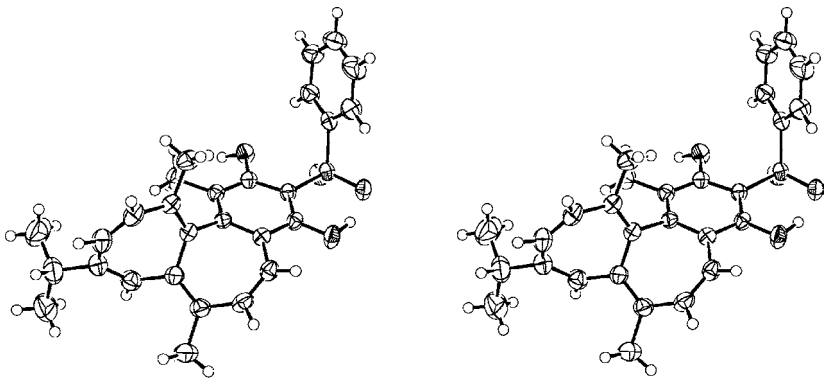
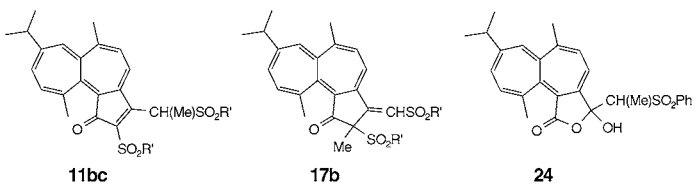
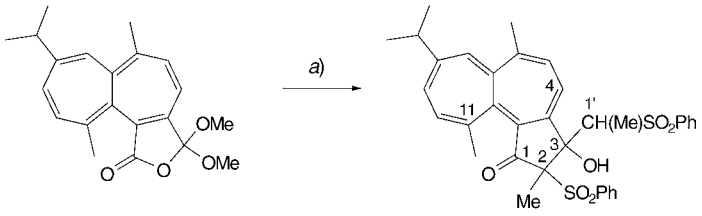


Fig. 1. *Stereoscopic view of the X-ray crystal structure of* **3c**



11bc **17b** **24**

Scheme 9



2'a **19c**

a) 2 Equiv. LiCH(Me)SO_2Ph/THF; $-78°$ to $-40°$, 3 h; 15% (yield of the *isolated* stereoisomer).

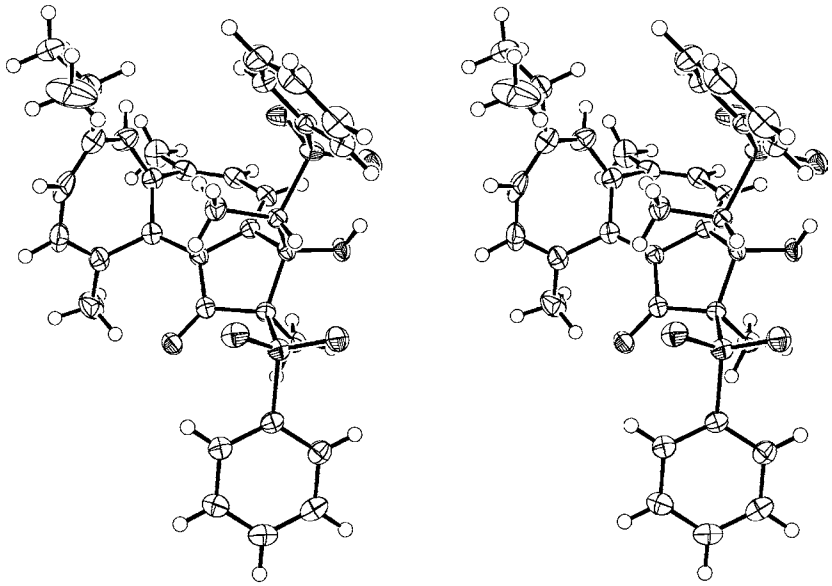


Fig. 2. *Stereoscopic view of the X-ray crystal structure of* **19c** ((*P**,2*R**,3*R**,1′*S**)-configuration)

similarly substituted model heptalenes. Independent of the position of the C=C bonds at the heptalene skeleton, all *C*(3)-substituted 3-oxido intermediates gave rise to lower calculated ΔH_f° values.

The crucial experiment with **15c** afforded, amazingly, the benzo[*a*]heptalene **4c** (*Scheme 8* and *Table 1*), when lithiomethyl phenyl sulfone was used. This result was unique because, for the first time, we could isolate a benzo[*a*]-heptalene-1,3-diol from such a reaction. Compound **4c** was also formed by treatment of **16b** with α-lithioethyl phenyl sulfone. The structure of **4c** was finally corroborated by X-ray crystal-structure analysis (*Fig. 3*; see also *Chapt. 2.2*). These results support our hypothesis that benzo[*a*]heptalene formation from intermediates of type **8** (*Scheme 3*) is hampered by the elimination of HO^-, which finally leads to the observed cyclopenta[*d*]heptalen-1(1*H*)-ones **11**.

With these results in hand and in view of the outcome of the reaction between **2′a** and lithiomethyl phenyl sulfone [3], we began to search for 'one-pot' conditions,

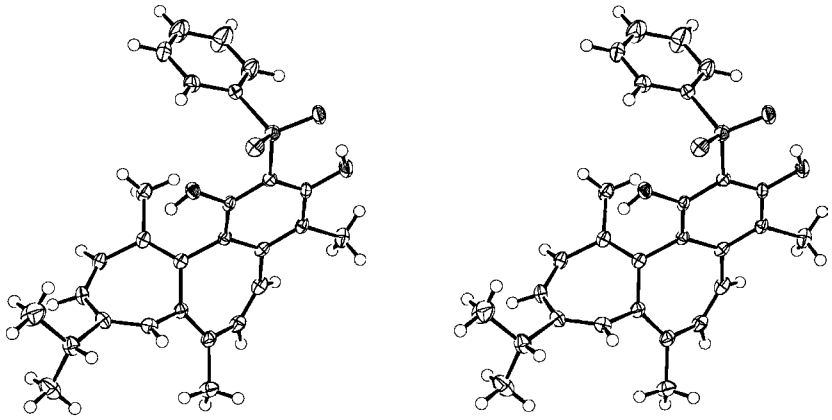


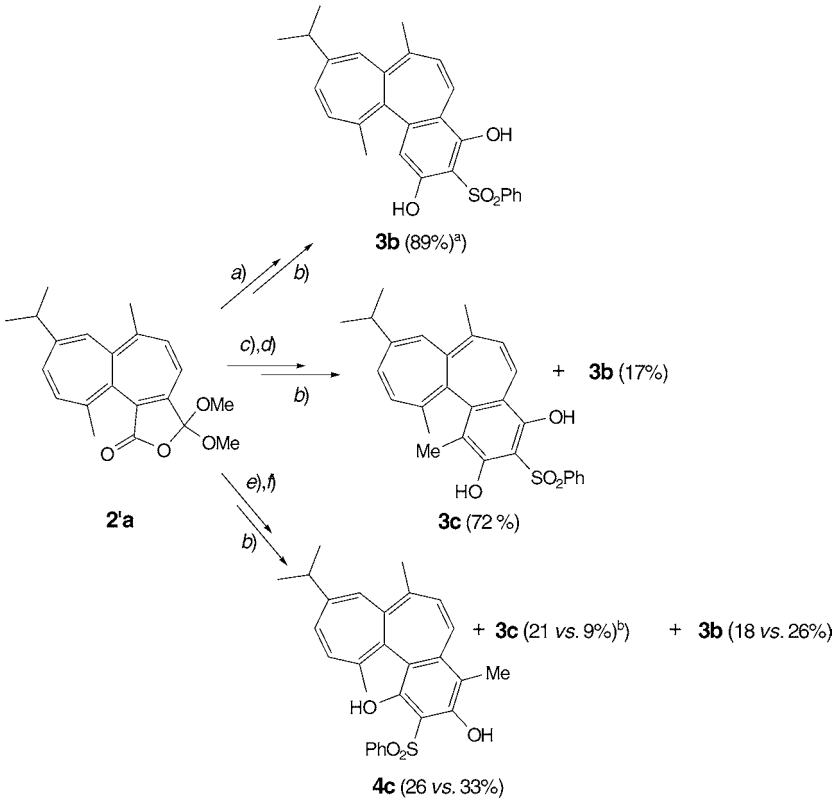
Fig. 3. *Stereoscopic view of the X-ray crystal structure of* **4c**

leading to the formation of the new benzo[*a*]heptalenediols **3c** and **4c** (*Scheme 10*). Indeed, when we treated **2′a** at $-78°$ first with 1.1 equiv. of α-lithioethyl phenyl sulfone and then, after warming to $-40°$, with 3 equiv. of lithiomethyl phenyl sulfone (C_1 source for the formation of **3c**), followed by the addition of excess BuLi, then we could isolate **3c** by chromatography in a total yield of 72%. In a second, slower-moving fraction, we also found 17% of benzo[*a*]heptalenediol **3b**. This result indicated that not all of **2′a** had reacted in the first step, but had also reacted in the second step with lithiomethyl sulfone. Nevertheless, the yield of **3c** in this reaction was much higher than in the case where we had started with **16c**[5]). The one-pot formation of **4c** from **2′a** was not as good as that of **3c**. Also, when using an excess of lithiomethyl phenyl sulfone in the first step, we isolated all three possible benzo[*a*]heptalenediols, **3b**, **3c**, and **4c**, in comparable amounts. In view of the good yield of **3c** in the former procedure, it seems that α-lithioethyl phenyl sulfone relative to lithiomethyl phenyl sulfone is the much better nucleophile under the reaction conditions applied. Nevertheless, our experiments showed that benzo[*a*]heptalene-1,3-diols of type **4c** with the biologically 'correct' substitution pattern at ring A are principally accessible from heptalene-4,5-dicarboxylates.

Benzo[*a*]heptalenediol **4c** was almost quantitatively transformed into the corresponding dimethoxy compound **20** (*Scheme 11*). Reductive desulfonylation of **20** with $LiAlH_4/TiCl_4$ in THF gave **21** in excellent yield. The latter was metallated at C(2) by BuLi, and treatment with $CuBr/O_2$, following a procedure described by *Razdan* and coworkers [10], gave the corresponding 2-hydroxy compound **22** in 59% yield. The structure of **22** was established by ^{1}H-NMR (absence of *s* for H–C(2) at 6.62 ppm and appearance of a new *s* at 5.69 ppm (HO–C(2)), and by an X-ray crystal-structure

[5]) It should be noted that the yields of the benzo[*a*]heptalenediols strongly depend on the quality of BuLi added in the final step to complete the reaction. In the case of **3c**, we isolated in a second run under identical condition, but with another batch of BuLi, only 53% of the product. Finally, we found that catalytic amounts of $FeCl_3$ or $CuBr_2$, added together with BuLi, or the application of the commercially available MeLi · LiBr complex, improved substantially the yields of the sulfonylated benzo[*a*]heptalenediols **3** and/or **4**.

Scheme 10



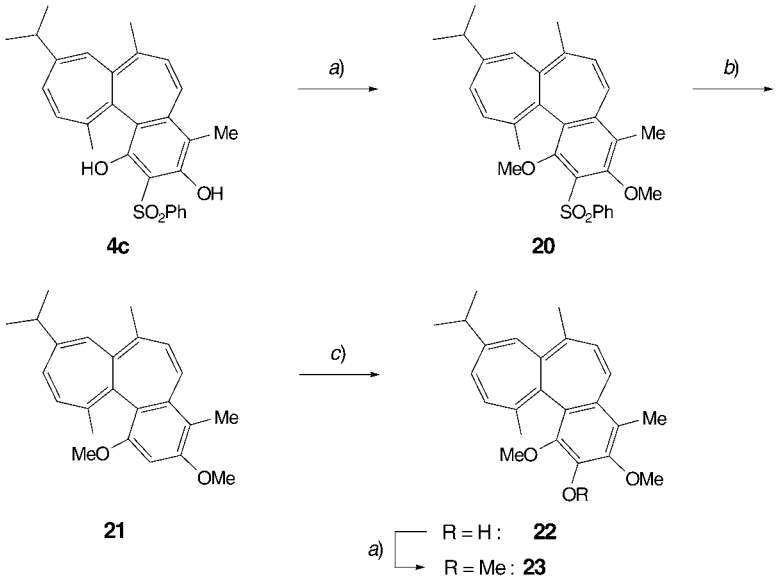
a) 4 Equiv. $LiCH_2SO_2Ph$/THF, $-78°$ to $-5°$, 3 h. *b*) 4 Equiv. BuLi, -5 to $+20°$, 3–15 h. *c*) 1.1 Equiv. $LiCH(Me)SO_2Ph$/THF; -78 to $-40°$, 2 h. *d*) 3 Equiv. $C_6H_5SO_2CH_2Li$/THF, -40 to $-5°$, 3 h. *e*) 1.1 Equiv. $LiCH_2SO_2Ph$/THF; -78 to $-40°$, 3 h. *f*) 3 Equiv. $LiCH(Me)SO_2Ph$/THF; -40 to $-5°$, 3 h.

[a]) Improved yield, following the procedure as described in [3]. [b]) Second values for 3 equiv. $LiCH_2SO_2Ph$/THF; -78 to $-40°$, 3 h.

determination (*Fig. 4*). Finally, methylation of **22** with MeI/K_2CO_3 in acetone gave, in almost quantitative yield, the 1,2,3-trimethoxy-4-methylbenzo[*a*]heptalene **23**.

2.2. *Spectroscopic and Structural Comparisons.* 2.2.1. *Double-Bond Shift and Ring Inversion in* **19c**. Compound **19c** was isolated in crystalline form from the mixture of products of the reaction of **2′a** with α-lithioethyl phenyl sulfone (*cf. Scheme 9*) as a single stereoisomer with the relative (*P**,2*R**,3*R**,1′*S**)-configuration (designated **19c**(**A**)), as revealed by X-ray analysis (*cf. Fig. 2*). In $CDCl_3$ solution, however, there are three other equilibrium forms (*Scheme 12*). When crystals of **19c**(**A**) were dissolved in cold $CDCl_3$, and when the ^{1}H-NMR spectrum (600 MHz) of this solution was recorded at $-25°$, then the signals of **19c**(**A**) (75%) were accompanied by a second set of signals (25%) assigned to the corresponding isomer **19′c**(**A**). Characteristic for **19′c**(**A**) with the exchanged positions of the C=C bonds are the much larger vicinal coupling constants ^3J(H–C(4,5)) and ^3J(H–C(9,10)) of 11.8–12.0 Hz as

Scheme 11



a) MeI/K_2CO_3/acetone, 20°, 8 h; 96%. *b*) $LiAlH_4$/$TiCl_4$/THF, −78 to +20°, 8 h; 87%. *c*) BuLi/CuBr/O_2/THF, −5°, 10 h; 59%.

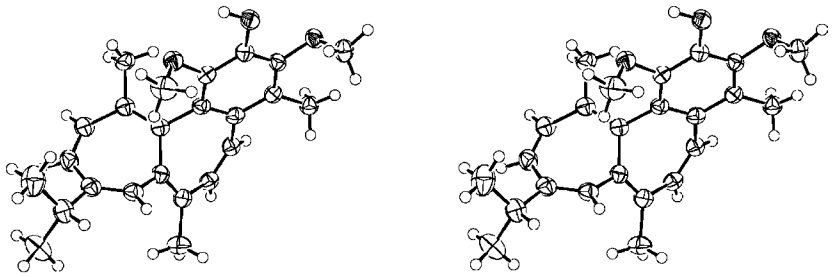


Fig. 4. *Stereoscopic view of the X-ray crystal structure of* **22**

compared to those of **19c**(**A**), which are in the range of 6.5–7.0 Hz (*cf. Table 2*). After storage of the solution of **19c**(**A**) and **19′c**(**A**) for one week at −20°, the ^{1}H-NMR spectrum indicated the presence of a third compound, whose signals could unequivocally be assigned to the ring-inversion product of **19′c**(**A**), namely **19′c**(**B**) with the relative (*M**,2*R**,3*R**,1′*S**)-configuration. The ratio of **19c**(**A**)/(**19′c**(**A**) + **19′c**(**B**)) amounted to 3:2. The identification of **19′c**(**B**) was mainly based on clear chemical-shift differences with respect to **19′c**(**A**), but similar coupling constants (*cf. Table 2* and the *Exper. Part*). Finally, the solution of the three isomers was heated to 40° for 2 h and then chilled again to −25° for NMR measurements. This procedure resulted in additional weak ^{1}H-NMR signals (4.5%) assigned to double-bond isomer **19c**(**B**) of **19′c**(**B**).

Scheme 12. *Equilibria Compositions of Isomeric Cyclopentaheptalenones of Type* **19c** *and* **19′c** (in $CDCl_3$ at 40°). DBS = Double-bond shift.

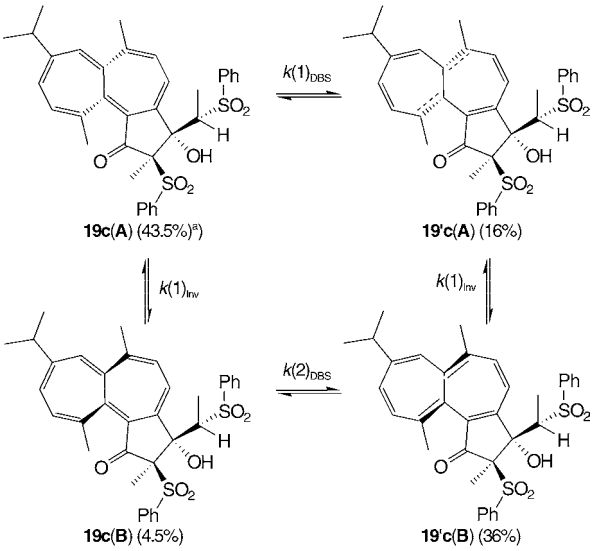


Table 2. *Characteristic* ^{1}*H-NMR Data of the Epimeric and Double-Bond-Shifted Forms of* **19c** (for structures, see *Scheme 12*). The spectra were recorded at 600 or 500 MHz in *ca.* 5% $CDCl_3$ soln. The main coupling constants are given in brackets.

Isomer	**19c**(**A**)	**19′c**(**A**)	**19c**(**B**)	**19′c**(**B**)
H–C(4)	6.83 [6.6]	7.20 [11.7]	6.58 [6.7]	6.85 [11.7]
H–C(5)	6.22 [6.5]	6.90 [11.9]	[a])	6.84 [11.7]
H–C(9)	6.23 [6.5]	6.31 [11.8]	[a])	6.24 [11.9]
H–C(10)	6.38 [7.0]	6.28 [12.0]	[a])	6.39 [11.9]
H–C(1′)	4.57	5.00	4.10	5.09
Me–C(2)	1.24	1.54	[a])	1.44
Me–C(11)	2.06	1.33	[a])	1.66
Me–C(1′)	1.14	1.15	[a])	1.37
HO–C(3)	5.66	6.50	5.64	6.24

[a]) Signal covered by the signals of the major isomers in the equilibrium mixture.

It is of interest to note that the chemical shifts of the OH signals of the four isomers, which appear in the ^{1}H-NMR spectra as sharp *s* in the range of 5.6–6.5 ppm (*Table 2*), are mainly determined by the C–C/C=C bond pattern (see pairs of double-bond isomers) and only slightly by the configuration at the central axis of chirality (see pairs of axial epimers). The X-ray crystal structure of **19c**(**A**) revealed the presence of a short (185 pm) intramolecular H-bridge between HO–C(3) and the (pro*S*)-O-atom of the $PhSO_2$ group at C(1′). Both the chemical shifts and shapes of the ^{1}H-NMR signals for HO–C(3) indicated the presence of such H-bonds also in $CDCl_3$ solution. We tried to substantiate this view by AM1 calculations. Indeed, we found in all cases the lowest ΔH_f° values (**19c**(**A**): –59.8; **19′c**(**A**): –56.0; **19c**(**B**): –58.3; **19′c**(**B**): –56.7 kcal·

mol^{-1}) for structures with an intramolecular H-bond between HO–C(3) and the (pro*S*)-O-atom of $PhSO_2$–C(1′), the length of which varied between 212 and 222 ppm. A comparison of the calculated ΔH_f° values showed that they reflect the relative ratios of the epimers quite well, assuming marginal differences in $\Delta\Delta S_f^\circ$ (**19c**(**A**)/**19c**(**B**) 10 : 1 (found) *vs.* 11 : 1 (calc.); **19′c**(**B**)/**19′c**(**A**) 2.3 : 1 (found) *vs.* 3 : 1 (calc.)), but not that of the double-bond isomers. This deviation seems not to be caused by large differences in ΔS_f° since, in other cases, the AM1-calculated $\Delta\Delta H_f^\circ$ values were in good accord with the experimentally determined equilibrium ratios of double-bond-shifted isomers. Probably, the strength of the intramolecular H-bonds was not predicted well-enough by the AM1 algorithm. Indeed, the ^{1}H-NMR chemical-shift differences of the OH signals are large between the double-bond isomers, but small between the axial epimers. The shift to lower field in going from **19c**(**A**) to **19′c**(**A**) (or from **19c**(**B**) to **19′c**(**B**)) speaks for much stronger H-bonds in the latter.

2.2.2. *$PhSO_2$-Substituted Benzo[*a*]heptalenediols.* The successful synthesis of the $PhSO_2$-substituted benzo[*a*]heptalen-1,3-diol **4c** allowed for the first time its spectral and structural comparison with analogous benzo[*a*]heptalene-2,4-diols, *e.g.*, **3b** or **3c** (*cf. Table 3*). We included in our examinations the structural data of the AM1-calculated structures. They showed that, in general, the X-ray data of **3b**, **3c**, and **4c** were quite well reproduced by the AM1 calculations. The *cisoid* torsion angles at the central heptalene bond (C(7a)–C(12a)) are slightly higher for the calculated structures, mainly as a consequence of the generally shorter length of this bond for the calculated structures. However, the main difference is found in the bond length of C(3/2)–S, which is distinctly shorter (by *ca.* 4.5%) in the calculated structures[6]). Nevertheless, the overall structure of the heptalenediols was well-reproduced.

Most striking was the comparison of the ^{1}H-NMR data of **3b**, **3c**, and **4c**. The trend to higher-field absorption for Me–C(12) in going from **3b** to **4c** could be explained with the additional screening effect of the substituents at C(1), which are close to Me–C(12) (*cf.* θ(1,12b,12a,12) in *Table 3*). We found the largest shift difference for the H-atom of the OH groups, whose signals appear as sharp *s* due to the presence of intramolecular H-bonds in all heptalenes. However, whereas HO–C(2) and HO–C(4) of both **3b** and **3c** appeared at *ca.* 9 ppm, **4c** and the isomeric **3c** displayed the corresponding signals for HO–C(1) at more than 2-ppm higher field, and those of HO–C(3) at *ca.* 1-ppm lower field ($\Delta\delta$ 3.5 ppm). The clearest answer for these different behaviors comes from the X-ray crystal-structure analyses of **3b** and **3c**, which are distinguished only by Me–C(1). Both compounds exhibit a strong intramolecular H-bond (187 and 167 pm, resp.) between one of the OH groups and the neighboring O-atom of the adjacent sulfonyl group. The other OH group forms an intermolecular H-bond with the other O-atom of the sulfonyl group of a neighboring molecule (201 and 187 pm, resp.). It is of interest to note that Me–C(1) has a decisive influence on this H-bonding pattern in the crystals, in such a way that the molecules of **3b** form an intermolecular H-bond with HO–C(4) (*Fig. 5*). For the molecules of **3c**, however, it is HO–C(2) that is engaged in intermolecular H-bonding (*Fig. 6*). In solution, the intermolecular H-bonding is

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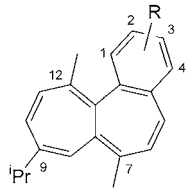
6) The same effect was observed for S–C_{ip} at the Ph ring.

Table 3. *Characteristic ^{1}H-NMR and X-Ray Data of Phenylsulfonyl-Substituted 9-Isopropyl-7,12-dimethylbenzo-[a]heptalenediols*



3b R = 2,4-OH, 3-(SO_2Ph)

3c R = 1-Me, 2,4-OH, 3-(SO_2Ph)

4c R = 4-Me; 1,3-OH, 2-(SO_2Ph)

No.	**3b**[a])	**3c**	**4c**
^{1}H-NMR (δ [ppm])			
HO–C(2/1))	8.62	8.89	6.56
HO–C(4/3))	9.22	9.08	10.02
Me–C(12)	1.67	1.49	1.38
X-Ray[b])			
θ [°]			
C(7,7a,12a,12b)	60.6(3) [61.4]	60.8(2) [62.7]	58.6(2) [61.9]
C(8,7a,12a,12)	60.7(3) [60.1]	61.1(3) [62.3]	58.5(2) [61.4]
C(1,12b,12a,12)	– 63.4(3) [– 60.4]	– 68.7(3) [– 67.5]	– 62.9(2) [– 64.1]
C(8,9,C(^{i}Pr),H)	0.3 [– 10.1]	143.0 [130.8]	– 15.2 [– 10.1]
d [pm]			
C(7a,12a)	148.7(3) [146.8]	147.5(3) [146.7]	149.8(2) [146.6]
C(3/2),S	176.4(2) [168.5]	176.1(2) [168.7]	176.6(2) [168.6]
C(2/1),O	135.7(3) [136.4]	135.6(2) [137.6]	136.3(2) [137.2]
C(4/3),O	135.8(3) [137.6]	135.4(2) [136.4]	136.3(3) [136.6]

[a]) Data taken from [1]. [b]) AM1-Calculated data in brackets.

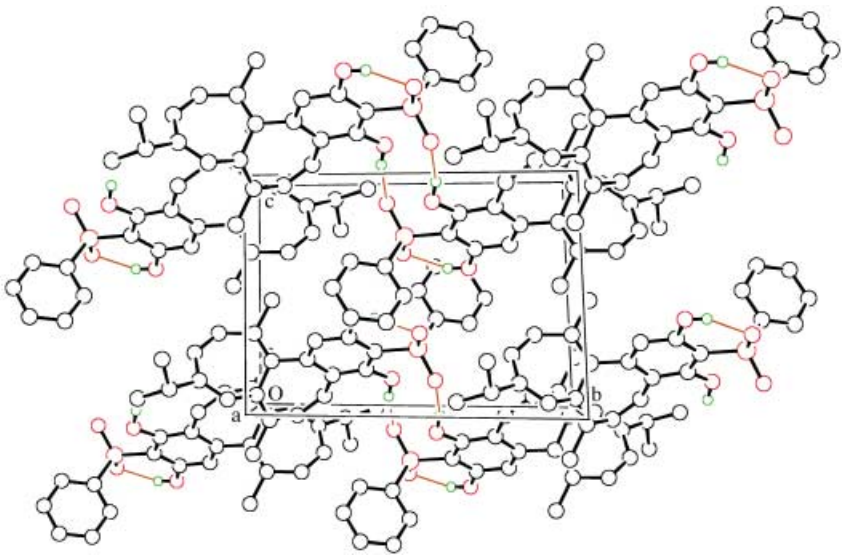


Fig. 5. *Crystal packing of* **3b** *with intra- and intermolecular H-bonds* (H-atoms not involved in H-bonds are omitted for the sake of clarity)

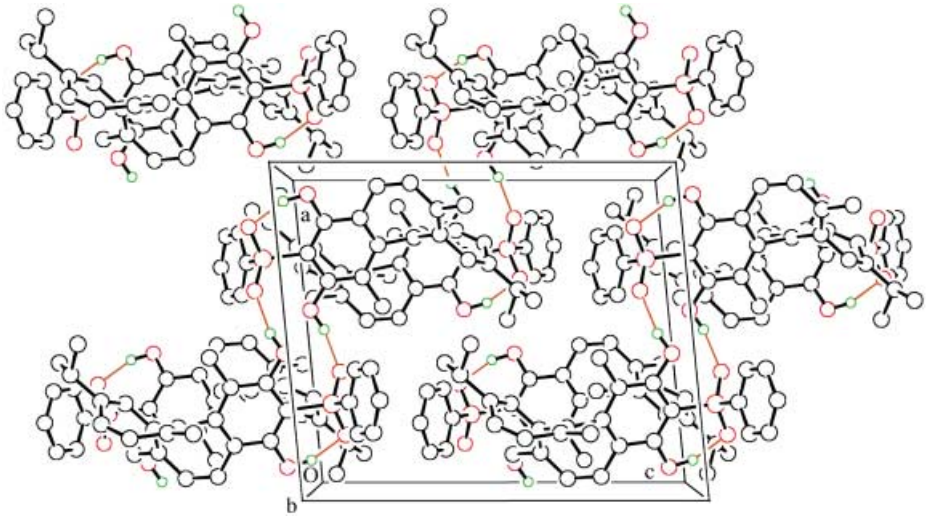


Fig. 6. *Crystal packing of* **3c** *with intra- and intermolecular H-bonds* (all H-atoms not involved in H-bonds are omitted for the sake of clarity)

destroyed, so that both OH groups of **3b** and **3c** must form intramolecular H-bonds with the two different O-atoms of the neighboring phenylsulfonyl group.

To gain more insight into the intramolecular H-bonding situation of benzo[*a*]heptalenediols, we performed AM1 calculations of the isopropyl-free forms **3b′**, **3c′**, and **4c′** (*cf. Tables 4* and *5*) for the sake of a reduction of conformers. We checked by additional AM1 calculations (*cf. Table 3*) that the omission of the i-Pr group had no influence on the H-bonding of the simplified model structures **3b′**, **3c′**, and **4c′**, for which only the orientations of the $PhSO_2$ group with respect to the benzoheptalene skeleton had to be regarded. These orientations may be designated as *syn* when the Ph group of $PhSO_2$ and Me–C(12) are on the same side of the benzoheptalene, and *anti* when both are on opposite sides (*cf. Fig. 7*). In the crystal structures of **3b** (*cf.* [1] and *Fig. 5*), **3c** (*Fig. 1*), and **4c** (*Fig. 3*), the Ph ring of the $PhSO_2$ group adopts a *syn* orientation with respect to Me–C(12). The AM1 calculations showed that the *syn*- and *anti*-conformers possess almost comparable ΔH_f° values and, as a consequence, almost equivalent lengths of the H-bridges between the OH groups and the two O-atoms of the adjacent sulfonyl group (*cf. Tables 4* and *5*). As mentioned, the calculated H-bridges were by 4–12% longer than the ones found in the corresponding X-ray crystal structures. The conformers **A** and **B** of **3b** or **3c**, and **B** and **C** of **4c**, respectively, represent local minima with respect to the torsion angle of the Ph group of $PhSO_2$. They showed, as expected, only marginal differences in their ΔH_f° values. However, the small twist of the Ph group is accompanied by an exchange of the length of the two involved H-bridges. An equilibrium between the *syn*- and *anti*-conformers, which also show only small differences in their ΔH_f° values, requires the cleavage of both H-bridges of the **A** and **B** or **B** and **C** (of **4c**) conformers. It also means that the *syn*/*anti* transformation leads to an exchange of the relative position of the (pro*R*)- and (pro*S*)-O-atom of the $PhSO_2$

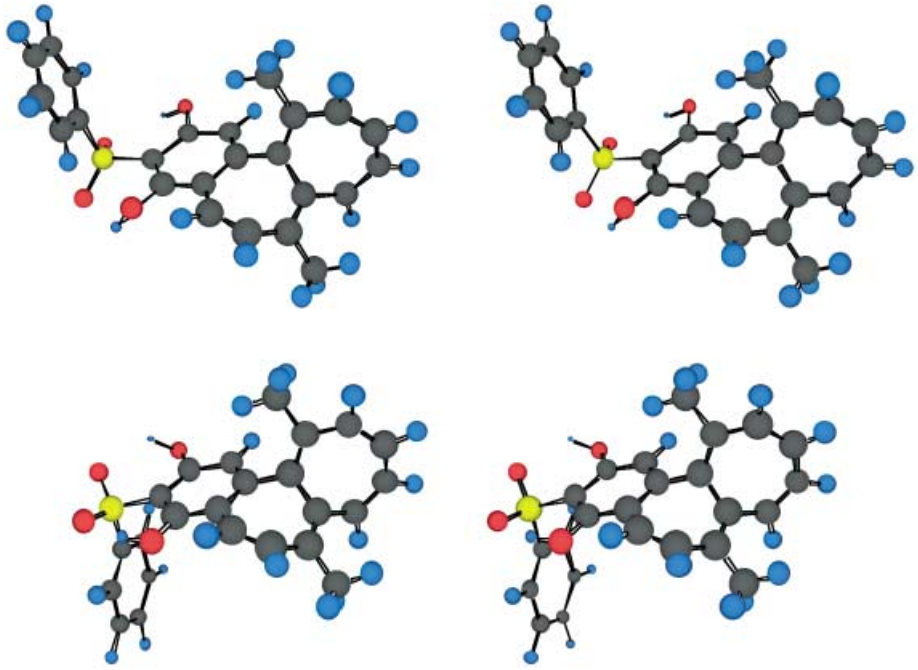


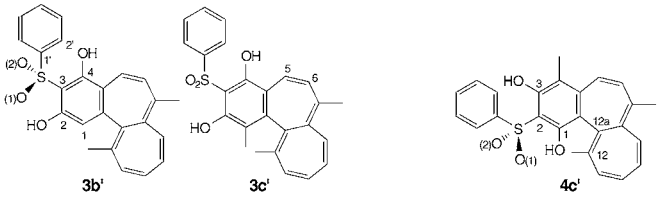
Fig. 7. *Stereoscopic view of the AM1-calculated* syn- (top) *and* anti-*conformers* (bottom) **A** *of* **3b′** (*cf. Tables 4* and *5* for details)

group. Nevertheless, both H-bridged conformers (*syn* and *anti*) should be present in solution and give rise to ^{1}H-NMR OH resonances at 8.6–9.2 ppm for **3b** and **3c**. Strong intramolecular H-bonding in solution was also evident from the IR spectrum of **3c** in $CHCl_3$. The (O–H) stretching region of a 1% (or more-diluted) solution showed only a single, intense absorption band at 3371 cm^{-1} (*Fig. 8*), which is typical of phenols with intramolecular H-bonds [11].

Of highest interest for us was the observation that the AM1 calculations of the *syn*- and *anti*-conformers of **4c** disclosed two further, energetically most-favorable forms, where HO–C(1) is engaged in an electrostatic interaction with the π-system of the C(12)=C(12a) bond of the adjacent heptalene backbone. Indeed, C(12)=C(12a) is ideally placed to form a type of π-pocket for the acidic H-atom of the OH group at C(1), which allows more-or-less equal interatomic distances of the involved H-atom with both C-atoms, regardless of the *syn*- or *anti*-orientation of the Ph residue of the $PhSO_2$ group[7]). The X-ray crystal structure of **4c** (*Fig. 3*) unequivocally showed the

[7]) Principally, the AM1 calculations demonstrate that the OH group at C(4) of **3c′** can also interact with the adjacent C(5)=C(6) bond. However, on grounds of its nonsymmetry, this H-bridge does not contribute to an energetically more-favorable situation as compared with that of a H-bond to the neighboring O-atom of the adjacent SO_2 group (*cf. Tables 4* and *5*).

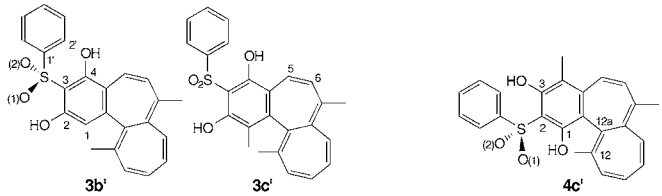
Table 4. *Structural Data of AM1-Calculated H-Bonded* syn *Conformers of Phenylsulfonyl-Substituted 7,12-Dimethylbenzo[*a*]heptalenediols*[a])



Conformers	**A**	**B**	**A**	**B**	**C**	**A**	**B**	**C**
ΔH_f° [kcal·mol^{-1}]	– 26.65	– 26.62	– 30.79	– 30.68	– 29.08	– 30.64	– 29.71	– 29.69
H-bond length *d* [pm]								
C(2/1)OH ··· O(1)SOPh	196.6	200.5	202.1	196.7	193.2	–	197.0	203.1
C(4/3)OH ··· O(2)SOPh	201.1	195.7	195.5	200.9	–	192.4	201.8	195.5
C(1)OH ··· C(12)=C(12a)	–	–	–	–	–	247/238	–	–
C(4)OH ··· C(5)=C(6)	–	–	–	–	245/349	–	–	–
Torsion angle θ [°]								
C(3/2)–S–C(1′)–C(2′)	102.3	78.2	78.9	101.7	89.9	94.5	103.3	78.7

[a]) The i-Pr group at C(9) was omitted in the calculations to reduce the number of conformers. The designator *syn* means that the Ph group of $PhSO_2$ and Me–C(12) are on the same side of the molecule (see *Fig. 7*).

Table 5. *Structural Data of AM1-Calculated H-Bonded* anti *Conformers of Phenylsulfonyl-Substituted 7,12-Dimethylbenzo[*a*]heptalenediols*[a])



Conformers	**A**	**B**	**A**	**B**	**C**	**A**	**B**	**C**
ΔH_f° [kcal mol^{-1}]	– 26.69	– 26.69	– 30.61	– 30.36	– 28.83	– 30.85	– 29.50	– 29.49
H-bond length *d* [pm]								
C(2/1)OH ··· O(1)SOPh	196.2	200.0	202.6	195.7	192.7	–	205.1	195.7
C(4/3)OH ··· O(2)SOPh	199.5	195.7	195.7	200.4	–	192.1	196.0	205.1
C(1)OH ··· C(12)=C(12a)	–	–	–	–	–	243/238	–	–
C(4)OH ··· C(5)=C(6)	–	–	–	–	238/349	–	–	–
Torsion angle θ [°]								
C(3/2)–S–C(1′)–C(2′)	77.3	103.0	102.0	77.0	93.3	88.7	102.5	79.6

[a]) The i-Pr group at C(9) was omitted to reduce the number of conformers. The designator *anti* means that the Ph group of $PhSO_2$ and Me–C(12) are on opposite sides of the molecule (see *Fig. 9*).

presence of an interaction between HO–C(1) and C(12)=C(12a) (interatomic distances of 245 (C(12) and 231 pm (C(12a), resp.; C(3)–OH ··· OS(O)Ph: 184 pm (AM1: 192 pm)) values, close to those calculated for the *syn* conformer of **4c′** (*cf.*

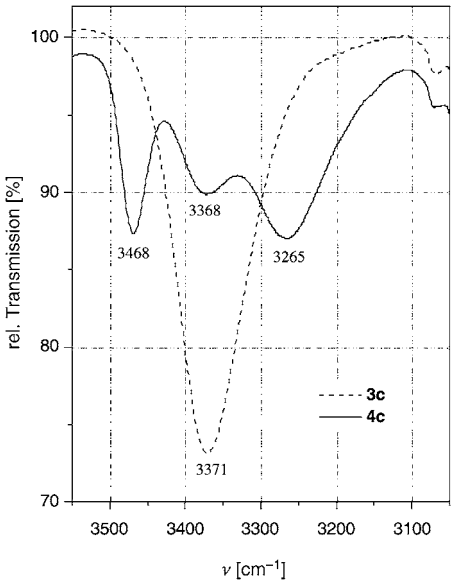


Fig. 8. *IR (O–H)-Stretching region of the isomeric compounds* **3c** *and* **4c** (in $CHCl_3$ solution)

Table 4), as well as for that of **4c** (*Table 3*)[8]). The AM1 calculations indicated that the electrostatic interaction between OH and C(12)=C(12a) is by only *ca.* 1 kcal mol^{-1} energetically more stable than the conformers **B** and **C** with H-bonds to both O-atoms of the sulfonyl group. Therefore, the situation in the rigid crystal lattice may not be comparable to the dynamic behavior of the compound in solution, despite the observation that the ^{1}H-NMR chemical shift of 6.56 ppm for HO–C(1) would be in agreement with a 'π-chelated' H-atom. The answer gave us the IR-spectrum of **4c** in $CHCl_3$ solution (higher degrees of dilution did not significantly change the spectrum). We observed three absorption bands in the (O–H)-stretching region (*Fig. 8*), whereby the wave number of the band at the middle corresponded very well with that for **3c**. Therefore, we assigned this band to (O–H)-stretching vibrations in conformers **B** and **C**, whereas the bands at 3468 and 3265 cm^{-1} were attributed to the (H–O)-stretching vibrations of the π- and sulfonyl-bound OH groups, respectively, of conformers **A** of **4c**. The integrated band intensities speak for a 3:1 ratio of **A**/(**B** + **C**) of **4c**, in good agreement with the calculated ΔH_f° values for the conformers of **4c′**.

We are extremely grateful to Dr. *A. Linden*, who skillfully performed all the X-ray crystal-structure analyses, and who also wrote the X-ray section of the *Exper. Part*. We thank our NMR laboratory for specific NMR measurements, our MS laboratory for recording mass spectra, and our microanalytical laboratory for elemental analyses. Financial support by the *Swiss National Science Foundation* is gratefully acknowledged.

[8]) OH ⋯ π Interactions in crystal and OH ⋯ σ interactions in strained molecules in solution are well established [12–14].

Experimental Part

General. See [1–3].

1. *Formation of Methyl [(R-Sulfonyl)acetyl]heptalenecarboxylates.* – 1.1. *Methyl 9-Isopropyl-1,6-dimethyl-5-[(phenylsulfonyl)acetyl]heptalene-4-carboxylate* (**16b**). A 2.5M soln. of BuLi (3.3 ml, 8.23 mmol) was added drop by drop at $-5°$ to a soln. of $MeSO_2Ph$ (1.1 g, 7.05 mmol) in anh. THF under Ar. After stirring for 30 min at 0°, a white precipitate had been formed. The mixture was cooled to $-78°$, and a soln. of **2′a** (0.80 g, 235 mmol) in THF was added slowly within 5 min. The brown mixture was stirred at $-78°$ for 2 h and poured onto ice/aq. HCl soln. (5%, 100 ml). After extraction with AcOEt (3×50 ml), the org. phase was washed with H_2O (50 ml) and brine (100 ml), and dried ($MgSO_4$). After removal of the solvent by distillation, the crude product was purified by CC (SiO_2 (100 g); hexane/AcOEt 3:2). Recrystallization from Et_2O gave pure **16b** (0.66 g, 60.4%). Orange crystals. M.p. 139.7–140.1°. R_f (hexane/AcOEt 3:2) 0.58. IR (KBr): 2964*m*, 1701*s*, 1638*w*, 1573*w*, 1436*m*, 1324*s*, 1281*s*, 1157*m*, 1085*m*, 854*m*, 811*m*, 765*m*, 690*m*, 563m. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.09 (*dd*, $^3J = 7.0$, $^4J = 1.1$, H_o of $PhSO_2$); 7.62 (*t*, $^3J = 7.4$. H_p of $PhSO_2$); 7.54 (*t*, $^3J = 7.0$, H_m of $PhSO_2$); 7.45 (*dd*, $^3J = 6.4$, $^4J = 0.9$, H–C(3)); 6.28 (*d*, $^3J = 6.6$, H–C(8)); 6.23 (*d*, $^3J = 6.4$, H–C(7)); 6.15 (*dd*, $^3J = 6.5$, $^4J = 1.4$, H–C(2)); 5.84 (*s*, H–C(10)); 4.67/4.64 (*AB*, $^2J_{AB} = 18.0/17.9$, $CH_2C(O)$–C(5)); 3.51 (*s*, MeOCO); 2.49 (*sept.*, $^3J = 6.9$, Me_2CH); 2.05 (*d*, $^4J = 1.0$, Me–C(1)); 1.82 (*s*, Me–C(6)); 1.09/1.06 (2*d*, $^3J = 6.9/6.9$, Me_2CH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 194.13(O=*C*–C(5)); 166.88 (O=*C*–C(4)); 150.27 (C(8)); 144.40 (C(1)); 141.62 (C(3)); 139.95 (C_{ip} of $PhSO_2$); 139.40 (C(5a)); 133.57 (C_p of $PhSO_2$); 132.08 (C(4)); 131.98 (C(10a)); 130.83 (C(5)), 129.45 (C(7)); 129.07 (C_o of $PhSO_2$); 128.71 (C_m of $PhSO_2$); 127.93 (C(6)); 125.88 (C(10)); 125.70 (C(2)); 124.80 (C(8)), 65.17 ($CH_2C(O)$–C(5)); 52.03 (*Me*OCO); 35.73 (Me_2CH); 25.18 (Me–C(1)); 23.72 (Me–C(6)); 23.02/22.62 (Me_2CH). EI-MS: 464 (6, $M^{+\cdot}$), 432 (5), 323 (100), 281 (9), 249 (17), 221 (14), 207 (13), 179 (18), 165 (13), 77 (19). Anal. calc. for $C_{27}H_{28}O_5S$ (464.58): C 69.80, H 6.07, S 6.90; found: C 69.73, H 6.15, S 6.85. X-Ray crystal structure: see *Table 6*.

1.2. *Methyl 9-Isopropyl-1,6-dimethyl-5-[(morpholinosulfonyl)acetyl]heptalene-4-carboxylate* (**16a**). BuLi Soln. (3.3 ml, 8.23 mmol) was added at $-5°$ to a soln. of methyl morpholino sulfone (1.165 g, 7.05 mmol) in anh. THF (40 ml) under Ar. After stirring during 30 min at 0°, a white precipitate had been formed. The mixture was cooled to $-78°$, and a soln. of the pseudo-ester **2′a** (0.8 g, 2.35 mmol) in THF (5 ml) was added drop by drop within 5 min. The yellow-orange mixture was stirred for 2 h at $-78°$ and poured onto ice and 10% aq. HCl soln. (100 ml). After extraction with Et_2O (3×50 ml), the org. layer was washed with H_2O (50 ml) and brine (100 ml), and dried (Na_2SO_4). Evaporation *in vacuo* left a solid residue, which was further purified by FC (SiO_2 (100 g); hexane/AcOEt 1:1). Recrystallization of the resulting solid from Et_2O gave **16a** (0.595 g, 53.5%). Yellow crystals. M.p. 180.2–180.6°. R_f (hexane/AcOEt 1:1) 0.48. IR (KBr): 2960*m*, 1694*s*, 1572*m*, 1449*m*, 1347*s*, 1281*s*, 1157*s*, 1113*s*, 1075*s*, 960*m*, 807*w*, 789*w*, 693*w*, 559*w*, 492*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.50 (*d*, $^3J = 6.6$, H–C(3)); 6.27 (*s*, H–C(7), H–C(8)); 6.19 (*dd*, $^3J = 6.2$, $^4J = 1.3$, H–C(2)); 5.87 (*s*, H–C(10)); 4.53/4.48 (*AB*, $^2J_{AB} = 18.1/18.0$, $CH_2C(O)$–C(5)); 3.73 (*s*, MeOCO); 3.72 (*m*, $O(CH_2CH_2)_2N$); 3.43 (*m*, $O(CH_2CH_2)_2N$); 2.49 (*sept.*, $^3J = 6.9$, Me_2CH); 2.08, 2.05 (2*s*, Me–C(1), Me–C(6)); 1.10/1.07 (2*d*, $^3J = 6.9/6.8$, Me_2CH). ^{13}C-NMR (75.5 MHz ,$CDCl_3$): 195.44 (O=*C*–C(5)); 167.31 (O=*C*–C(4)); 150.19 (*s*); 144.60 (*s*); 141.62 (*d*); 139.48/132.29/132.05/130.99 (4*s*); 129.45 (*d*); 128.12 (*s*); 125.94/ 125.62/124.81 (3*d*); 66.81 (*t*, $O(CH_2CH_2)_2N$); 59.89 (*t*, $CH_2C(O)$–C(5)); 52.33 (*q*, *Me*OCO); 45.88 (*t*, $O(CH_2CH_2)_2N$); 35.69 (*d*, Me_2CH); 25.25 (*q*, Me–C(1)); 23.98 (*q*, Me–C(6)); 23.00/22.60 (2*q*, Me_2CH). CI-MS: 474 (85, $[M+1]^+$), 459 (10, $[(M+1)-Me]^{+\cdot}$), 442 (8, $[(M+1)-MeOH]^+$), 325 (19), 310 (37), 293 (100). Anal. calc. for $C_{25}H_{31}NO_6S$ (473.59); C 63.40, H 6.60, N 2.96, S 6.77; found: C 63.11, H 6.60, N 2.85, S 6.16. X-Ray crystal structure: see *Table 6*.

1.3. *Methyl 9-Isopropyl-1,6-dimethyl-4-[(phenylsulfonyl)acetyl]heptalene-5-carboxylate* (**15b**) *and Dimethyl 3,4-Dihydro-9-isopropyl-1,6-dimethyl-3-[(phenylsulfonyl)methyl]heptalene-4,5-dicarboxylate* (**17b**). BuLi soln. (3.3 ml, 8.25 mmol) was added at 0° to a soln. of $MeSO_2Ph$ (0.705 g, 4.5 mmol) in THF (25 ml). After 30 min, the mixture was cooled to $-40°$. Then, a soln. of **1a** [1] (1.50 g, 4.5 mmol) in THF (8 ml) was added within 5 min. After additional stirring at $-40°$ for 4 h, the mixture was poured onto ice and 10% aq. HCl soln. (100 ml). After extraction with AcOEt (3×100 ml), the org. layer was washed with H_2O (100 ml), brine (100 ml), and then dried (Na_2SO_4). Evaporation *in vacuo* left a solid residue, which, on TLC (hexane/AcOEt 2:1), showed two new main spots (R_f 0.33 (yellow) and 0.25 (colorless)) and another (yellow) spot of residual reactant **1a**. FC (SiO_2 (180 g); hexane/AcOEt 3:1) afforded **1a** (0.59 g, 39%), **15b** (0.79 g, 64% rel. to reacted **1a**), and **17b** (0.24 g, 18%).

Data of **15b**. Yellow crystals. M.p. 186.5–187.1° (Et_2O). R_f (hexane/AcOEt 2:1) 0.33. IR (KBr): 2960*m*, 1710*s*, 1648*s*, 1564*m*, 1447*m*, 1432*m*, 1322*s*, 1289*s*, 1233*m*, 1151*s*, 1084*m*, 1061*w*, 989*w*, 855*m*, 809*m*, 755*m*, 687*m*, 564*m*, 530*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.86 (*dd*, $^3J = 7.1$, $^4J = 1.1$, H_o of $PhSO_2$); 7.60 (*tt*, $^3J = 7.5$, $^4J = 1.3$, H_p

Table 6. *Crystallographic Data for Compounds* **3c**, **4c**, **15c**, **16a**, **16b**, **17c**, **19c**, **21**, *and* **22**

	3c	**4c**	**15c**
Crystallized from	CH_2Cl_2	AcOEt/hexane	AcOEt/hexane
Empirical formula	$C_{28}H_{28}O_4S$	$C_{28}H_{28}O_4S$	$C_{28}H_{30}O_5S$
Formula weight [g mol^{-1}]	460.59	460.59	478.60
Crystal color, habit	yellow, plate	yellow, plate	red, prism
Crystal dimensions [mm]	$0.15 \times 0.25 \times 0.35$	$0.05 \times 0.25 \times 0.30$	$0.15 \times 0.20 \times 0.25$
Temperature [K]	298(1)	160(1)	160(1)
Crystal system	monoclinic	triclinic	triclinic
Space group	$P2_1/n$	$P\bar{1}$	$P\bar{1}$
Z	4	2	2
Reflections for cell determination	6555	27429	4257
2θ Range for cell determination [°]	5 – 73	5 – 55	4 – 50
Unit-cell parameters a [Å]	12.3491(2)	9.2798(1)	10.3133(6)
b [Å]	13.1741(2)	9.6655(1)	10.4297(7)
c [Å]	14.7740(3)	15.5237(3)	12.4598(9)
α [°]	90	93.9905(5)	71.090(3)
β [°]	95.6415(7)	101.5660(5)	88.276(3)
γ [°]	90	117.7053(9)	79.218(3)
V [Å^3]	2391.91(7)	1186.25(3)	1244.8(1)
$F(000)$	976	488	508
D_x [g cm^{-3}]	1.279	1.289	1.277
μ(Mo$K\alpha$) [mm^{-1}]	0.167	0.169	0.166
Scan type	ω	ϕ and ω	ϕ and ω
2θ (max) [°]	55	55	50
Total reflections measured	31132	31398	22865
Symmetry-independent reflections	5456	5425	4374
R_{int}	0.041	0.072	0.063
Reflections with $I > 2\sigma(I)$	4363	21259	3603
Reflections used in refinement	4363	31383	3603
Parameters refined	299	312	307
R [on F; $I > 2\sigma(I)$ reflections]	0.0512	0.0607	0.0691
wR [on F; $I > 2\sigma(I)$ reflections]	0.0631	–	0.0787
wR [on F^2; all indept. reflections]	–	0.2134	–
Weighting parameter [p][a])	0.011	–	0.005
Weighting parameters [a; b][b])	–	0.1355; 0	–
Goodness of fit	2.689	1.041	4.130
Secondary extinction coefficient	$1.3(5) \times 10^{-6}$	–	–
Final Δ_{max}/σ	0.0004	0.001	0.0003
$\Delta\rho$ (max; min) [e Å^{-3}]	0.31; −0.32	0.56; −0.39	0.47; −0.61

of $PhSO_2$); 7.51 (t, $^3J = 7.4$, H_m of $PhSO_2$); 7.32 (dd, $^3J = 6.3$, $^4J = 0.8$, H−C(3)); 6.27 (d, $^3J = 6.5$, H−C(8)); 6.22 (dd, $^3J = 6.3$, $^4J = 1.3$, H−C(2)); 6.12 (dd, $^3J = 6.5$, $^4J = 1.3$, H−C(7)); 5.88 (s, H−C(10)); 4.51/4.39 (AB, $^2J_{AB} = 14.1$, $PhSO_2CH_2C(O)$−C(4)); 3.58 (s, MeOCO); 2.49 (*sept.*, $^3J = 6.8$, Me_2CH); 2.10 (d, $^4J = 1.0$, Me−C(1)); 1.97 (s, Me−C(6)); 1.10/1.07 ($2d$, $^3J = 6.9/6.8$, Me_2CH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 187.87 (O=*C*−C(4)); 167.38 (O=*C*−C(5)); 148.27/147.01/145.63 (3*s*); 143.01 (*d*); 140.22/138.72 (2*s*); 133.99 (*d*); 131.18 (*s*); 129.05 (*d*); 128.52 (*s*); 127.29/126.11/125.79/125.65/125.32 (5*d*); 122.32 (*s*); 63.17 ($CH_2C(O)$−C(4)); 51.99 (*Me*OCO); 35.58 (Me_2CH); 25.63 (Me−C(1)); 23.04 (Me−C(6)); 22.43/22.26 (Me_2CH). EI-MS: 464 (55, $M^{+\cdot}$), 416 (12), 370 (90), 355 (12), 340 (42), 323 (45), 309 (14), 281 (20), 256 (28), 221 (18), 198 (100), 183 (29), 151 (16). Anal. calc. for $C_{27}H_{28}O_5S$ (464.58): C 69.80, H 6.07, S 6.90; found: C 69.59, H 6.14, S 6.73.

Data of **17b**. Colorless crystals. M.p. 153.5 – 154.8° (Et_2O). R_f (hexane/AcOEt 2 :1) 0.25. IR (KBr): 2955*m*, 1748*s*, 1701*s*, 1646*w*, 1596*w*, 1519*w*, 1447*m*, 1437*m*, 1397*w*, 1379*w*, 1304*s*, 1274*m*, 1228*m*, 1204*s*, 1141*s*, 1087*m*,

Table 6 (cont.)

	16a	**16b**	**17c**
Crystallised from	AcOEt/hexane	Et_2O	Et_2O/hexane
Empirical formula	$C_{25}H_{31}NO_6S$	$C_{27}H_{28}O_5S$	$C_{29}H_{34}O_6S$
Formula weight [g mol^{-1}]	473.58	464.57	510.64
Crystal color, habit	yellow, prism	yellow, tablet	colourless, prism
Crystal dimensions [mm]	$0.22 \times 0.25 \times 0.25$	$0.15 \times 0.17 \times 0.22$	$0.10 \times 0.12 \times 0.20$
Temperature [K]	160(1)	160(1)	160(1)
Crystal system	triclinic	monoclinic	triclinic
Space group	$P\bar{1}$	$P2_1/c$	$P\bar{1}$
Z	2	4	2
Reflections for cell determination	6791	5543	7870
2θ Range for cell determination [°]	4–60	2–55	4–60
Unit-cell parameters a [Å]	10.3411(1)	10.2858(1)	10.3707(1)
b [Å]	11.1604(2)	30.4871(3)	11.0794(2)
c [Å]	11.1606(2)	7.7947(1)	12.9903(2)
α [°]	98.3541(6)	90	90.9012(7)
β [°]	101.7919(7)	103.3773(4)	113.5066(7)
γ [°]	104.5579(6)	90	98.9718(6)
V [Å^3]	1193.81(3)	2377.98(5)	1346.98(4)
$F(000)$	504	984	544
D_x [g cm^{-3}]	1.317	1.298	1.259
μ(Mo$K\alpha$) [mm^{-1}]	0.176	0.172	0.160
Scan type	ϕ and ω	ϕ and ω	ϕ and ω
2θ (max) [°]	60	55	60
Total reflections measured	30966	38443	57127
Symmetry-independent reflections	6977	5441	7897
R_{int}	0.038	0.056	0.044
Reflections with $I > 2\sigma(I)$	5480	3838	6344
Reflections used in refinement	5480	3838	6344
Parameters refined	298	298	325
R [on F; $I > 2\sigma(I)$ reflections]	0.0443	0.0449	0.0476
wR [on F; $I > 2\sigma(I)$ reflections]	0.0460	0.0443	0.0531
wR [on F^2; all indept. reflections]	–	–	–
Weighting parameter [p][a])	0.005	0.01	0.005
Weighting parameters [a; b][b])	–	–	–
Goodness of fit	2.490	1.990	3.227
Secondary extinction coefficient	–	–	–
Final Δ_{max}/σ	0.0005	0.0004	0.0006
$\Delta\rho$ (max; min) [e Å^{-3}]	0.31; −0.43	0.24; −0.29	0.36; −0.45

1026*m*, 922*w*, 895*m*, 822*m*, 794*w*, 755*m*, 733*m*, 709*w*, 692*m*, 633*m*, 592*m*, 532*m*, 510*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.00 (*dd*, $^3J = 7.0$, $^4J = 1.2$, H_o of $PhSO_2$); 7.64 (*t*, $^3J = 7.2$, H_p of $PhSO_2$); 7.55 (*t*, $^3J = 7.1$, H_m of $PhSO_2$); 6.38 (*s*, H−C(10)); 6.28 (*d*, $^3J = 6.6$, H−C(8)); 6.21 (*dd*, $^3J = 6.0$, $^4J = 1.2$, H−C(2)); 6.15 (*dd*, $^3J = 6.6$, $^4J = 1.3$, H−C(7)); 4.00/3.04 (*AB*, $^2J_{AB} = 14.1$, $PhSO_2CH_2$−C(3)); 3.88 (*d*, $^3J = 2.5$, H−C(4)); 3.68 (*s*, MeOCO−C(5)); 3.55 (*d*, $^3J = 6.0$, H−C(3)); 3.46 (*s*, MeOCO−C(4)); 2.54 (*sept.*, $^3J = 6.8$, Me_2CH); 1.98 (*d*, $^4J = 1.3$, Me−C(6)); 1.90 (*d*, $^4J = 1.2$, Me−C(1)); 1.13/1.08 (2*d*, $^3J = 6.8/6.8$, Me_2CH). EI-MS: 496 (10, $M^{+\cdot}$), 355 (46), 256 (100), 241 (11), 225 (11), 209 (15), 77 (12).

1.4. *Methyl 9-Isopropyl-1,6-dimethyl-4-[2-methyl-2-(phenylsulfonyl)acetyl]heptalene-5-carboxylate* (**15c**) *and Dimethyl 3,4-Dihydro-9-isopropyl-1,6-dimethyl-3-[1-(phenylsulfonyl)ethyl]heptalene-4,5-dicarboxylate* (**17c**). BuLi soln. (1.4 ml, 3.5 mmol) was added at 0° to a soln. of $EtSO_2Ph$ (0.51 g, 3.00 mmol) in THF (20 ml). After 30 min, the white precipitate was cooled to −78°, and a soln. of **1a** [1] (1.021 g, 3.00 mmol) in THF (8 ml) was added drop by drop within 5 min. After additional stirring at −78° for 3 h, the mixture was

Table 6 (cont.)

	19c	**21**	**22**
Crystallized from	Et_2O	Et_2O/hexane	Et_2O/hexane
Empirical formula	$C_{35}H_{36}O_6S_2 \cdot C_4H_{10}O$	$C_{24}H_{28}O_2$	$C_{24}H_{28}O_3$
Formula weight [g mol^{-1}]	690.91	348.48	364.48
Crystal color, habit	orange, plate	yellow, prism	yellow, prism
Crystal dimensions [mm]	$0.10 \times 0.25 \times 0.27$	$0.10 \times 0.20 \times 0.25$	$0.15 \times 0.20 \times 0.25$
Temperature [K]	160(1)	160(1)	160(1)
Crystal system	triclinic	triclinic	orthorhombic
Space group	$P\bar{1}$	$P\bar{1}$	*Pbca*
Z	2	2	8
Reflections for cell determination	10313	5602	4071
2θ Range for cell determination [°]	4–60	4–60	4–50
Unit-cell parameters a [Å]	10.0109(2)	9.8391(3)	10.8411(3)
b [Å]	13.9148(2)	10.3155(4)	16.9914(5)
c [Å]	14.5077(3)	11.8368(6)	22.5004(8)
α [°]	63.8252(7)	107.690(1)	90
β [°]	86.8650(7)	103.079(1)	90
γ [°]	81.6153(9)	110.896(2)	90
V [Å^3]	1794.19(6)	990.81(8)	4144.7(2)
$F(000)$	736	376	1568
D_x [g cm^{-3}]	1.279	1.168	1.168
μ (Mo$K\alpha$) [mm^{-1}]	0.197	0.0723	0.0754
Scan type	ϕ and ω	ϕ and ω	ϕ and ω
2θ (max) [°]	60	60	50
Total reflections measured	53885	25490	31633
Symmetry-independent reflections	10463	5767	3646
R_{int}	0.069	0.119	0.106
Reflections with $I > 2\sigma(I)$	6538	3628	2326
Reflections used in refinement	10455	5764	3640
Parameters refined	482	243	255
R [on F; $I > 2\sigma(I)$ reflections]	0.0529	0.0764	0.0593
wR [on F; $I > 2\sigma(I)$ reflections]	–	–	–
wR [on F^2; all indept. reflections]	0.1462	0.2236	0.1565
Weighting parameter [p][a])	–	–	–
Weighting parameters [a; b][b])	0.0728; 0.0088	0.1201; 0	0.059; 1.2049
Goodness of fit	1.078	1.025	1.089
Secondary extinction coefficient	–	0.03(1)	–
Final Δ_{max}/σ	0.001	0.001	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.43; −0.40	0.47; −0.35	0.22; −0.19

[a]) $w^{-1} = \sigma^2(F_o) + (pF_o)^2$; [b]) $w^{-1} = \sigma^2[(F_o^2 + (aP)^2 + bP]$, where $P = (F_o^2 + 2F_c^2)/3$.

poured onto ice and 10% aq. HCl soln. (100 ml). After extraction with AcOEt (100 ml), the org. layer was washed with H_2O (100 ml), brine (100 ml), and then dried (Na_2SO_4). Evaporation *in vacuo* left a solid residue which was purified by FC (SiO_2 (170 g); hexane/AcOEt 2:1) to afford **15c** (0.24 g, 17%; mixture of two diastereoisomers) and **17c** (1.10 g, 72%).

Data of **15c**. Red crystals. M.p. 156.9–157.8° (AcOEt/hexane). R_f (hexane/AcOEt 2:1) 0.46. Major isomer: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.72 (*dd*, $^3J = 7.2$, $^4J = 1.4$, H_o of $PhSO_2$); 7.61 (*t*, $^3J = 7.4$, H_p of $PhSO_2$); 7.48 (*t*, $^3J = 6.7$, H_m of $PhSO_2$); 7.42 (*d*, $^3J = 6.2$, H–C(3)); 6.29 (*d*, $^3J = 6.5$, H–C(8)); 6.25 (*dd*, $^3J = 6.3$, $^4J = 1.3$, H–C(2)); 6.12 (*d*, $^3J = 6.4$, H–C(7)); 5.90 (*s*, H–C(10)); 4.79 (*q*, $^3J = 7.0$, $PhSO_2CH(Me)C(O)$–C(4)); 3.56 (*s*, MeOCO); 2.52 (*sept.*, $^3J = 6.9$, Me_2CH); 2.10 (*s*, Me–C(1)); 1.97 (*s*, Me–C(6)); 1.42 (*d*, $^3J = 7.0$, $PhSO_2CH(Me)$); 1.12/1.08 (2*d*, $^3J = 7.0/6.9$, Me_2CH). Minor isomer: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.78 (*d*, $^3J = 7.1$, H_o of $PhSO_2$); 7.63

(t, $^3J = 6.6$, H_p of $PhSO_2$); 7.53 (t, $^3J = 6.7$, H_m of $PhSO_2$); 7.33 (d, $^3J = 5.7$, H–C(3)); 6.29 (d, $^3J = 6.5$, H–C(8)); 6.25 (dd, $^3J = 6.3$, $^4J = 1.3$, H–C(2)); 6.13 (d, $^3J = 6.4$, H–C(7)); 5.90 (s, H–C(10)); 4.66 (q, $^3J = 7.0$, $PhSO_2CH(Me)$); 3.69 (s, MeOCO); 2.52 (*sept.*, $^3J = 6.9$, Me_2CH); 2.10 (s, Me–C(1)); 2.01 (s, Me–C(6)); 1.37 (d, $^3J = 6.9$, $PhSO_2CH(Me)$); 1.12/1.08 (2d, $^3J = 7.0/6.9$, Me_2CH). ^{13}C-NMR (75.5 MHz, $CDCl_3$; both isomers): 193.15/192.40 (2s, O=*C*–C(4)); 167.39/167.28 (2s, O=*C*–C(5)); 148.32/146.59 (2s); 141.80/141.76 (2d); 140.58/140.35/135.90 (3s); 133.96 (d); 131.32 (s); 130.02/129.94/128.71 (3d); 128.49 (s); 127.16/127.15/126.03/125.72/125.55/125.34 (6d); 65.18 (d, Me*C*H); 52.47/52.35 (2q, *Me*OCO); 35.65 (d, Me_2CH); 25.56 (q, Me–C(1)); 23.01 (q, Me–C(6)); 22.37/22.33 (2q, Me_2CH); 13.90/13.44 (2q, *Me*CH). Anal. calc. for $C_{28}H_{30}O_5S$ (478.61): C 70.27, H 6.32, S 6.70; found: C 70.04, H 6.45, S 6.59. X-Ray crystal structure: see *Table 6*.

Data of **17c**. Colorless crystals. M.p. 199.6–200.1° (Et_2O/hexane). R_f (hexane/AcOEt 2:1) 0.54.. IR (KBr): 2956*m*, 1743*s*, 1701*s*, 1446*m*, 1304*s*, 1242*m*, 1208*s*, 1148*s*, 1100*w*, 1084*w*, 1043*w*, 1005*w*, 893*w*, 817*w*, 769*m*, 731*s*, 692*m*, 619*s*, 571*m*, 534*w*, 461*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.00 (dd, $^3J = 6.9$, $^4J = 1.6$, H_o of $PhSO_2$); 7.67–7.54 (m, H_m, H_p of $PhSO_2$); 6.38 (s, H–C(10)); 6.27 (d, $^3J = 6.5$, H–C(7)); 6.14 (dd, $^3J = 6.5$, $^4J = 1.2$, H–C(8)); 6.01 (dd, $^3J = 5.3$, $^4J = 1.0$, H–C(2)); 3.97 (q, $^3J = 6.9$, $PhSO_2CH(Me)$–C(3)); 3.96 (d, $^3J = 2.3$, H–C(4)); 3.85 (br. s, H–C(3)); 3.68 (s, MeOCO–C(5)); 3.47 (s, MeOCO–C(4)); 2.55 (*sept.*, $^3J = 6.9$, Me_2CH); 1.96, 1.95 (2dd, $^4J = 2.6$, 1.6, Me–C(1), Me–C(6)); 1.31 (d, $^3J = 7.0$, $PhSO_2CH(Me)$–C(3)); 1.13/1.09 (2d, $^3J = 6.9/6.9$, Me_2CH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 171.12 (O=*C*–C(4)); 167.48 (O=*C*–C(5)); 150.31/147.11/138.43/133.99 (4s); 133.31 (d); 131.89 (s); 129.14/128.94/127.84/127.07/123.97/123.37 (6d); 121.3 (s); 59.97 ($PhSO_2CH(Me)$–C(3)); 51.84/51.70 (*Me*OCO–C(4,5)); 44.77/36.76 (H–C(4,3)); 35.95 (Me_2CH); 26.49 (Me–C(1)); 23.36 (Me–C(6)); 22.47/22.46 (Me_2CH); 11.24 ($PhSO_2CH(Me)$–C(3)). Anal. calc. for $C_{29}H_{34}O_6S$ (510.65): C 68.21, H 6.71, S 6.28; found: C 67.91, H 6.79, S 6.29. X-Ray crystal structure: see *Table 6*.

1.4.1. *Formation of* **15c** *by Methylation of* **15b**. K_2CO_3 (0.28 g, 2.0 mmol) was suspended in anh. acetone (20 ml). The mixture was cooled to 0°, and **15b** (0.93 g, 2.0 mmol) was added under stirring. Then, MeI (4 ml) was added drop by drop, and stirring was continued at r.t. overnight. The mixture was diluted with H_2O (50 ml) and extracted with AcOEt (2 × 50 ml). The org. layer was separated and dried (Na_2SO_4). Evaporation *in vacuo* gave pure orange-colored crystalline **15c**. Recrystallization from AcOEt/hexane resulted in orange-red crystals (0.81 g, 85%).

1.5. *Methyl 9-Isopropyl-1,6-dimethyl-4-[(morpholinosulfonyl)acetyl]heptalene-5-carboxylate* (**15a**) *and Dimethyl 3,4-Dihydro-9-isopropyl-1,6-dimethyl-3-[(morpholinosulfonyl)methyl]heptalene-4,5-dicarboxylate* (**17a**). See [1].

1.6. *Methyl 9-Isopropyl-1,6-dimethyl-5-[2-methyl-2-(phenylsulfonyl)acetyl]heptalene-4-carboxylate* (**16c**). Starting with **2′a** and α-lithioethyl phenyl sulfone, following the procedure for the synthesis of **15c**, **16c** was obtained in a yield of 15%.

1.6.1. *Formation of* **16c** *by Methylation of* **16b**. K_2CO_3 (0.14 g, 1.0 mmol) was suspended in anh. acetone (15 ml). The mixture was cooled to 0°, and **16b** (0.46 g, 1.0 mmol) was added within 10 min under stirring. Then, MeI (3 ml) was added drop by drop, and stirring was continued at r.t. over night. The mixture was diluted with H_2O (50 ml) and extracted with AcOEt (2 × 25 ml). The org. layer was separated and dried (Na_2SO_4). Evaporation *in vacuo* left **16c** as a brown oil. Purification by FC (SiO_2 (100 g); hexane/AcOEt 3:1) gave **16c** (0.40 g, 84%) as an oily mixture of diastereoisomers. R_f (hexane/AcOEt 2:1) 0.48. ^{1}H-NMR (300 MHz, $CDCl_3$; selected signals of the main diastereoisomer): 7.77–7.45 (m, 5 H, $PhSO_2$); 7.46 (d, $^3J = 6.8$, H–C(3)); 6.35–6.20 (m, H–C(2), H–C(7), H–C(8)); 5.84 (s, H–C(10)); 4.68 (q, $^3J = 7.0$, $PhSO_2CH(Me)$); 3.42 (s, MeOCO); 2.46 (*sept.*, Me_2CH); 1.96, 1.92 (2s, Me–C(1), Me–C(6)); 1.52 (d, $^3J = 7.1$, $PhSO_2CH(Me)C(O)$–C(5)); 1.09/1.08 (2d, $^3J = 6.7/6.7$, Me_2CH). Anal. calc. for $C_{28}H_{30}O_5S$ (478.61): C 70.27, H 6.32, S 6.70; found: C 7.20, H 6.20, S 6.76.

1.7. *2,3-Dihydro-3-hydroxy-8-isopropyl-2,6,11-trimethyl-2-(phenylsulfonyl)-3-[(1-phenylsulfonyl)ethyl]-1*H*-cyclopenta[*d*]heptalen-1-one* (**19c**). At −5°, a 2.5M soln. of BuLi (1.92 ml, 4.80 mmol) was added drop by drop under Ar to a soln. of $EtSO_2Ph$ (0.681 g, 4.00 mmol) in anh. THF (15 ml). After stirring for 30 min at 0°, a white precipitate had been formed. The mixture was cooled to −78°, and a soln. of **2′a** (0.681 g, 2.00 mmol) in THF (6 ml) was added slowly. The brown mixture was allowed to warm to −40° within 3 h. After all **2′a** had been consumed, the mixture became clear and changed its color to reddish-brown. The mixture was treated with ice/H_2O, poured onto 1N aq. HCl soln. (100 ml), and extracted with AcOEt (100 ml). The org. phase was washed with H_2O (100 ml) and brine (100 ml). After drying (Na_2SO_4), the solvent was distilled off in a rotatory evaporator. The crude product was purified by FC (SiO_2 (150 g); hexane/AcOEt 3:2). Recrystallization from Et_2O gave diastereoisomer **A** of **19c** (0.18 g, 15%) as orange crystals. An X-ray crystal-structure analysis (*cf. Fig. 2* and *Table 6*) showed **19c**(**A**) in the rel. (*P**,2*R**,3*R**,1′*S**)-configuration. In soln. ($CDCl_3$), at −25 to 40°, **19c**(**A**) underwent double-bond isomerization to **19′c**(**A**) (*(P*,2R*,3R*,1′S*)-2,3-Dihydro-3-hydroxy-8-isopropyl-2,6,11-trimethyl-2-(phenylsulfonyl)-3-[(1-phenylsulfonyl)ethyl]-1*H*-cyclopenta[*a*]heptalen-1-one*). In a

slightly slower process, epimerization at the heptalene axis was also observed, leading to **19c**(**B**) (*(*S*,2*R*,3*R*,1′*S*)*-configuration) and finally also to **19′c**(**B**) (*(*S*,2*R*,3*R*,1′*S*)-2,3-dihydro-3-hydroxy-8-isopropyl-2,6,11-trimethyl-2-(phenylsulfonyl)-3-[(1-phenylsulfonyl)ethyl]-1*H*-cyclopenta[a]heptalen-1-one). When the $CDCl_3$ soln. was warmed to 40° (2 h) and then rapidly cooled to −25°, the equilibrium mixture consisted of 43.5% **19c**(**A**), 16% **19′c**(**A**), 36% **19′c**(**B**), and 4.5% **19c**(**B**).

Data of **19c**(**A**). M.p. 148.7–151.4°. R_f (hexane/AcOEt 2:1) 0.46. ^{1}H-NMR (600 MHz; $CDCl_3$, −25°): 6.829 (*d*, ^3J = 6.6, H−C(4)); 6.376 (*d*, ^3J = 7.0, H−C(10)); 6.229 (*d*, ^3J = 6.5, H−C(9)); 6.219 (*dd*, ^3J = 6.5, ^4J = 1.1, H−C(5)); 6.018 (*s*, H−C(7)); 5.655 (*s*, HO−C(3)); 4.568 (*q*, ^3J = 6.8, $PhSO_2CH$(Me)−C(3)); 2.528 (*sept.*, ^3J = 6.7, Me_2CH−C(8)); 2.085 (*s*, Me−C(6)); 2.059 (*s*, Me−C(11)); 1.241 (*s*, Me−C(2)); 1.139 (*d*, ^3J = 6.9, $PhSO_2CH$(*Me*)−C(3)); 1.114/1.090 (2*d*, ^3J = 6.9/6.8, *Me*$_2$CH−C(8)) (the arom. signals were not analyzed due to heavy superposition). ^{13}C-NMR (150 MHz; $CDCl_3$, −25°): 191.90 (C(1)); 149.77 (C(8)); 142.19 (C(11a)); 140.93 (C(3a)); 134.45 (C(6)); 134.12 (C_p of $PhSO_2$−C(1′)); 133.29 (C(6a)); 130.36 (C(11)); 129.74 (C(10)); 128.40 (C_o of $PhSO_2$−C(1′)); 128.28 (C(4)); 126.84 (C(11b)); 126.78 (C(7)); 125.92 (C(5)); 84.30 (C(3)); 79.95 (C(2)); 64.59 (C(1′)); 36.17 (Me_2CH−C(8)); 25.53 (*Me*−C(6)); 23.44/22.09 (*Me*$_2$CH−C(8)); 22.54 (*Me*−C(11)); 21.12 (*Me*−C(2)); 14.26 (*Me*−C(1′)). The signals of the arom. C-atoms were only partially assigned.

Data of **19′c**(**A**). ^{1}H-NMR (600 MHz; $CDCl_3$, −25°): 7.201 (*d*, ^3J = 11.7, H−C(4)); 6.895 (*d*, ^3J = 11.9, H−C(5)); 6.495 (*s*, HO−C(3)); 6.308 (*d*, ^3J = 11.8, H−C(9)); 6.276 (*d*, ^3J = 12.0, H−C(10)); 5.484 (*s*, H−C(7)); 5.000 (*q*, ^3J = 6.9, $PhSO_2CH$(Me)−C(3)); 2.469 (*sept.*, ^3J = 6.9, Me_2CH−C(8)); 1.708 (*s*, Me−C(6)); 1.537 (*s*, Me−C(2)); 1.333 (*s*, Me−C(11)); 1.153 (*d*, ^3J = 6.9, $PhSO_2CH$(*Me*)−C(3)); 1.090/1.067 (2*d*, ^3J = 6.9/6.8, *Me*$_2$CH−C(8)). The arom. signals were not analyzed due to heavy superposition. ^{13}C-NMR (150 MHz; $CDCl_3$, −25°): 195.50 (C(1)); 166.83 (C(3a)); 149.90 (C(8)); 137.18 (C(6a)); 135.49 (C(10)); 135.12 (C(11)); 134.25 (C_p of $PhSO_2$−C(1′)); 133.61 (C(9)); 131.07 (C(6)); 129.30 (C(5)); 128.43 (C_o of $PhSO_2$−C(1′)); 127.44 (C(11b)); 123.28 (C(11a)); 124.52 (C(4)); 121.71 (C(7)); 84.33 (C(3)); 83.89 (C(2)); 62.41 (C(1′)); 34.64 (Me_2CH−C(8)); 24.58 (*Me*−C(2)); 22.50/22.34 (*Me*$_2$CH−C(8)); 18.71 (*Me*−C(6)); 18.62 (*Me*−C(11)); 14.10 (*Me*−C(1′)). The signals of the arom. C-atoms were only partially assigned.

Data of **19′c**(**B**). ^{1}H-NMR (600 MHz; $CDCl_3$, −25°): 6.854 (*d*, ^3J = 11.7, H−C(4)); 6.837 (*d*, ^3J = 11.7, H−C(5)); 6.386 (*d*, ^3J = 11.9, H−C(10)); 6.236 (*d*, ^3J = 11.9, H−C(9)); 6.235 (*s*, HO−C(3)); 5.396 (*s*, H−C(7)); 5.087 (*q*, ^3J = 6.9, $PhSO_2CH$(Me)−C(3)); 2.419 (*sept.*, ^3J = 6.7, Me_2CH−C(8)); 1.746 (*s*, Me−C(6)); 1.663 (*s*, Me−C(11)); 1.438 (*s*, Me−C(2)); 1.368 (*d*, ^3J = 6.9, $PhSO_2CH$(*Me*)−C(3)); 1.050/1.020 (2*d*, ^3J = 6.9/6.8, *Me*$_2$CH−C(8)) (the arom. region was not analyzed due to heavy superposition). ^{13}C-NMR (150 MHz; $CDCl_3$, −25°): 193.88 (C(1)); 168.01 (C(3a)); 149.75 (C(8)); 144.00 (C(5)); 137.26 (C(6a)); 135.49 (C(11)); 136.14 (C(10)); 134.31 (C_p of $PhSO_2$−C(1′)); 132.51 (C(9)); 131.21 (C(6)); 128.55 (C_o of $PhSO_2$−C(1′)); 126.78 (C(11b)); 123.42 (C(11a)); 124.86 (C(4)); 122.34 (C(7)); 85.60 (C(3)); 79.89 (C(2)); 62.12 (C(1′)); 34.68 (Me_2CH−C(8)); 24.31 (*Me*−C(2)); 22.42/22.32 (*Me*$_2$CH−C(8)); 18.99 (*Me*−C(11)); 17.81 (*Me*−C(6)); 16.40 (*Me*−C(1′)) (the signals of the arom. C-atoms were only partially assigned).

Data of **19c**(**B**). The small amount of this form in the equilibrium mixture allowed only the identification of some separated ^{1}H-NMR signals. ^{1}H-NMR (500 MHz; $CDCl_3$, −25°): 6.58 (*d*, ^3J = 6.7, H−C(4)); 5.64 (*s*, HO−C(3)); 4.10 (*q*, ^3J = 6.9, $PhSO_2CH$(Me)−C(3)); 2.16 (br. *s*, Me−C(6)); 0.85/0.86 (2*d*, superimposed to *t*, *Me*$_2$CH−C(8)).

1.8. *1,3-Dihydro-3-hydroxy-8-isopropyl-6,11-dimethyl-3-[1-(phenylsulfonyl)ethyl]heptaleno[4,5-c]furan-1-one* (**24**). Compound **15c** (0.10 g, 0.21 mmol) was added at r.t. to a soln. of KOH (0.20 g, 3.57 mmol) in MeOH (6 ml). After stirring for 15 h, the brown mixture was poured into ice/H_2O and acidified to pH 1 with conc. HCl (0.5 ml) to give a yellow precipitate. The mixture was extracted with AcOEt (3 × 50 ml). The AcOEt extracts were washed with brine (10 ml), dried (Na_2SO_4), and the solvent was evaporated. The solid residue was recrystallized from Et_2O/hexane to give **24** (0.40 g, 41%) as a yellowish powder. M.p. 135–136°. R_f (hexane/AcOEt 1:1) 0.61. ^{1}H-NMR ($CDCl_3$): 8.01 (*dd*, ^3J = 7.1, ^4J = 1.5, H_o of $PhSO_2$); 7.67 (*tt*, ^3J = 7.5, ^4J = 1.3, H_p of $PhSO_2$); 7.58 (*t*, ^3J = 7.1, H_m of $PhSO_2$), 7.13 (*dd*, ^3J = 6.7, ^4J = 0.5, H−C(4)); 7.11 (*s*, HO−C(3)), 6.35 (*dd*, ^3J = 6.8, ^4J = 1.4, H−C(5)); 6.27 (*dd*, ^3J = 6.3, ^4J = 1.4, H−C(10)); 6.14 (*d*, ^3J = 6.3, H−C(9)); 5.68 (*s*, H−C(7)); 3.92 (*q*, ^3J = 7.0, $PhSO_2CH$(Me)−C(3)); 2.40 (*sept.*, ^3J = 6.8, Me_2CH); 2.31 (*s*, Me−C(6)); 2.17 (*d*, ^4J = 0.7, Me−C(11)); 0.99 (*d*, ^3J = 6.9, $PhSO_2CH$(*Me*)−C(3)); 0.98 (*d*, ^3J = 6.9, *Me*$_2$CH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 168.64 (O=C); 151.42/139.39/136.15 (3*s*); 134.89/134.44 (2*d*); 132.68/131.14 (2*s*); 130.94 (*d*); 130.80 (*s*); 130.58/128.73/127.47/126.77 (4*d*); 126.68 (*s*); 124.45 (*d*); 103.30 (*s*, C(3)); 64.99 (*d*, $PhSO_2CH$(Me)−C(3)); 35.99 (*d*, Me_2CH); 25.41/23.91 (2*q*, Me); 22.88/22.43 (2*q*, Me_2CH); 12.55 (*q*, $PhSO_2CH$(*Me*)−C(3)). EI-MS: 464 (29, $M^{+\cdot}$), 322 (55), 307 (100), 279 (40), 251 (25), 235 (41), 207 (92), 191 (72), 178 (63), 165 (79), 152 (52), 110 (24), 78 (26).

2. *Benzo[*a*]heptalene-Forming Reactions.* – 2.1. *9-Isopropyl-1,7,12-trimethyl-3-(phenylsulfonyl)benzo[*a*]-heptalene-2,4-diol* (**3c**) *and 9-Isopropyl-7,12-dimethyl-3-(phenylsulfonyl)benzo[*a*]heptalene-2,4-diol* (**3b**). 2.1.1. *First Approach* (formation of **3c** and **3b**). A 2.5M soln. of BuLi (0.76 ml, 1.90 mmol) was added drop by drop under Ar to a soln. of $EtSO_2Ph$ (0.29 g, 1.70 mmol) in anh. THF (15 ml), kept at 0°. After 30 min at 0°, a white precipitate had been formed. The mixture was cooled to −78°, and a soln. of **2′a** (0.51 g, 1.50 mmol) in THF (5 ml) was added within 5 min. The brown mixture was stirred at −78° for 2 h, whereupon a part of **2′a** had reacted. In another flask, lithiated $MeSO_2Ph$ was generated under Ar by stirring the sulfone (0.703 g, 4.50 mmol) and BuLi (2.40 ml, 6.0 mmol) in THF (15 ml) at 0° for 30 min. After cooling to −78°, the soln. was added *via* a cannula drop by drop to the above mixture, kept at −60°. The brown soln. was warmed within 3 h to −5°. After addition of more BuLi (2.40 ml, 6.0 mmol) at −5°, the yellow-red soln. was stirred at r.t. for 15 h. Usual workup led to a solid that was subjected to CC (SiO_2 (170 g); hexane/AcOEt 3:1). A first fraction yielded **3c** (0.495 g, 72%) as yellow crystals. A second fraction gave **3b** (0.115 g, 17%) as yellow crystals (m.p. 207–208° (Et_2O/hexane); lit. 207–208° [1]. R_f (hexane/AcOEt 2:1) 0.49).

Data of **3c**. M.p. 208.6–209.5° (CH_2Cl_2/hexane). R_f (hexane/AcOEt 2:1) 0.63. IR (KBr): 3348*s*, 3237*s*, 3013*w*, 2960*m*, 1586*m*, 1569*m*, 1556*m*, 1450*m*, 1437*m*, 1421*m*, 1350*m*, 1270*m*, 1242*m*, 1221*m*, 1134*s*, 1113*m*, 1076*m*, 1025*w*, 996*w*, 860*m*, 803*m*, 741*m*, 721*m*, 687*m*, 633*m*, 607*s*, 559*w*, 452*w*, 411*w*. ^{1}H-NMR (600 MHz, $CDCl_3$): 9.08 (*s*, HO–C(4)); 8.89 (*s*, HO–C(2)); 7.97 (*dd*, ^3J = 8.3, ^4J = 1.2, H_o of $PhSO_2$); 7.65 (*tt*, ^3J = 7.5, ^4J = 1.0, H_p of $PhSO_2$); 7.54 (*t*, ^3J = 8.2, H_m of $PhSO_2$); 7.08 (*d*, ^3J = 11.8, H–C(5)); 6.41 (*dd*, ^3J = 11.9, ^4J = 1.2, H–C(11)); 6.40 (*dd*, ^3J = 11.7, ^4J = 1.8, H–C(10)); 6.20 (*d*, ^3J = 11.9, H–C(6)); 5.77 (*s*, H–C(8)); 2.56 (*sept.*, ^3J = 6.8, Me_2CH–C(9)); 1.88 (*s*, Me–C(1)); 1.67 (*d*, ^4J = 0.7, Me–C(7)); 1.49 (*s*, Me–C(12)); 1.14/1.12 (2*d*, ^3J = 6.9/6.9, Me_2CH–C(9)). ^{13}C-NMR (125 MHz, $CDCl_3$): 154.53 (C(2)); 150.45 (C(4)); 147.26 (C(9)); 144.92 (C(12b)); 141.38 (C_{ip} of $PhSO_2$); 135.13 (C(11)); 134.24 (C_p of $PhSO_2$); 133.24 (C(7a)); 131.73 (C(12)); 131.62 (C(6, 10)); 130.21 (C(12a)); 129.55 (C_o of $PhSO_2$); 128.75 (*s*, C(7)); 126.15 (C_m of $PhSO_2$); 124.88 (C(5)); 121.54(C(8)); 119.11(C(4a)); 115.84 (C(1)); 107.48 (C(3)); 34.61 (Me_2CH–C(9)); 22.89/22.83 (Me_2CH–C(9)); 18.14 (Me–C(12)); 16.67 (Me–C(7)); 11.89 (Me–C(1)). EI-MS: 460 (100, $M^{+\cdot}$), 445 (21), 390 (16), 338 (33), 273 (20), 193 (25), 157 (28), 105 (22), 91 (36). Anal. calc. for $C_{28}H_{28}O_4S$ (460.59): C 73.02, H 6.13, S 6.96; found: C 73.31, H 6.71, S 5.96. X-Ray crystal structure: *cf. Fig. 1* and *Table 6*.

2.1.2. *Second Approach* (formation of **3c**). BuLi soln. (0.69 ml, 1.72 mmol) was added at −5° to a soln. of $EtSO_2Ph$ (0.22 g, 1.29 mmol) in anh. THF (10 ml) under Ar. After stirring during 30 min at 0°, a white precipitate had been formed. The mixture was cooled to −40°, and a soln. **15b** (0.20 g, 0.43 mmol) in THF (4 ml) was added slowly within 5 min. The temp. was elevated over 3 h to −10°, and more BuLi (0.69 ml, 1.72 mmol) was slowly added, whereupon the color of the mixture changed immediately to dark reddish-brown. The mixture was allowed to warm to r.t., and stirring was continued for 6 h. The mixture was poured on ice/H_2O, acidified with 1N aq. HCl soln. (50 ml), and extracted with AcOEt. The org. phase was washed with H_2O (100 ml) and brine (100 ml), dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was purified by CC. Recrystallization gave **3c** (0.055 g, 28%) as yellow crystals.

2.1.3. *Third Approach* (formation of **3c**). BuLi soln. (0.69 ml, 1.72 mmol) was added at −5° to a soln. of $MeSO_2Ph$ (0.20 g, 1.29 mmol) in anh. THF (10 ml) under Ar. After stirring for 30 min at 0°, the mixture was cooled to −40°, and a soln. of **16c** (0.20 g, 0.43 mmol) in THF (4 ml) was added within 5 min. The above reaction conditions and workup gave **3c** (0.047 g, 24%).

2.2. *9-Isopropyl-4,7,12-trimethyl-2-(phenylsulfonyl)benzo[*a*]heptalene-1,3-diol* (**4c**), *9-Isopropyl-1,7,12-trimethyl-3-(phenylsulfonyl)benzo[*a*]heptalene-2,4-diol* (**3c**), *and 9-Isopropyl-7,12-dimethyl-3-(phenylsulfonyl)-benzo[*a*]heptalene-2,4-diol* (**3b**). 2.2.1. *First Approach* (formation of **4c**, **3c**, and **3b**). Under Ar, a 2.5M soln. of BuLi (0.76 ml, 1.90 mmol) was added drop by drop to an ice-cold soln. of $MeSO_2Ph$ (0.265 g, 1.70 mmol) in anh. THF (15 ml). After stirring for 30 min at 0°, a white precipitate had been formed. The mixture was cooled to −78°, and a soln. of **2′a** (0.51 g, 1.50 mmol) in THF (5 ml) was added within 5 min. The brown mixture was stirred at −78° for 2 h, whereupon part of **2′a** had been consumed. In another flask, under Ar and at 0°, lithiated $EtSO_2Ph$ was generated from BuLi (2.40 ml, 6.0 mmol) and ethyl phenyl sulfone (0.766 g, 4.5 mmol) in anh. THF (15 ml) in the usual way. This lithiated sulfone, cooled to −78°, was added drop by drop *via* a cannula to the above mixture, kept at −40°. The brown soln. was warmed within 3 h to −5°. After addition of more BuLi (2.40 ml, 6.0 mmol) at −5°, the yellow-red soln. was stirred during 15 h at r.t. The usual workup procedure led to a solid, which was purified by CC (SiO_2 (170 g); hexane/AcOEt 3:1). A first fraction consisted of **4c** (0.18 g, 26%; ^{1}H-NMR analysis) and **3c** (0.145 g, 21%; ^{1}H-NMR analysis). A second fraction contained **3b** (0.12 g, 18%).

2.2.2. *Second Approach* (formation of **4c**). BuLi soln. (2.88 ml, 7.2 mmol) was added at 0° to a soln. of $MeSO_2Ph$ (0.836 g, 5.34 mmol) in anh. THF (15 ml) under Ar. After stirring for 30 min at 0°, a white precipitate

had been formed. The mixture was cooled to $-40°$, and a soln. of **15c** (0.640 g, 1.34 mmol) in THF (5 ml) was added slowly within 5 min. The temp. was raised during 3 h to 10–12°, and a 1.5M soln. of MeLi·LiBr in hexane (4 ml, 6 mmol) was slowly added. Immediately, the color of the mixture changed to a dark reddish-brown. Stirring was continued for 2 h. Then, ice-water was added, and the mixture was acidified with 1N aq. HCl (50 ml), followed by extraction with AcOEt. The org. phase was washed with brine (100 ml), dried (Na_2SO_4), and evaporated. Purification of the crude product by FC and recrystallization (AcOEt/hexane) yielded pure **4c** (0.115 g, 19%). Yellow crystals. M.p. 205.0–206.2°. R_f (hexane/AcOEt 2:1) 0.67. ^{1}H-NMR (600 MHz, $CDCl_3$): 10.02 (*s*, HO–C(3)); 7.97 (*dd*, $^3J = 8.2$, $^4J = 0.9$, H_o of $PhSO_2$); 7.58 (*tt*, $^3J = 7.2$, $^4J = 1.3$, H_p of $PhSO_2$); 7.49 (*t*, $^3J = 7.9$, H_m of $PhSO_2$); 6.91 (*d*, $^3J = 12.1$, H–C(5)); 6.56 (*s*, HO–C(1)); 6.41 (*dd*, $^3J = 11.9$, $^4J = 1.1$, H–C(10); 6.39 (d, $^3J = 11.9$, H–C(11)); 6.33 (*d*, $^3J = 12.2$, H–C(6)); 5.76 (*s*, H–C(8)); 2.56 (*sept.*, $^3J = 6.9$. Me_2CH); 2.21 (*s*, Me–C(4)); 1.69 (*s*, Me–C(7)); 1.38 (*s*, Me–C(12)); 1.13/1.12 (2*d*, $^3J = 6.9$, Me_2CH). ^{13}C-NMR (150 MHz, $CDCl_3$): 152.89 (C(3)); 148.38 (C(1)); 147.37 (C(9)); 143.98 (C(4a)); 142.00 (C_{ip} of $PhSO_2$); 135.89 (C(6)); 135.70 (C(7a)); 134.86 (C(11)); 134.43 (C(12)); 133.48 (C_p of $PhSO_2$); 131.92 (C(10)); 128.84 (C_m of $PhSO_2$); 128.74 (C(5)); 128.09 (C(7)); 126.93 (C_o of $PhSO_2$); 126.09 (C(12a)); 121.80 (C(8)); 117.73 (C(12b)); 115.73 (C(4)); 109.05 (C(2)); 34.63 (Me_2CH); 22.79/22.78 (Me_2CH); 18.20 (Me–C(12)); 16.72 (Me–C(7)); 11.22 (Me–C(4)). Anal. calc. for $C_{28}H_{28}O_4S$ (460.59): C 73.02, H 6.13, S 6.96; found: C 72.79, H 6.18, S 6.94. X-Ray crystal structure: *cf. Fig. 3* and *Table 6*.

2.2.3. *Third Approach* (formation of **4c**). $EtSO_2Ph$ (0.22 g, 1.29 mmol) in anh. THF (10 ml) was lithiated with BuLi soln. (0.69 ml, 1.72 mmol) in the usual manner. The mixture was cooled to $-40°$, and a soln. **16b** (0.20 g, 0.43 mmol) in THF (4 ml) was added slowly within 5 min. The above reaction conditions and workup gave pure, crystalline **4c** (0.057 g, 29%).

2.3. *9-Isopropyl-7,12-dimethyl-3-(morpholinosulfonyl)benzo[*a*]heptalene-2,4-diol* (**3a**). 2.3.1. *From* **16b** *and Lithiomethyl Morpholino Sulfone.* Methyl morpholino sulfone (0.084 ml, 0.51 mmol) was dissolved in dry THF (8 ml). The soln. was cooled to $-5°$, and BuLi soln. (0.25 ml, 0.61 mmol) was added slowly. While stirring at $-5°$, a white precipitate was formed. After 30 min, the mixture was cooled to $-40°$, and a soln. of **16b** (0.08 g, 0.17 mmol) in THF (2 ml) was added. The temp. was raised within 3 h to $-5°$. Additional BuLi soln. (0.28 ml, 0.70 mmol) was added, and the mixture was allowed to warm to r.t. (30 min). After stirring at r.t. for 4 h, the mixture was poured onto ice and 10% aq. HCl soln. (100 ml). The aq. phase was extracted with AcOEt (2 × 20 ml). The org. phase was washed with H_2O (3 × 30 ml), brine (1 × 30 ml), and dried (Na_2SO_4). The solvent was distilled off, and the residue was chromatographed (SiO_2 (80 g); hexane/AcOEt 2:1) to afford **3a** (0.027 g, 35%) as yellow crystals identical to an authentic probe (*cf.* [1]).

2.3.2. *From* **15a** *and* $LiCH_2SO_2Ph$. Following the above procedure, $MeSO_2Ph$ (0.08 g, 0.51 mmol) was reacted with BuLi soln. (0.25 ml, 0.61 mmol) and **15a** (0.081 g, 0.17 mmol) in THF (10 ml). After addition of more BuLi soln. (0.28 ml, 0.7 mmol) at $-5°$, the mixture was stirred at r.t. for 4 h. The usual workup, followed by FC (SiO_2 (80 g); hexane/AcOEt 2:1), gave pure **3a** (0.021 g, 26%) as yellow crystals (*cf.* [1]).

2.4. *9-Isopropyl-7,12-dimethyl-3-(phenylsulfonylbenzo[*a*]heptalene-2,4-diol* (**3b**). 2.4.1. *From* **16a** *and* $LiCH_2SO_2Ph$. Following the procedure of *Sect. 2.3.1*, $MeSO_2Ph$ (0.16 g, 1.02 mmol) was reacted with BuLi soln. (0.50 ml, 1.22 mmol) and **16a** (0.162 g, 0.34 mmol) in THF (15 ml). After addition of more BuLi soln. (0.56 ml, 1.4 mmol) at $-5°$, the mixture was stirred at r.t. for 4 h. The usual workup, followed by FC (SiO_2 (130 g); hexane/AcOEt 2:1) gave pure **3b** (0.056 g, 37%) as yellow crystals (*cf.* [1]).

2.4.2. From **15b** *and Lithiomethyl Morpholino Sulfone.* Following the procedure of *Sect. 2.3.1*, methyl morpholino sulfone (0.084 g, 0.51 mmol) was reacted with BuLi soln. (0.25 ml, 0.61 mmol) and **15b** (0.08 g, 0.17 mmol) in THF (10 ml). After addition of more BuLi soln. (0.28 ml, 0.70 mmol) at $-5°$, the mixture was stirred at r.t. during 4 h. The usual workup, followed by FC (SiO_2 (80 g); hexane/AcOEt 2:1) gave pure **3b** (0.018 g, 23%) as yellow crystals.

2.5. *8-Isopropyl-6,11-dimethyl-2-(morpholinosulfonyl)-3-[(phenylsulfonyl)methyl]-1*H*-cyclopenta[*d*]heptalen-1-one* (**11ab**). BuLi soln. (0.34 ml, 0.84 mmol) was added at $-5°$ to a soln. of methyl morpholino sulfone (0.104 g, 0.63 mmol) in anh. THF (10 ml) under Ar. After stirring for 30 min at 0°, a white precipitate had been formed. The mixture was cooled to $-78°$, and a soln. of **15b** (0.10 g, 0.21 mmol) in THF (2 ml) was added drop by drop within 5 min. After additional stirring at $-78°$ for 1 h, the temp. was raised slowly within 2 h to $-10°$. The mixture was poured onto ice. Usual workup and FC (SiO_2 (80 g); hexane/AcOEt 1:1) gave **11ab** (0.027 g, 22%) as a yellow microcrystalline powder. M.p. 258–259° (AcOEt). R_f (hexane/AcOEt 3:5) 0.51. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.00 (*dd*, $^3J = 7.1$, $^4J = 0.8$, H_o of $PhSO_2$); 7.68 (*t*, $^3J = 7.4$, H_p of $PhSO_2$); 7.58 (*t*, $^3J = 7.7$, H_m of $PhSO_2$); 6.85 (*d*, $^3J = 7.2$, H–C(4)); 6.47 (*dd*, $^3J = 7.0$, $^4J = 1.0$, H–C(10)); 6.29 (*m*, H–C(5), H–C(9)); 6.19 (*s*, H–C(7)); 5.07/4.88 (*AB*, $^2J_{AB} = 12.8$, $PhSO_2CH_2$–C(3)); 3.71 (*m*, $O(CH_2CH_2)_2N$); 3.52/3.48 (2*m*, $O(CH_2CH_2)_2N$); 2.53 (*sept.*, $^3J = 6.8$, Me_2CH–C(8)); 2.25 (*s*, Me–C(6)); 2.18 (*s*, Me–C(11)); 1.14/1.12

(2*d*, ^3J = 6.9/6.8, *Me*$_2$CH–C(8)). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 181.49 (O=C); 151.43/148.71/144.63/139.94/139.62/138.19 (6*s*); 137.88 (C(2)); 134.28 (*d*); 132.86/131.52 (2*s*); 131.35/129.73/129.43/128.34/126.68/126.63 (6*d*); 125.14 (*s*); 66.96 (O(*C*H$_2$CH$_2$)$_2$N), 52.96 (PhSO$_2$*C*H$_2$–C(3)); 46.08 (O(CH$_2$*C*H$_2$)$_2$N); 35.97 (Me$_2$*C*H–C(8)); 25.82, 24.56 (Me–C(6), Me–C(11)); 23.01/22.92 (*Me*$_2$CH–C(8)).

2.6. *8-Isopropyl-6,11-dimethyl-2-(phenylsulfonyl)-3-[(morpholinosulfonyl)methyl]-1*H*-cyclopenta[*d*]heptalen-1-one* (**11ba**). BuLi soln. (0.34 ml, 0.84 mmol) was added at −5° to a soln. of methyl phenyl sulfone (0.098 g, 0.63 mmol) in anh. THF (10 ml) under Ar. After stirring for 30 min at 0°, a white precipitate had been formed. The mixture was cooled to −78°, and a soln. of **15a** (0.10 g, 0.21 mmol) in THF (2 ml) was added drop by drop within 5 min. After additional stirring at −78° for 1 h, the temp. was raised slowly within 2 h to −10°. The mixture was poured onto ice. Usual workup and FC (SiO_2 (80 g); hexane/AcOEt 1:1) gave **11ba** (0.024 g, 20%) as an orange microcrystalline powder. M.p. 251–252° (AcOEt). R_f (hexane/AcOEt 3:5) 0.52. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.22 (*dd*, ^3J = 6.9, ^4J = 1.2, H$_o$ of PhSO$_2$); 7.53 (*tt*, ^3J = 6.2, ^4J = 1.4, H$_p$ of PhSO$_2$); 7.49 (*t*, ^3J = 6.8, H$_m$ of PhSO$_2$); 6.91(*d*, ^3J = 6.7, H–C(4)); 6.39 (*dd*, ^3J = 6.9, ^4J = 1.3, H–C(10)); 6.28 (*m*, H–C(5), H–C(9)); 6.13 (*d*, ^4J = 1.3, H–C(7)); 5.04/4.96 (*AB*, $^2J_{AB}$ = 12.5, CH$_2$–C(3)); 3.80 (*m*, O(C*H*$_2$CH$_2$)$_2$N); 3.46 (*m*, O(CH$_2$C*H*$_2$)$_2$N); 2.47 (*sept.*, ^3J = 6.8, Me$_2$C*H*–C(8)); 2.14 (*d*, ^4J = 0.7, Me–C(6)), 2.12 (*s*, Me–C(11)); 1.09/1.07 (2*d*, ^3J = 6.9/6.7, *Me*$_2$CH–C(8)). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 180.12 (O=C); 153.32/148.45/144.36/140.57/140.10/139.94/138.04 (7*s*); 137.40 (C(2)); 133.65 (*d*); 132.51 (*s*); 131.46 (*d*); 131.20 (*s*); 129.58/129.09/128.60/128.47/126.61/126.02/125.31 (7*d*); 125.03 (*s*); 66.49 (O(*C*H$_2$CH$_2$)$_2$N); 46.19 (O(CH$_2$*C*H$_2$)$_2$N); 45.01 (*C*H$_2$–C(3)); 35.79 (Me$_2$*C*H); 25.76, 24.32 (Me–C(6), Me–C(11)); 22.86/22.73 (*Me*$_2$CH).

3. *Synthesis of 9-Isopropyl-1,2,3-trimethoxy-4,7,12-trimethylbenzo[*a*]heptalene* (**23**). 3.1. *9-Isopropyl-1,3-dimethoxy-4,7,12-trimethyl-2-(phenylsulfonyl)benzo[*a*]heptalene* (**20**). A suspension of K_2CO_3 (0.4 g) in anh. acetone (10 ml) was cooled to 0°, and a soln. of **4c** (0.10 g, 0.22 mmol) in acetone (3 ml) was added under stirring. To this mixture, MeI (0.80 ml) was added drop by drop, and stirring was continued for 8 h at r.t. The mixture was diluted with H_2O (50 ml) and extracted with AcOEt (2 × 30 ml). The org. layer was separated and dried (Na_2CO_3). Almost pure **20** (0.103 g, 96%) was obtained after evaporation of the solvent. It was recrystallized from Et_2O to give **20** as a yellow, microcrystalline powder. M.p. 183.1–184.3° (Et_2O/hexane). R_f (hexane/AcOEt 2:1) 0.63. ^{1}H-NMR (600 MHz, $CDCl_3$): 7.90 (*dd*, ^3J = 7.0, ^4J = 1.2, H$_o$ of PhSO$_2$); 7.49 (*tt*, ^3J = 7.2, ^4J = 1.4, H$_p$ of PhSO$_2$); 7.42 (*t*, ^3J = 7.1, H$_m$ of PhSO$_2$); 6.89 (*d*, ^3J = 12.1, H–C(5)); 6.39 (*d*, ^3J = 12.1, H–C(6)); 6.36 (*d*, ^3J = 11.9, H–C(11)); 6.33 (*dd*, ^3J = 11.9, ^4J = 1.2, H–C(10)); 5.78 (*s*, H–C(8)); 3.92 (*s*, MeO–C(3)); 3.58 (*s*, MeO–C(1)); 2.55 (*sept.*, ^3J = 6.7, Me$_2$C*H*); 2.28 (*s*, Me–C(4)); 1.75 (*s*, Me–C(7)); 1.21 (*s*, Me–C(12)); 1.12/1.11 (2*d*, ^3J = 6.9/6.8, *Me*$_2$CH). ^{13}C-NMR (150 MHz, $CDCl_3$): 156.01 (C(3)); 154.26 (C(1)); 147.24 (C(9)); 144.71 (C(4a)); 144.57 (C$_{ip}$ of PhSO$_2$); 136.73 (C(7a)); 135.89 (C(6), C(11)); 134.44 (C(12)); 132.26 (C$_p$ of PhSO$_2$)); 131.16 (C(10)); 129.02 (C(12b)); 128.66 (C(7)); 128.44 (C(5)); 128.25 (C$_m$ of PhSO$_2$); 127.71 (C(2)); 126.93 (C(12a)); 126.86 (C$_o$ of PhSO$_2$); 126.26 (C(4)); 122.58 (C(8)); 63.21 (MeO–C(3)); 62.27 (MeO–C(1)); 34.77 (Me$_2$*C*H); 22.83/22.74 (*Me*$_2$CH); 18.65 (Me–C(12)); 16.91 (Me–C(7)); 12.51 (Me–C(4)).

3.2. *9-Isopropyl-1,3-dimethoxy-4,7,12-trimethylbenzo[*a*]heptalene* (**21**). Under Ar, $TiCl_4$ (0.26 ml, 2.4 mmol) was added drop by drop at −78° to anh. THF (8 ml). A 1M soln. of $LiAlH_4$ (7.1 ml, 7.1 mmol) in THF was then slowly added, whereby a dark grey-colored suspension was formed, which was allowed to warm to −10° within 3 h. Then, the mixture was cooled again to −78°, and a soln. of **20** (0.090 g, 0.184 mmol) in THF (4 ml) was added slowly under Ar. After 0.5 h at −78°, the temp. was raised within 2 h to r.t., and stirring was continued for an additional 2 h. The still dark-grey mixture was added slowly to a sat. aq. soln of NH_4Cl (150 ml), and the mixture was stirred for *ca.* 1.5 h. After extraction with AcOEt (3 × 50 ml), the org. layer was washed with H_2O (50 ml), brine (50 ml), and dried (Na_2SO_4). Evaporation *in vacuo* led to a solid, which was purified by FC (SiO_2 (70 g); hexane/AcOEt 4:1) to give pure **21** (0.056 g, 87%). Yellow crystalline powder. M.p. 132.5–132.9° (Et_2O/hexane). R_f (hexane/AcOEt 3:1) 0.75. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.99 (*d*, ^3J = 12.0, H–C(5)); 6.62 (*s*, H–C(2)); 6.44 (*d*, ^3J = 11.8, H–C(11)); 6.34 (*dd*, ^3J = 11.8, ^4J = 1.2, H–C(10)); 6.26 (*d*, ^3J = 12.0, H–C(6)); 5.74 (*s*, H–C(8)); 3.84 (*s*, MeO–C(3)); 3.68 (*s*, MeO–C(1)); 2.58 (*sept.*, ^3J = 6.9, Me$_2$C*H*); 2.22 (*s*, Me–C(4)); 1.72 (*s*, Me–C(7)); 1.56 (*s*, Me–C(12)); 1.16/1.15 (2*d*, ^3J = 6.9/6.8, *Me*$_2$CH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 156.75 (C(3)); 154.52 (C(1)); 146.34 (C(9)); 138.03/136.31 (2*s*); 135.59 (C(11)); 133.25 (C(6)); 132.19 (*s*); 130.15 (C(10)); 129.67 (C(5)); 128.31/127.28/122.06 (3*s*); 121.28 (C(8)); 116.64 (*s*); 98.56 (C(2)); 57.27/55.97 (MeO–C(1,3)); 34.63 (Me$_2$*C*H); 23.05/22.81 (*Me*$_2$CH); 18.96 (Me–C(12)); 16.72 (Me–C(7)); 11.20 (Me–C(4)). X-Ray crystal structure: see *Table 6*.

3.3. *9-Isopropyl-1,3-dimethoxy-4,7,12-trimethylbenzo[*a*]heptalen-2-ol* (**22**). Under Ar, a 2.5M soln. of BuLi (0.60 ml, 1.51 mmol) was added drop by drop to a soln. of **21** (0.075 g, 0.215 mmol) in anh. THF (20 ml), cooled to 0°. After stirring for 4 h at 0°, CuBr (0.217 g, 1.51 mmol) was added to the resulting dark brown soln. The

mixture was stirred at 0°, until all cuprous bromide had disappeared (*ca.* 3 h). The vessel, containing the organocopper compound, was then equipped with a *Pasteur* pipette with an attached drying tube (filled with P_2O_5 (*Fluka*) with moisture indicator). Dry air was drawn at 0° for 2 h through the reaction mixture *via* the pipette by applying a slight vacuum at the reaction vessel. Thereby, the color of the mixture became deep green. Ice-cold 1M aq. HCl (30 ml) was added, and the resulting mixture was extracted with AcOEt (100 ml). The org. layer was washed with brine (2 × 50 ml) and dried ($MgSO_4$). The residue was purified by FC (SiO_2; hexane/AcOEt 3:1) to give **22** (0.046 g, 59%). Yellow crystals. M.p. 147–148° (Et_2O/hexane). R_f (hexane/AcOEt 3:1) 0.55. ^{1}H-NMR (600 MHz, $CDCl_3$): 6.89 (*d*, ^3J = 12.0, H–C(5)); 6.44 (*d*, ^3J = 11.9, H–C(11)); 6.35 (*dd*, ^3J = 11.9, ^4J = 1.2, H–C(10)); 6.21 (*d*, ^3J = 12.0, H–C(6)); 5.75 (*s*, H–C(8)); 5.69 (*s*, HO–C(2)); 3.84 (*s*, MeO–C(3)); 3.64 (*s*, MeO–C(1)); 2.56 (*sept.*, ^3J = 6.9, Me_2CH); 2.28 (*s*, Me–C(4)); 1.74 (*s*, Me–C(7)); 1.58 (*s*, Me–C(12)); 1.13/1.12 (2*d*, ^3J = 6.9/6.8, Me_2CH). ^{13}C-NMR (150 MHz, $CDCl_3$): 146.85/144.98/143.16/141.72 (4*s*); 135.97 (C(11)); 134.13/133.19 (2*s*); 131.46 (C(6)); 130.89 (C(10)); 129.55 (C(5)); 128.65/128.54/128.16/127.63 (4*s*); 124.61 (C(4)); 122.49 (C(8)); 61.25 (MeO–C(1); 60.53 (MeO–C(3)); 34.64 (Me_2CH); 22.93/22.81 (Me_2CH); 19.28 (Me–C(12)); 16.93 (Me–C(7)); 12.21 (Me–C(4)). Anal. calc. for $C_{24}H_{28}O_3$ (364.49) C 79.09, H 7.74; found: C 78.92, H 7.67. X-Ray crystal-structure: *cf. Fig. 4* and *Table 6*).

3.4. *Formation of* **23**. K_2CO_3 (0.50 g) was suspended in anh. acetone (10 ml). The mixture was cooled to 0°, and **22** (0.090 g, 0.247 mmol) was added under stirring. To this mixture, MeI (1.0 ml) was added drop by drop, and stirring was continued at r.t. for 8 h. The mixture was diluted with H_2O (20 ml) and extracted with AcOEt (2 × 30 ml). The org. layer was separated and dried (Na_2SO_4). Evaporation *in vacuo* gave pure **23** (0.090 g, 95%) as a yellow oil. R_f (hexane/AcOEt 3:1) 0.73. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.91 (*d*, ^3J = 12.0, H–C(5)); 6.44 (*d*, ^3J = 11.8, H–C(11)); 6.35 (*dd*, ^3J = 11.8, ^4J = 1.1, H–C(10)); 6.25 (*d*, ^3J = 12.0, H–C(6)); 5.75 (*s*, H–C(8)); 3.90 (*s*, MeO–C(2)); 3.84 (*s*, MeO–C(3)); 3.60 (*s*, MeO–C(1)); 2.57 (*sept.*, ^3J = 6.8, Me_2CH); 2.26 (*s*, Me–C(4)); 1.73 (*s*, Me–C(3)); 1.58 (*s*, Me–C(12)); 1.14, 1.13 (2*d*, ^3J = 6.9/6.8, Me_2CH).

4. *X-Ray Crystal-Structure Determinations for Compounds* **3c**, **4c**, **15c**, **16a**, **16b**, **17c**, **19c**, **21**, *and* **22**[9]). All measurements were conducted on a *Nonius KappaCCD* area-detector diffractometer [15] with graphite-monochromated Mo$K\alpha$ radiation (λ = 0.71073 Å) and an *Oxford Cryosystems Cryostream-700* cooler. The data collection and refinement parameters are given in *Table 6*, views of the molecules are shown in *Figs. 1–6*. Except for **4c**, data reduction was performed with HKL DENZO and SCALEPACK [16], and equivalent reflections were merged. Examination of the diffraction images for **4c** revealed that there were two interpenetrating lattices. These lattices could be indexed independently using DIRAX [17], and it was found that they were related by a 180° rotation about the normal to the *xy*-plane, indicating that the crystals were twinned. Several crystals were tested and all possessed the same twinning properties. Integration of the diffraction images and data reduction was performed with EvalCCD [15][18]. The final data set incorporated all reflections from both twin domains with overlapping and nonoverlapping reflections appropriately indexed. Equivalent reflections were not merged because of the nature of the twinned data set. The volume fraction of the major twin domain refined to 0.6528(6). The intensities for each structure were corrected for *Lorentz* and polarization effects, but not for absorption. Each structure was solved by direct methods using SIR92 [19], which revealed the positions of all non-H-atoms. The asymmetric unit of **19c** contained one molecule of the heptalene derivative plus one ordered molecule of Et_2O. In this structure, the isopropyl group and part of its parent heptalene ring were disordered (two conformations). Two positions were defined for C(8), C(9), C(31) and C(32)[10]), and refinement of the site-occupation factors of these two conformations yielded a value of 0.627(9) for the major conformer. Atom C(33) of the isopropyl substituent was common to both conformations. Restraints were applied to all chemically equivalent bond lengths involving disordered heptalene-ring atoms so as to maintain reasonable geometry. Pseudo-isotropic restraints were also applied to the atomic-displacement parameters of some of the disordered atoms. The non-H-atoms of each structure were refined anisotropically. The OH H-atoms in **3c**, **4c**, **19c**, and **22** were placed in the positions indicated by difference-*Fourier* maps and, except for **3c**, their positions were allowed to refine together with individual isotropic displacement parameters. The OH H-atom positions in **3c** were not refined, and each of these H-atoms was assigned a fixed isotropic displacement parameter with a value equal to 1.2U_{eq} of its parent O-atom. All remaining H-atoms in the

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[9]) The supplementary crystallographic data for this paper have been deposited as CCDC 220539–CCDC 220547. These data can be obtained, free of charge, *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

[10]) For C-atoms with numbers > 12, see CCDC.

structures were placed in geometrically calculated positions, and each was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom ($1.5U_{eq}$ for the Me groups of **4c**, **19c**, **21**, and **22**). For **17c**, peaks corresponding to two disordered orientations of the H-atoms of the C(24) Me group were observed in a difference-electron-density map, so these Me H-atoms were defined using two equally occupied orientations. The structures of **3c**, **15c**, **16a**, **16b**, and **17c** were refined on F using full-matrix least-squares procedures, which minimized the function $\Sigma w(|F_o|-|F_c|)^2$. For **4c**, **19c**, **21**, and **22**, the refinement was carried out on F^2 by minimizing the corresponding function based on F^2. Corrections for secondary extinction were applied in the case of **3c** and **21**. Except for **3c** and **15c**, between three and 16 low-angle reflections were omitted from the final refinement of each structure because the observed intensities of these reflections were much lower than the calculated values as a result of being partially obscured by the beam stop. Neutral atom scattering factors for non-H-atoms were taken from [20a], and the scattering factors for H-atoms were taken from [21]. The values of the mass-attenuation coefficients were those of [20b]. All calculations for **4c**, **19c**, **21**, and **22** were performed using SHELXL97 [22], while the teXsan crystallographic software package [23] was used for the remaining structures. The crystallographic diagrams were drawn with ORTEPII [24].

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