Studies for a Variable Synthesis of Colchicinoids: Construction of Ring A on a Heptalene Moiety

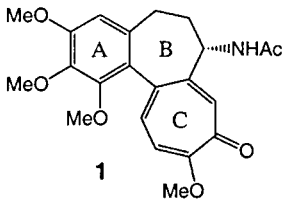
by **Markus Meyer**[1]), **Khaled Abou-Hadeed**, and **Hans-Jürgen Hansen***

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

Dedicated to *Albert Eschenmoser* on the occasion of his 75th birthday

It is shown that heptalene-4,5-dicarboxylates **2**, which react with lithiated methyl sulfones mainly in a *Michael* fashion at C(3) (*cf. Scheme 2*), so that the formation of 3-sulfonylbenzo[*a*]heptalene-2,4-diols **5** is repressed or completely suppressed, can be transformed into corresponding pseudo-esters **15** (*Scheme 4*). These pseudo-esters, on treatment with lithiated methyl sulfones, followed by addition of BuLi, furnish the 3-sulfonylbenzo[*a*]heptalene-2,4-diols **5** in excellent-to-moderate yields without formation of *Michael* adducts or their follow-up products (*cf. Scheme 5* and *6*). The reaction of the pseudo-ester **15a** with Li[^{13}C]H_2SO_2Ph, followed by treatment with non-labeled $LiCH_2SO_2Ph$ and then BuLi, led to the exclusive formation of 3-(phenylsulfonyl)-[1-^{13}C]benzo[*a*]heptalene-2,4-diol **5a*** (*Scheme 9*). This experiment demonstrates that the (phenylsulfonyl)acetyl groups at C(4) and C(5) of the heptalene core retain their individual positions in the course of the benzo[*a*]heptalene-2,4-diol formation. These findings are only compatible with an intramolecular rearrangement mechanism as depicted in *Scheme 10*.

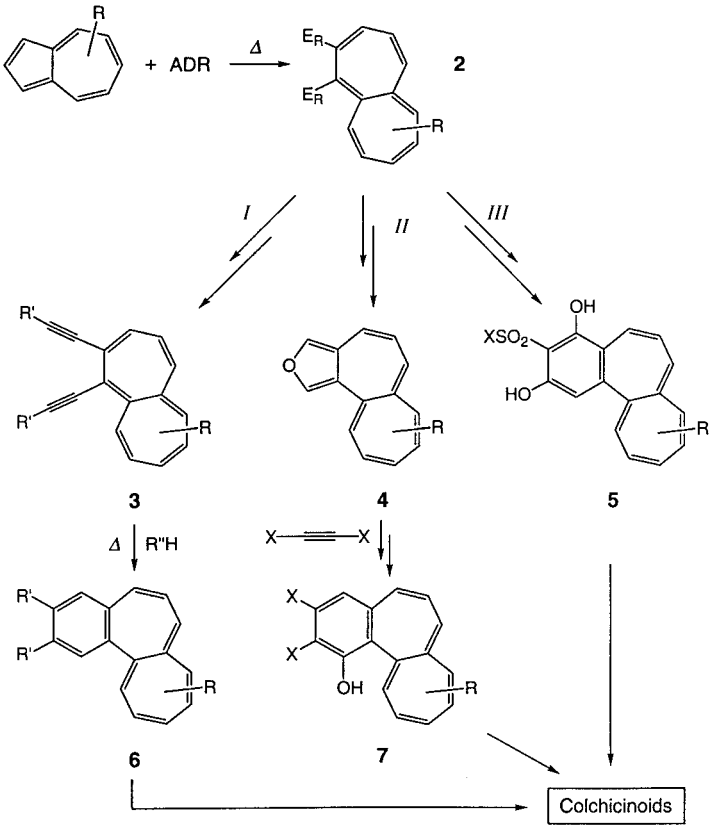
1. Introduction. – All syntheses of colchicine (**1**) and its derivatives have one feature in common, they all start or introduce in later steps the intact aromatic ring A (*cf.* [1][2]). This fact determined two general synthetic strategies, namely, to form ring C on an A–B fragment (A–B → A–B–C) or to start with an A–C part and construct ring B on it (A–C → A–B–C). Progress in heptalene chemistry, especially *Hafner*'s synthesis of heptalene-4,5-dicarboxylates **2** by thermal reaction of azulenes with acetylenedicarboxylates (ADR) (*cf.* [3][4]), allows to test a third general approach to the synthesis of colchicinoids that relies on **2** as B–C component at which the aromatic ring A has to be anellated (B–C → A–B–C). A closer inspection of **2** reveals (*Scheme 1*) that C(4) and C(5) with their two carbonyl C-atoms may represent already 4 of the 6 C-atoms of ring A. In other words, only two additional C-atoms are necessary for a ring-A-forming process. *Scheme 1* presents three modes (*I–III*) for the formation



1

[1]) Part of the planned Ph.D. thesis of *M. M.*

Scheme 1

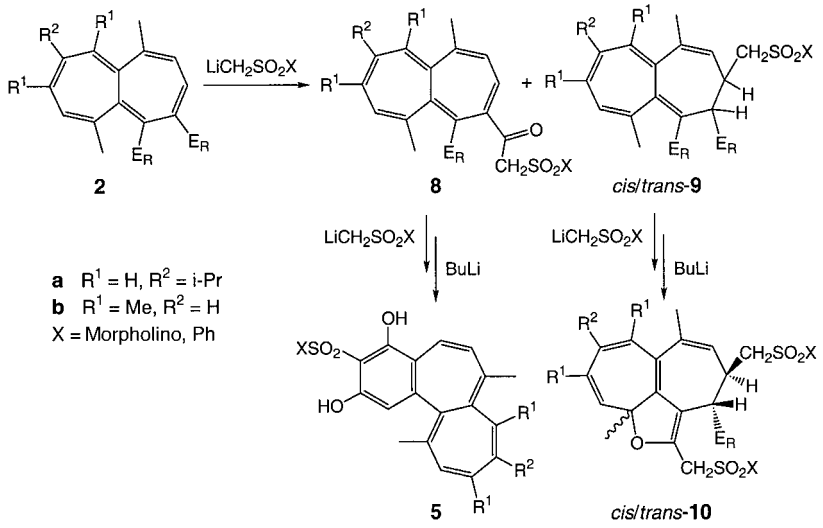


of ring A starting with **2** which we are testing presently. Mode *I* involves a *Bergman* cyclization of corresponding bis(ethynyl)heptalenes **3**, which indeed can be realized[2]). Mode *II* takes advantage of the fact that the heptaleno[1,2-*c*]furans **4** are easily available from **2** (*cf.* [6]) and represent 1,2-bis(methylidene)heptalenes as diene components for *Diels-Alder* reactions. Finally, mode *III* represents a new 'one-pot' benzo-anellation procedure starting directly from **2** and lithiated methyl sulfones as C_1 source that we have found (*cf.* [7][8]). This latter procedure is attractive in a way that it also converts the two oxo functionalities of the heptalene-4,5-diesters into phenolic OH groups at ring A. Here, we report on our investigation of the question whether this benzo-anellation is generally applicable to all types of heptalene-4,5-diesters **2**.

2. Results and Discussion. – A disadvantage of the benzo-anellation of heptalene-4,5-dicarboxylates of type **2** with lithiated methyl sulfones is the fact that the lithiomethyl nucleophiles not only undergo a 1,2-addition to the ester C=O group at C(4) (**2** → **8**), but also a *Michael*-type 1,4-addition at C(3) of **2** (**2** → **9**) in the initiating

[2]) We will report on this procedure soon in this journal [5].

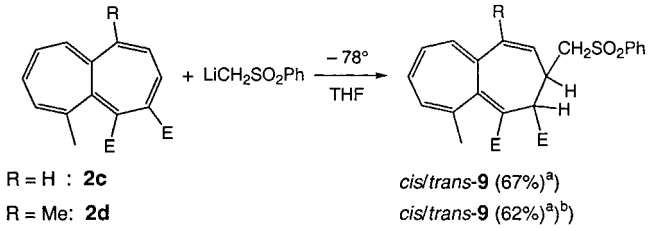
Scheme 2



step of the whole reaction sequence, leading finally to 3-sulfonylbenzo[*a*]heptalene-2,4-diols **5** (**8** → **5**; *Scheme 2*) [7]. The *Michael* adducts with excess of the lithiated methyl sulfones give rise to the formation of the heptaleno[1,10-*bc*]furans **10** (**9** → **10**). In the case of the heptalene-4,5-dicarboxylate **2a**, from guaiazulene and dimethyl acetylenedicarboxylate (ADM), the amount of the formed benzo[*a*]heptalene-2,4-diol **5a** does not exceed 40% with lithiomethyl morpholino sulfone, since 34% of the *Michael*-adduct-derived furans **10a** are also formed. The drawback of 1,4-addition is still much more pronounced in the case of the dimethyl 1,6,8,10-tetramethylheptalene-4,5-dicarboxylate (**2b**). It forms with lithiomethyl phenyl sulfone ($LiCH_2SO_2Ph$) only 6% of the expected benzo[*a*]heptalene-2,4-diol **5b**, but 37% of the furans **10b**. We have demonstrated in the latter case that the 1,4-addition of the lithiomethyl nucleophile can be completely suppressed in favor of the formation of **5b** (65%), when the double-bond-shifted (DBS) isomer of **2b**, namely dimethyl 5,6,8,10-tetramethylheptalene-1,2-dicarboxylate, is applied in the benzo-anellation procedure [8]. However, **2b** and its DBS isomer are separated by an energy barrier (E_a) of > 26 kcal/mol [3]. This is not the case for **2a** and simpler substituted heptalene-4,5-dicarboxylates, all of which are at or below room temperature in thermal equilibrium with their thermodynamically much less favored DBS isomers (*cf.* [9][10]). Moreover, for mono- and dimethyl-substituted heptalene-4,5-dicarboxylates such as **2c** and **2d**, the 1,4-addition of lithiomethyl sulfones becomes the dominating reaction path, and the formation of benzo[*a*]heptalene-2,4-diols is almost completely suppressed (*cf. Scheme 3*) [10].

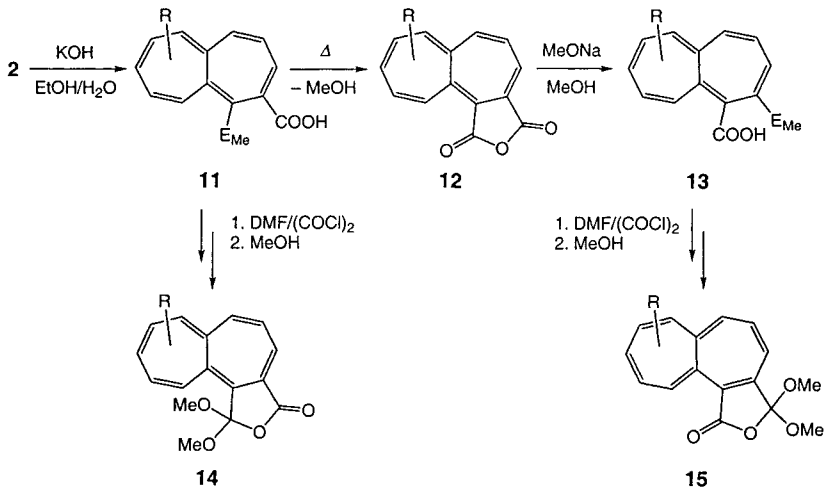
Therefore, we had to search for modified starting materials based on **2** that would not undergo *Michael*-addition reactions with lithiated methyl sulfones, but would still form 3-sulfonylbenzo[*a*]heptalene-2,4-diols **5**. Several years ago, we reported on the formation of the isomeric pseudo-esters **14** and **15** of **2** by reaction of the corresponding half-esters **11** and **13**, respectively, with the (chloromethyl)iminium salt, formed from

Scheme 3



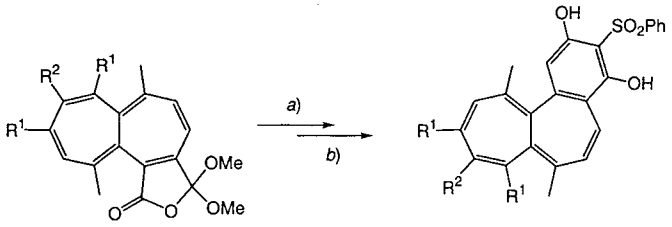
a) *Ca.* 1:2 mixture of the *trans*- and *cis*-form.
b) The 4-(phenylsulfonyl)acetyl derivative **8d** was isolated in 3% yield.

Scheme 4



DMF and oxalyl chloride, followed by addition of MeOH (*Scheme 4*) [11]. The pseudo-esters of type **14** exist at and below room temperature mainly as heptaleno[4,5-*c*]-furan-3-ones, whereas the isomeric pseudo-esters **15** occur as heptaleno[1,2-*c*]furan-1-ones [12]. Since the pseudo-esters of type **14** still contain a conformationally fixed, but sterically well accessible s-*cis*-α,β-unsaturated carbonyl system, we decided to investigate their isomers **15**, which do not possess such an exposed substructure. Indeed, when we reacted the known pseudo-esters **15a** and **15b** [11] with $LiCH_2SO_2Ph$ and then with BuLi under the usual conditions [7], the expected benzo[*a*]heptalene-2,4-diols **5a** and **5b**, respectively, were formed in excellent yields (*Scheme 5*). Furthermore, no *Michael* adducts or their follow-up products were observed under these conditions (*cf.* [7]). To establish the suitability of the pseudo-ester procedure for the synthesis of simpler substituted benzo[*a*]heptalene-2,4-diols **5**, we prepared the pseudo-esters **15c** and **15d** from the corresponding heptalene-4,5-dicarboxylates **2c** and **2d** (*cf.* [3] and *Scheme 4*), respectively, according to our protocol [11][12]. The heptalene-diesters **2c** and **2d** were obtained by thermal reaction of the corresponding

Scheme 5

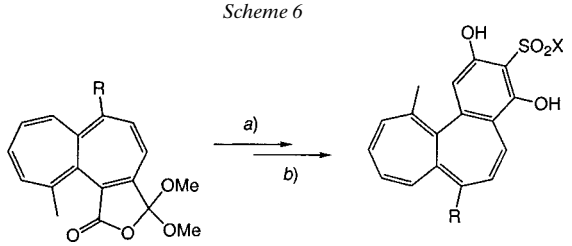


R^1 = H, R^2 = i-Pr: **15a**
R^1 = Me, R^2 = H : **15b**

5a (79%)
5b (76%)

a) 5 Mol-equiv. $LiCH_2SO_2Ph$/THF, $-78 \rightarrow -5°$, 3 h.
b) 4 Mol-equiv. BuLi, $-5 \rightarrow 20°$, 3 h.

Scheme 6



R = H : **15c**

X = Ph : **5c** (15 %[a])/27 %[b]))
X = $N(CH_2CH_2)_2O$: **5c'** (35 %[a]))

R = Me : **15d**

X = Ph : **5d** (21 %[c]))
X = $N(CH_2CH_2)_2O$: **5d'** (41 %[c]))

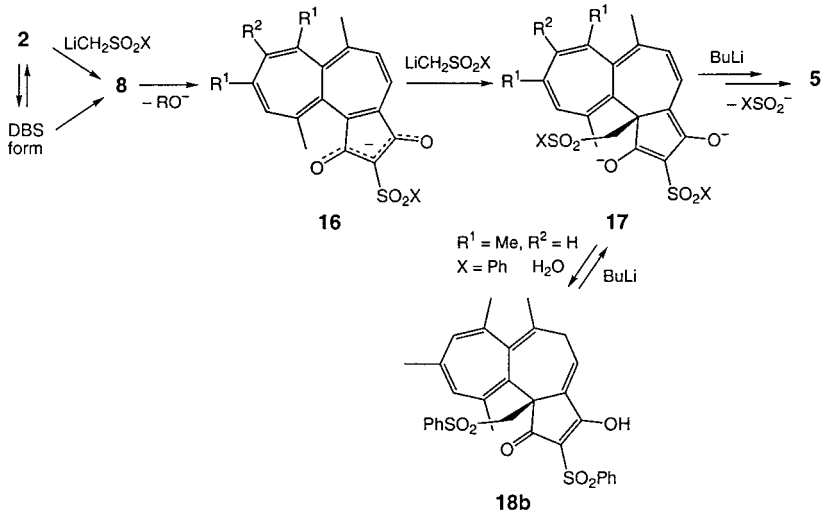
a) and *b*) as in *Scheme 5*; for reaction times of step *b*, see Footnotes.

[a]) 2 h. [b]) 12 h. [c]) 5 h.

azulenes with ADM in toluene at 130° (*cf.* [7][13]) in 40%[3]) and 68% yield, respectively. The pseudo-esters **15c** and **15d** were synthesized from **2c** and **2d** in an overall yield of 46 and 44%, respectively. Both pseudo-esters were reacted in the described manner with $LiCH_2SO_2Ph$, as well as lithiomethyl morpholino sulfone, respectively, followed by treatment with BuLi in excess. Under these conditions, the expected benzo[*a*]heptalene-2,4-diols **5** were formed in acceptable yields (*Scheme 6*), which have not been optimized. The reaction time at 20° plays an important role, since the yield of **5c** could nearly be doubled, when the reaction time was prolonged from 2 to 12 h. On the other hand, elevation of the temperature was not very successful. The results clearly indicated, however, that lithiomethyl morpholino sulfone gave constantly better yields than $LiCH_2SO_2Ph$.

[3]) In addition, we also found dimethyl 10-methylheptalene-4,5-dicarboxylate in a yield of 15% (see *Exper. Part*), in contrast to the results of *Hafner et al.* [3], who observed only the formation of **2c** in 35% yield (tetralin, 207°).

Scheme 7



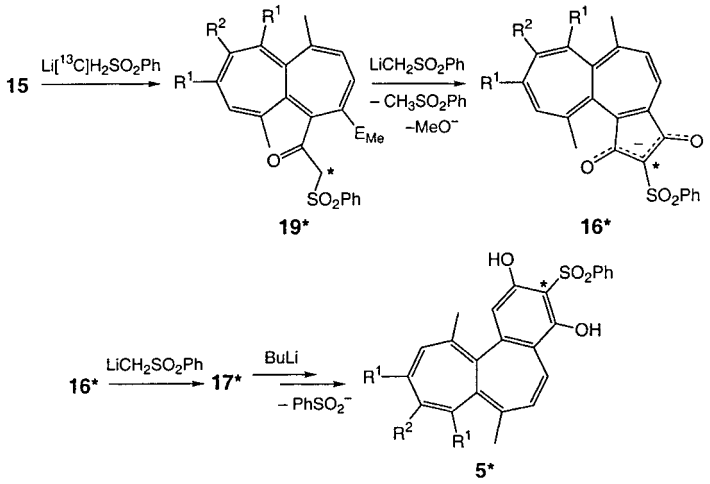
Recently, we have postulated the mechanism depicted in *Scheme 7* (see also *Scheme 2*) for the formation of the 3-sulfonylbenzo[*a*]heptalene-2,4-diols **5** starting from the heptalene-dicarboxylates **2** or their DBS isomers [8], since we had isolated and characterized (X-ray crystal-structure analysis) the intermediate **18b**, derived from the bis-anion **17b**, which, on treatment with an excess of BuLi, rearranged to the corresponding benzo[*a*]heptalene-2,4-diol **5b** in high yield. The formation of **5** from the pseudo-esters **15** seems to be in agreement with this mechanism, since nucleophilic attack of $LiCH_2SO_2X$ (X = Ph) at the C=O group of **15** should lead to a constitutional isomer of **8** with a reversed position of E_{Me} and $PhSO_2CH_2(C{=}O)$ (see **19**; *Scheme 8*), which will undergo cyclization to form the intermediate anion **16**.

The introduction of $Li[^{13}C]H_2SO_2Ph$ would allow to confirm the postulated mechanism (*Scheme 7*), since the ^{13}C-atoms should appear as C(3) of **5** (*Scheme 8*), if **16*** is the precursor for **17***, and the second step is realized with non-labeled $LiCH_2SO_2Ph$. Reaction of **15a** with $Li[^{13}C]H_2SO_2Ph$[4]) in THF at $-70°$ gave the expected **19a***, together with some of the cyclopenta[*d*]heptalen-1(1*H*)-one **20a**** (*Scheme 9*). When purified **19a*** was reacted with $LiCH_2SO_2Ph$ and then with BuLi in THF in the usual manner, but with a much shorter reaction time (0.5 h) for the second step, **5a***, as well as **20a***, were formed in 6 and 10% yield, respectively. The ^{13}C-NMR spectrum ($CDCl_3$) of **5a*** revealed that C(1) carried exclusively all of the ^{13}C-label, in contradiction to what has been discussed above, based on *Schemes 7* and *8*. The ^{13}C-NMR spectrum ($CDCl_3$) of **20a*** showed the ^{13}C-label at C(2) (*cf. Scheme 9*). Moreover, the recovered $MeSO_2Ph$ was free of any excess of [^{13}C] at the Me group. These results clearly demonstrate that **16** cannot be the precursor for the formation of the crucial intermediates of type **17** (*Scheme 7*). There must be an other precursor for

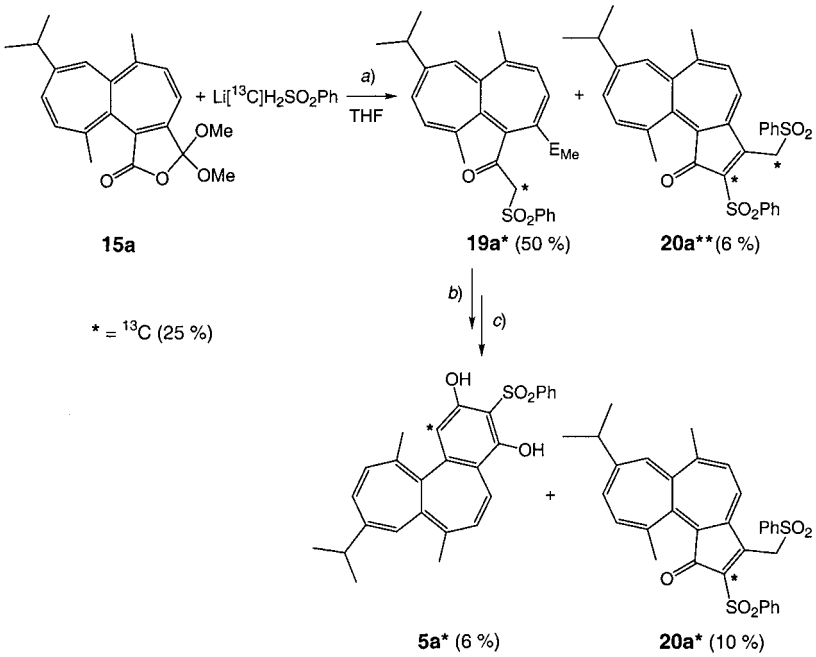
---

4) [^{13}C]Methyl phenyl sulfone can easily be prepared from $[^{13}C]H_3I$ and $PhSO_2Na$ in 1,2-dimethoxyethane in the presence of Bu_4NBr.

Scheme 8



Scheme 9



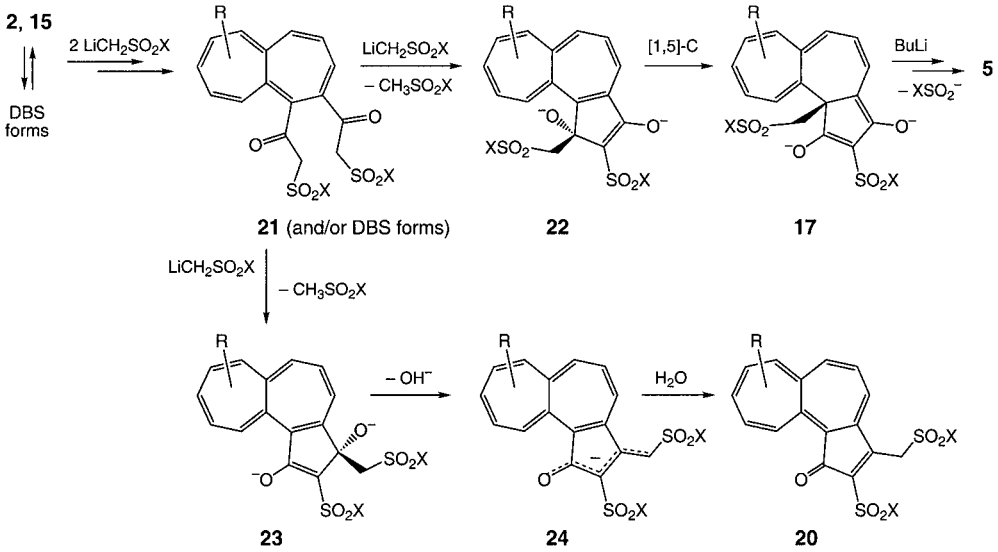
a) 1.6 Mol-equiv. $[^{13}C]H_3SO_2Ph$/1.5 mol-equiv. BuLi, $-5°$, 5 h; then, 1 mol-equiv. **15a**, $-70°$, 1 h; 39% of **15a** were recovered.

b) 5 Mol-equiv. $LiCH_2SO_2Ph$/THF, $-70 \rightarrow 0°$, 3 h.

c) 4 Mol-equiv. BuLi, $0 \rightarrow 20°$, 0.5 h.

17a* that would allow an intramolecular shift of the ^{13}C-labeled (phenylsulfonyl)-methyl moiety of the C=O group at C(5) to C(5) itself (see **21** in *Scheme 10*), thus resulting finally in the formation of **17a***. We, therefore, assume that the decisive step is the formation of bis-anions of type **22**, which are generated by base-induced ring closure of the corresponding 4,5-bis(X-sulfonylacetyl)heptalenes **21**, followed by further deprotonation (*Scheme 10*). The appearance of the bis-anions **17** can then be explained by a sigmatropic [1,5]-C shift in the bis-anions **22**. The driving force for these rearrangements can be ascribed to the conversion of the oxido-enolate structure of **22** into the better resonance-stabilized bis-enolate structure of **17**.

Scheme 10



The reaction of **19a*** with $LiCH_2SO_2Ph$ and then with BuLi led also to the formation of **20a***, which was also found as **20a**** as side-product of the reaction of **15a** with $Li[^{13}C]H_2SO_2Ph$ (*cf. Scheme 9*). The precursor of products of type **20**, which we also observed in other cases (*cf.* [7]), must be bis-anions of type **23** that result from the reverse cyclization of the 4,5-bis(X-sulfonylacetyl)heptalenes **21** (*Scheme 10*). However, what we do not understand at the moment is the observation that the analogous bis-anions of type **22** and **23** exhibit different chemical behavior in a way that the bis-anions **22** undergo [1,5]-C shifts, whereas the bis-anions **23** are subjected to the loss of OH^-. Nonetheless, both reactions lead to better resonance-stabilized anions (*cf.* **17** and **24**, resp., in *Scheme 10*). The exclusive formation of 3-sulfonylbenzo[*a*]heptalene-2,4-diols **5** and the absence of the corresponding isomeric 2-sulfonylbenzo[*a*]heptalene-1,3-diols (*cf.* [7]) with the substitution pattern of colchicinoids at ring A may, therefore, be mainly the result of competing kinetic steps at the stage of the bis-anions **22** and **23**, respectively. We will come back to these points in a forthcoming publication [14].

We thank our NMR laboratory for specific NMR measurements, Prof. *M. Hesse* and his group for mass-spectrometric analyses, and our Microanalytical Laboratory for elemental analyses. The financial support of this work by the *Swiss National Science Foundation* is gratefully acknowledged.

Experimental Part

General. See [7].

1. Synthesis of the Pseudo-esters 15. – 1.1. *1,3-Dihydro-8-isopropyl-3,3-dimethoxy-6,11-dimethylheptaleno[1,2-c]furan-1-one* (**15a**). See [11]. 1.2. *1,3-Dihydro-3,3-dimethoxy-6,7,9,11-tetramethylheptaleno[1,2-c]furan-1-one* (**15b**). See [11]. 1.3. *1,3-Dihydro-3,3-dimethoxy-11-methylheptaleno[1,2-c]furan-1-one* (**15c**). 1.3.1. *Dimethyl 6-Methylheptalene-4,5-dicarboxylate* (**2c**) *and Dimethyl 10-Methylheptalene-4,5-dicarboxylate* (**25**; *cf.* [3]). 4-Methylazulene (9.80 g, 69 mmol; prepared according to [15]) and ADM (26.2 ml; 30.4 g, 213 mmol) were heated in toluene (20 ml) in a closed 100-ml *Schlenk* vessel at 130° during 22 h. The usual workup gave a dark oil, which was subjected to CC (silica gel (250 g); hexane/AcOEt 4:1). The yellow-colored eluate gave, after crystallization (Et_2O), pure **2c** as red crystals. Recrystallization of the residue of the mother liquor gave a mixture of red crystals of **2c** and orange-colored crystals of **25**. A small amount of the mixture was separated mechanically. Total yields: **2c**: 7.85 g (40%); **25**: 2.95 g (15%). In soln. at r.t., **25** was in thermal equilibrium with 21.5% of its DBS isomer.

Data of **2c**: Red crystals. M.p. 115–116° (*cf.* [3]: 112–113°). R_f (hexane/AcOEt 2:1 [9:1]) 0.40 [0.13]. UV/VIS (EtOH): λ_{max} 206 (4.40), 261 (4.17), 326 (sh, 3.53), 401 (sh, 2.79); λ_{min} 244 (4.15). ^{1}H-NMR (600 MHz, $CDCl_3$): 7.53 (*d*, ^3J = 6.2, H–C(3)); 6.47 (*ABXY*, $\delta_A > \delta_B$, J_{AB} = 11.0, J_{AX} = 6.1, J_{BY} = 5.9, H–C(8), H–C(9)); 6.32 (*dd*, ^3J = 10.2, ^3J = 6.3, H–C(2)); 6.20 (*d*, ^3J = 5.4, H–C(7)); 6.06 (*d*, ^3J = 10.2, H–C(1)); 5.72 (*d*, ^3J = 5.4, H–C(10)); 3.718 (*s*, MeOCO–C(4)); 3.709 (*s*, MeOCO–C(5)); 2.036 (*s*, Me–C(6)). ^{13}C-NMR (150 MHz, $CDCl_3$): 167.80 (*s*, O=*C*–C(5)); 167.11 (*s*, O=C–C(4)); 145.54 (*s*, C(5a)); 140.19 (*d*, C(3)); 135.32 (*d*, C(1)); 134.70 (*s*, C(4)); 131.25 (*d*, C(8)); 130.65 (*d*, C(2)); 129.75 (*s*, C(6)); 129.30 (*d*, C(9)); 127.99 (*d*, C(10)); 127.85 (*s*, C(10a)); 127.44 (*d*, C(7)); 124.20 (*s*, C(5)); 52.16 (*q*, *Me*OCO–C(4)); 52.01 (*q*, *Me*OCO–C(5)); 23.29 (*q*, *Me*–C(6)).

Data of **25**: Orange crystals. M.p. 137°. R_f (hexane/AcOEt 2:1 [9:1]) 0.40 [0.13]. ^{1}H-NMR (600 MHz, $CDCl_3$; in the presence of 21.5% of its DBS isomer): 7.47 (*d*, ^3J = 5.8, H–C(3)); 6.47 (*d*, ^3J = 11.2, H–C(9)); 6.44 (*dd*, ^3J = 11.5, ^3J = 5.8, H–C(8)); 6.27 (*dd*, ^3J = 10.3, ^3J = 5.8, H–C(2)); 6.20 (*dd*, ^3J = 10.6, ^3J = 5.7, H–C(7)); 6.04 (*d*, ^3J = 10.6, H–C(6)); 5.92 (*d*, ^3J = 10.3, H–C(1)); 3.705 (*s*, MeOCO–C(4)); 3.650 (*s*, MeOCO–C(5)); 1.784 (*s*, Me–C(10)). ^{13}C-NMR (150 MHz, $CDCl_3$; in the presence of 21.5% of its DBS isomer): 167.46 (O=*C*–C(4)); 167.01 (O=*C*–C(5)); 146.36 (C(5a)); 140.49 (C(3)); 136.12 (C(9)); 135.33 (C(1)); 135.09 (C(10)); 134.79 (C(4)); 132.00 (C(8)); 129.69 (C(2)); 129.22 (C(7)); 126.20 (C(10a); 125.41 (C(6)); 122.95 (C(5)); 52.11 (*Me*OCO–C(4)); 51.63 (*Me*OCO–C(5)); 13.35 (*Me*–C(10)).

Data of the DBS Isomer of **25** (*Dimethyl 6-Methylheptalene-1,2-dicarboxylate*): ^{1}H-NMR (600 MHz, $CDCl_3$; in the presence of 78.5% of its DBS isomer): 6.60 (*dd*, ^3J = 11.7, ^3J = 6.0, H–C(4)); 6.57 (*d*, ^3J = 11.4, H–C(3)); 6.40 (*dd*, ^3J = 11.3, ^3J = 6.5, H–C(9)); *ca.* 6.20 (*dd*, $^3J \approx 10.6$, $^3J \approx 5.7$, H–C(8)); 6.05 (covered *d*, $^3J \approx$ 5.4, H–C(7)); 5.79 (*d*, ^3J = 6.0, H–C(5)); 5.73 (*d*, ^3J = 6.3, H–C(10)); 3.798 (*s*, MeOCO–C(2)); 3.762 (*s*, MeOCO–C(1)); 2.152 (*s*, Me–C(6)). ^{13}C-NMR (150 MHz, $CDCl_3$; in the presence of 78.5% of its DBS isomer): 167.35 (O=*C*–C(1)); 166.56 (O=*C*–C(2)); 146.33 (C(5a)); 137.67 (C(2)); 135.73 (C(6)); 131.89 (C(1)); 131.31 (C(8)); 131.19 (C(9)); 129.69 (C(10)); 128.18 (C(10a)); 128.08 (C(7)); 127.24 (C(3)); 124.59 (C(5)); 52.61 (*Me*OCO–C(1)); 52.57 (*Me*OCO–C(2)); 24.53 (*Me*–C(6)).

1.3.2. *5-(Methoxycarbonyl)-6-methylheptalene-4-carboxylic Acid* (**11c**). Finely powdered **2c** (1.82 g, 6.42 mmol) was suspended in a soln. of KOH (11.0 g, 196 mmol) in EtOH/H_2O (50 ml/50 ml). Stirring at r.t. for 4.5 h gave a clear dark-yellow soln. It was acidified with conc. HCl, poured onto ice, and extracted with Et_2O (3 × 100 ml). The org. phase was washed with H_2O and dried ($MgSO_4$). The residue of the org. layer was recrystalized from CH_2Cl_2/Et_2O/hexane to give pure **11c** (1.46 g, 84%). Red-brown crystals. M.p. 145–148° (dec. under formation of **12c**). ^{1}H-NMR ($CDCl_3$): 7.62 (*d*, ^3J = 6.2, H–C(3)); 6.51–6.31 (*m*, H–C(8), H–C(9)); 6.33 (*dd*, ^3J = 10.2, ^3J = 6.3, H–C(2)); 6.19 (*d*, ^3J = 4.7, H–C(7)); 6.10 (*d*, ^3J = 10.2, H–C(1)); 5.73 (*d*, ^3J = 4.7, H–C(10)); 3.699 (*s*, MeOCO); 2.037 (*d*, ^4J = 0.7, Me–C(6)). ^{13}C-NMR ($CDCl_3$): 171.97 (*s*, O=*C*–C(4)); 167.80 (*s*, O=*C*–C(5)); 146.02 (*s*, C(5a)); 142.07 (*d*, C(3)); 136.41 (*d*, C(1)); 134.14 (*s*, C(4)); 131.51 (*d*, C(8)); 130.62 (*d*, C(2)); 129.83 (*s*, C(6)); 129.41 (*d*, C(9)); 128.36 (*d*, C(10)); 127.85 (*s*, C(10a)); 127.68 (*d*, C(7)); 124.10 (*s*, C(5)); 52.21 (*q*, *Me*OCO); 23.30 (*q*, *Me*).

1.3.3. *1,3-Dihydro-11-methylheptaleno[4,5-c]furan-1,3-dione* (**12c**). Mono-acid **11c** (1.40 g, 5.18 mmol) was stirred in toluene (80 ml) under N_2 at reflux temp. for 4 h. After removal of the solvent, recrystallization of the

crude product from Et_2O furnished pure **12c** (1.36 g, 93%). Black shining crystals. M.p. 177–178°. R_f (hexane/Et_2O 1:1) 0.40. ^{1}H-NMR ($CDCl_3$): 7.01 (*d*, ^3J = 7.5, H–C(4)); 6.49 (*dd*, ^3J = 10.3, ^3J = 7.4, H–C(5)); 6.47 (*d*, ^3J = 7.3, H–C(10)); 6.44–6.35 (7-line *m*, H–C(8), H–C(9)); 5.70 (*d*, ^3J = 7.7, H–C(7)); 5.59 (*d*, ^3J = 10.0, H–C(6)); 2.211 (*s*, Me–C(11)). ^{13}C-NMR ($CDCl_3$): 164.08, 159.39 (2*s*, 2 CO); 134.55 (*d*); 134.39 (*s*); 134.05 (*s*); 133.59 (*d*); 133.28 (*d*); 132.89 (*s*); 132.49 (*d*); 132.19 (*d*); 131.97 (*d*); 131.89 (*d*); 122.18 (*s*); 23.53 (*q*, Me). Anhydride **12c** slowly decomposed on silica gel. Therefore, CC is not a convenient method for its purification.

1.3.4. *4-(Methoxycarbonyl)-6-methylheptalene-5-carboxylic Acid* (**13c**). Anhydride **12c** (1.35 g, 5.67 mmol) was suspended in MeOH (40 ml), and a soln. of MeONa in MeOH (0.55M; 10.5 ml) was added slowly. After 20 min, the resulting clear yellow soln. was acidified with 1N aq. HCl soln., diluted with H_2O (50 ml), and extracted with Et_2O (3 × 50 ml). The org. phase was washed with H_2O (3 × 100 ml) and dried ($MgSO_4$). The solvent was distilled off, and the residue was crystallized from Et_2O to give pure **13c** (1.38 g, 90%; ^{1}H-NMR analysis of the residue of the mother liquor showed that 5% of **11c** were also present). Orange crystals. M.p. 120–122° → 171–172° (dec. under formation of **12c**). ^{1}H-NMR (500 MHz, $CDCl_3$; 280 K): 7.54 (*d*, ^3J = 6.2, H–C(3)); 6.53–6.46 (*m*, H–C(8), H–C(9)); 6.35 (*dd*, ^3J = 10.2, ^3J = 6.2, H–C(2)); 6.21 (*d*, ^3J = 5.2, H–C(7)); 6.07 (*d*, ^3J = 10.2, H–C(1)); 5.76 (*d*, ^3J = 5.2, H–C(10)); 3.716 (*s*, MeOCO); 2.122 (*s*, Me–C(6)). At r.t., the ^{1}H-NMR of **13c** showed broadened signals due to fast DBS. ^{13}C-NMR (150 MHz, $CDCl_3$; 280 K): 172.83 (*s*, O=*C*–C(5)); 167.22 (*s*, O=*C*–C(4)); 147.09 (*s*, C(5a)); 140.57 (*d*, C(3)); 135.34 (*d*, C(1)); 134.53 (*s*, C(4)); 131.23 (*d*, C(8)); 130.84 (*d*, C(2)); 129.43 (*d*, C(9)); 129.25 (*s*, C(6)); 128.09 (*d*, C(10)); 127.56 (*d*, C(7)); 127.36 (*s*, C(10a)); 123.26 (*s*, C(5)); 52.21 (*q*, *Me*OCO); 23.44 (*q*, Me).

Mono-acid **13c** is not stable in $CDCl_3$. It slowly decomposed to anhydride **12c** ($t_{1/2}$ *ca.* 26 h).

1.3.5. *Formation of Pseudo-ester* **15c**. Oxalyl chloride (0.95 ml; 1.40 g, 11.1 mmol) was slowly added under Ar to an ice-cooled soln. of DMF (2.8 ml) in MeCN (7.0 ml), followed by a suspension of **13c** (1.32 g, 4.88 mmol) in MeCN (14 ml). After stirring for 1 h at 0°, MeOH (0.7 ml) was added. TLC showed the formation of **15c** and a smaller amount of **12c**. The mixture was poured onto ice and extracted with Et_2O (3 × 50 ml). The org. phase was washed with H_2O (4 × 100 ml) and brine (100 ml) and dried ($MgSO_4$). After removal of the solvent, the crude product was purified by CC (silica gel (250 g); hexane/Et_2O 4:1). Recrystallization from Et_2O/hexane gave pure **15c** (0.873 g, 63%). Dark-brown, black shining crystals. M.p. 131°. R_f (hexane/Et_2O 1:1) 0.47. IR (KBr): 3511*w*, 3006*w*, 2971*w*, 2951*m*, 2839*w*, 1765*s* (C=O), 1625*w*, 1592*m*, 1554*w*, 1511*m*, 1440*m*, 1297*s*, 1216*m*, 1192*m*, 1123*s*, 1098*m*, 1050*w*, 1030*w*, 997*m*, 899*s*, 850*m*, 799*m*, 747*m*, 623*w*, 564*w*, 473*w*. ^{1}H-NMR (600 MHz, $CDCl_3$): 6.75 (*dd*, ^3J = 10.9, ^3J = 7.2, H–C(5)); 6.37 (*d*, ^3J = 11.5, H–C(10)); 6.25 (*dd*, ^3J = 11.5, ^3J = 6.6, H–C(9)); 6.22 (*d*, ^3J = 11.1, H–C(4)); 6.08 (*dd*, ^3J = 10.6, ^3J = 6.6, H–C(8)); 5.73 (*d*, ^3J = 10.6, H–C(7)); 5.32 (*dd*, ^3J = 7.3, ^5J = 0.7, H–C(6)); 3.436/3.433 (2*s*, 2 MeO–C(3)); 1.670 (*s*, Me–C(11)). ^{13}C-NMR (150 MHz, $CDCl_3$): 165.81 (*s*, C(1)); 158.35 (*s*, C(3a)); 142.87 (*s*, C(6a)); 140.76 (*d*, C(5)); 137.97 (*d*, C(10)); 137.35 (*s*, C(11)); 133.04 (*d*, C(8)); 132.57 (*d*, C(9)); 129.87 (*d*, C(7)); 127.96 (*d*, C(6)); 123.74 (*s*, C(11b)); 123.61 (*s*, C(11a)); 120.68 (*d*, C(4)); 117.56 (*s*, C(3)); 51.91/51.81 (*q*, *Me*O–C(3)); 19.82 (*q*, *Me*–C(1)). EI-MS: 285 (6, $[M+1]^+$), 284 (40, $M^{+\bullet}$), 269 (93, $[M-Me]^+$), 254 (20), 241 (25), 225 (13), 211 (13), 199 (24), 166 (32), 165 (100), 164 (29), 163 (27), 152 (17), 139 (31), 115 (5). Anal. calc. for $C_{17}H_{16}O_4$ (284.31): C 71.82, H 5.67; found: C 71.84, H 5.75.

1.4. *1,3-Dihydro-3,3-dimethoxy-6,11-dimethylheptaleno[1,2-c]furan-1-one* (**15d**). 1.4.1. *Dimethyl 1,6-Dimethylheptalene-4,5-dicarboxylate* (**2d**; *cf.* [3]). 1,4-Dimethylazulene (7.25 g, 48.1 mmol; prepared according to [15]) and ADM (17.4 ml; 19.8 g, 140 mmol) were heated in toluene (18 ml) in a closed 100-ml *Schlenk* vessel at 130° during 23 h. The usual workup gave a dark oil that was subjected to CC (silica gel (250 g); hexane/AcOEt 4:1). The yellow-colored eluate gave, after crystallization (AcOEt/hexane), pure **2d** (9.76 g, 68%). Orange crystals. M.p. 136°. R_f (hexane/AcOEt 4:1) 0.22. UV/VIS (EtOH): λ_{max} 209 (4.39), 257 (4.18), 277 (4.18), 325 (sh, 3.53), 389 (sh, 2.99); λ_{min} 241 (4.15), 269 (4.17). ^{1}H-NMR (600 MHz, $CDCl_3$): 7.47 (*dq*-like, ^3J = 6.3, ^5J = 0.7, H–C(3)); 6.49 (*ABXY*, $J_{AB} \approx 12.4$, $J_{AX} = J_{BY} \approx 6.2$, H–C(8), H–C(9)); 6.21 (*dd*, ^3J = 6.5, ^4J = 1.4, H–C(7)); 6.19 (*dq*, ^3J = 6.3, ^4J = 1.3, H–C(2)); 5.92 (3-line signal, ^3J = 6.5, H–C(10)); 3.705 (*s*, MeOCO–C(5)); 3.701 (*s*, MeOCO–C(4)); 2.064 (*s*, Me–C(1)); 2.028 (*d*, ^4J = 1.1, Me–C(6)). ^{13}C-NMR (150 MHz, $CDCl_3$): 167.78 (*s*, O=*C*–C(5)); 167.30 (*s*, O=*C*–C(4)); 144.33 (*s*, C(1)); 143.29 (*s*, C(6)); 140.17 (*d*, C(3)); 132.29 (*s*, C(4)); 131.78 (*s*, C(10a)); 131.31 (*d*, C(8)); 130.03 (*s*, C(5a)); 129.15 (*d*, C(9)); 127.15 (*d*, C(7)); 125.93 (*d*, C(2)); 125.13 (*d*, C(10)); 123.81 (*s*, C(5)); 52.07/52.04 (*q*, *Me*OCO–C(4,5)); 25.33 (*q*, *Me*–C(1)); 22.67 (*q*, *Me*–C(6)).

1.4.2. *5-(Methoxycarbonyl)-1,6-dimethylheptalene-4-carboxylic Acid* (**11d**). Finely powdered **2d** (1.53 g, 5.13 mmol) was suspended in a soln. of KOH (9.0 g, 160 mmol) in EtOH/H_2O (40 ml/40 ml). It was stirred at r.t. for 8.5 h. The resulting clear dark yellow soln. was acidified with conc. HCl, poured onto ice, and extracted with Et_2O (3 × 100 ml). The org. layer was washed with H_2O (4 × 100 ml) and brine, and dried ($MgSO_4$). Removal of Et_2O by distillation and recrystallization of the crude product from CH_2Cl_2/Et_2O/hexane gave pure **11d** (1.43 g,

98%). Red-brown crystals. M.p. 149–152° → 165.5–166.3° (dec. under formation of **12d**). ^{1}H-NMR (600 MHz, $CDCl_3$): 7.56 (*dd*, ^3J = 6.2, ^4J = 0.9, H–C(3)); 6.48 (not resolved *ABXY*, H–C(8), H–C(9)); 6.23–6.19 (*m*, H–C(2), H–C(7)); 5.92 (3-line signal, ^3J = 6.5, H–C(10)); 3.689 (*s*, MeOCO); 2.073 (*s*, Me–C(1)); 2.024 (*d*, ^4J = 1.2, Me–C(6)). ^{13}C-NMR (150 MHz, $CDCl_3$): 171.91 (*s*, O=*C*–C(4)); 167.70 (*s*, O=*C*–C(5)); 145.48 (*s*, C(1)); 143.57 (*s*, C(5a)); 142.01 (*d*, C(3)); 131.64 (*s*, C(10a)); 131.56 (*s*, C(4)); 131.46 (*d*, C(8)); 130.01 (*s*, C(6)); 129.16 (*d*, C(9)); 127.28 (*d*, C(7)); 125.90 (*d*, C(2)); 125.34 (*d*, C(10)); 123.65 (*s*, C(5)); 52.17 (*q*, *Me*OCO); 25.46 (*q*, *Me*–C(1)); 22.62 (*q*, *Me*–C(6)).

1.4.3. *1,3-Dihydro-6,11-dimethylheptaleno[4,5-c]furan-1,3-dione* (**12d**). Mono-acid **11d** (1.36 g, 4.80 mmol) was stirred under N_2 in toluene (80 ml) at reflux during 4 h. After removal of the solvent *in vacuo*, crystallization of the crude product from Et_2O gave pure **12d** (1.09 g, 90%). Black shining crystals. M.p. 167°. R_f(hexane/Et_2O 1:1) 0.42. ^{1}H-NMR ($CDCl_3$): 7.16 (*d*, ^3J = 6.8, H–C(4)); 6.61–6.42 (*m*, H–C(8), H–C(9), H–C(10)); 6.35 (*dq*-like, ^3J = 6.9, ^4J = 1.1, H–C(5)); 6.02 (*d*, ^3J = 6.7, H–C(7)); 2.335 (*s*, Me–C(6)); 2.198 (*s*, Me–C(11)). ^{13}C-NMR ($CDCl_3$; selected signals): 164.58, 159.13 (2*s*, 2 CO); 26.03 (*q*, *Me*–C(6)); 23.82 (*q*, *Me*–C(11)).

1.4.4. *4-(Methoxycarbonyl)-1,6-dimethylheptalene-5-carboxylic Acid* (**13d**). A soln. of MeONa in MeOH (0.55M, 8 ml) was slowly added to a suspension of **12d** (1.03 g, 4.07 mmol) in MeOH (30 ml). After 30 min, the resulting clear dark yellow soln. was acidified with 1N aq. HCl soln., diluted with 50 ml H_2O, and extracted with Et_2O (3 × 50 ml). The org. phase was washed with H_2O (3 × 100 ml) and dried ($MgSO_4$). The solvent was distilled off, and the residue was recrystallized from Et_2O to give pure **13d** (0.94 g, 81%). Analysis of the residue of the mother liquor by ^{1}H-NMR revealed that 18% of **11d** had also been formed.

Data of **13d**: Yellow crystals. M.p. 142 → 166° (dec. under formation of **12d**). ^{1}H-NMR ($CDCl_3$): 7.47 (*dd*, ^3J = 6.2, ^4J = 1.0, H–C(3)); 6.50 (not resolved *ABXY*, H–C(8), H–C(9)); 6.24–6.19 (*m*, H–C(2), H–C(7)); 5.94 (3-line signal, ^3J = 6.7, H–C(10)); 3.701 (*s*, MeOCO); 2.112 (*t*, ^4J = 1.2, Me–C(1)); 2.062 (*t*, ^4J = 1.1, Me–C(6)). ^{13}C-NMR ($CDCl_3$): 172.33 (*s*, O=*C*–C(5)); 167.30 (*s*, O=*C*–C(4)); 144.72 (*s*, C(1)); 144.24 (*s*, C(5a)); 140.34 (*d*, C(3)); 132.28 (*s*, C(10a)); 131.46 (*s*, C(4)); 131.21 (*d*, C(8)); 129.57 (*s*, C(6)); 129.19 (*d*, C(9)); 127.22 (*d*, C(7)); 126.00 (*d*, C(2)); 125.13 (*d*, C(10)); 123.04 (*s*, C(5)); 51.97 (*q*, *Me*OCO); 25.32 (*q*, *Me*–C(1)); 22.61 (*q*, *Me*–C(6)).

1.4.5. *Formation of Pseudo-ester* **15d**. Oxalyl chloride (0.67 ml; 1.00 g, 7.8 mmol) was slowly added under Ar to an ice-cooled soln. of DMF (2.0 ml) and MeCN (8.0 ml). A suspension of **13d** (0.835 g, 2.94 mmol) in MeCN (5 ml) was added. After stirring for 1 h at 0°, MeOH (0.5 ml) was added. TLC showed that **15d** and a smaller amount of **12d** had been formed. The mixture was poured onto ice and extracted with Et_2O (3 × 50 ml). The org. phase was washed with H_2O (4 × 100 ml) and brine (100 ml), and dried ($MgSO_4$). After removal of the solvent by distillation, the crude product was purified by CC (silica gel (250 g), hexane/Et_2O 5:1). Recrystallization from Et_2O/hexane gave pure **15d** (0.545 g, 62%). Dark-brown, black shining crystals. M.p. 144°. R_f (hexane/Et_2O 1:1) 0.52. IR (KBr): 3502*w*, 3022*w*, 2937*w*, 2841*w*, 1766*s* (C=O), 1624*w*, 1589*w*, 1509*w*, 1445*m*, 1375*w*, 1308*s*, 1195*m*, 1162*w*, 1101*s*, 1003*m*, 883*s*, 806*m*, 793*m*, 725*w*, 624*w*, 587*w*, 570*w*, 498*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): At r.t., signal broadening of **15d** indicated that a rapid DBS process took place, which is frozen to an equilibrium mixture of **15d** and its DBS isomer at 263 K, consisting of 72% of **15d** and 28% of the DBS isomer of **15d**. Signals of **15d** at 263 K: 6.77 (*d*, ^3J = 11.4, H–C(4)); 6.42 (*d*, ^3J = 10.8, H–C(10)); 6.37 (*dd*, ^3J = 11.6, ^3J = 5.8, H–C(9)); 6.31 (*d*, ^3J = 11.4, H–C(5)); 6.20 (*dd*, ^3J = 10.3, ^3J = 5.8, H–C(8)); 5.67 (*d*, ^3J = 10.4, H–C(7)); 3.460/3.426 (2*s*, 2 MeO); 1.722 (*s*, Me–C(6)); 1.673 (*s*, Me–C(11)). Selected signals of the DBS isomer of **15d** (*1,3-dihydro-3,3-dimethoxy-6,11-dimethylheptaleno[4,5-c]furan-1-one*): 3.390/3.345 (2*s*, 2 MeO); 2.304 (*s*, Me–C(6)); 2.122 (*s*, Me–C(11)). ^{13}C-NMR (125 MHz, $CDCl_3$; 263 K; signals of **15d**): 166.01 (*s*, C(1)); 156.67 (*s*, C(3a)); 145.27 (*d*, C(5)); 136.70 (*d*, C(10)); 136.57 (*s*, C(6)); 135.95 (*s*, C(11)); 132.51 (*d*, C(9)); 131.62 (*s*, C(6a)); 131.40 (*d*, C(8)); 127.43 (*d*, C(7)); 124.22 (*s*, C(11b)); 121.64 (*s*, C(11a)); 120.40 (*d*, C(4)); 117.58 (*s*, C(3)); 52.11/51.98 (*q*, MeO–C(3)); 19.07 (*q*, Me–C(6)); 18.20 (*q*, Me–C(11)). Selected signals of the DBS isomer: 142.28 (C(6a)); 134.10 (C(10)); 133.57 (C(11)); 132.26 (C(5)); 131.10; 130.59; 130.48 (C(6)); 127.62; 126.52 (C(11a)); 125.76; 121.09; *ca.* 118.4 (C(3)); 51.76/51.43 (*Me*O–C(3)); 25.53 (*Me*–C(6)); 24.05 (*Me*–C(11)). EI-MS: 299 (11, $[M+1]^+$), 298 (79, $M^{+\bullet}$), 283 (97, $[M-Me]^+$), 267 (19), 255 (20), 239 (17), 224 (15), 213 (33), 208 (26), 180 (25), 170 (83), 178 (61), 165 (100), 153 (32), 152 (43), 139 (12), 115 (9). Anal. calc. for $C_{18}H_{18}O_4$ (298.34): C 72.47, H 6.08; found: C 72.10, H 6.13.

2. Reaction of Pseudo-esters 15 with Lithiated Methylsulfonyl Compounds. – 2.1. *General Procedure* (*GP*). A 2.5M soln. of BuLi (5.5 equiv.) was added dropwise at −5° to a soln. of the methylsulfonyl compound (5.0 equiv.) in dry THF under Ar. After stirring during 30 min at 0°, a white precipitate formed. The mixture was cooled to −75°, and a soln. of the pseudo-ester **15** (1.0 equiv.) in THF was added slowly. The brown mixture was allowed to warm to −5° within 3 h. At −60°, all of **15** had been consumed, and, at *ca.* −40°, the mixture became clear and changed its color to red. At −5°, another 4.0 equiv. of BuLi were slowly added. Immediately, the color

of the mixture changed to dark reddish-brown. The mixture was allowed to warm to r.t. and was stirred at this temp. for 2–12 h. Then, the mixture was treated with ice-water, acidified with 1N aq. HCl soln., and extracted with AcOEt. The org. phase was washed with 1N aq. HCl soln. and brine. After drying ($MgSO_4$), the solvent was distilled off in a rotatory evaporator. The crude product was purified by CC and recrystallization.

2.1.1. *9-Isopropyl-7,12-dimethyl-3-(phenylsulfonyl)benzo[a]heptalene-2,4-diol* (**5a**). According to *GP*, $MeSO_2Ph$ (2.30 g, 14.75 mmol) was reacted with BuLi soln. (6.47 ml, 16.17 mmol) and **15a** (1.00 g, 2.94 mmol) [11] in THF (50 ml). After addition of another amount of BuLi soln. (4.7 ml, 11.76 mmol) at $-5°$, the mixture was stirred at r.t. for 3 h. Usual workup led to a residue that was chromatographed (silica gel (120 g); hexane/AcOEt 3:1) and then crystallized from Et_2O/hexane to give **5a** (1.035 g, 79%) as yellow crystals with m.p. 207–208° ([7]: 207–208°).

Pseudo-ester **14a** gave under the same reaction conditions **5a** only in trace amounts (^{1}H-NMR evidence).

2.1.2. *7,8,10,12-Tetramethyl-3-(phenylsulfonyl)benzo[a]heptalene-2,4-diol* (**5b**). According to *GP*, $MeSO_2Ph$ (2.39 g, 15.32 mmol) was reacted with BuLi soln. (6.73 ml, 16.83 mmol) and **15b** (1.00 g, 3.06 mmol) [11] in THF (50 ml). After addition of another amount of BuLi soln. (4.9 ml, 12.24 mmol) at $-5°$, the mixture was stirred at r.t. for 3 h. Usual workup led to a solid that was chromatographed (silica gel (120 g); hexane/AcOEt 3:1) and recrystallized (Et_2O/hexane) to give pure **5b** (1.01 g, 76%) as yellow crystals with m.p. 203–204° ([7][8]: 203–204°).

2.1.3. *12-Methyl-3-(phenylsulfonyl)benzo[a]heptalene-2,4-diol* (**5c**). According to *GP*, $MeSO_2Ph$ (0.880 g, 5.63 mmol) was reacted with BuLi soln. (2.5 ml, 6.2 mmol) and **15c** (0.320 g, 1.13 mmol) in THF (23 ml). After addition of another amount of BuLi soln. (1.81 ml, 4.52 mmol) at $-5°$, the mixture was stirred at r.t. for 2 h. CC (silica gel; hexane/AcOEt 6:1) and recrystallization from Et_2O/hexane yielded pure crystals of **5c** (0.066 g, 15%). The same run with a reaction time of 12 h in the last step gave **5c** (0.119 g) in a yield of 27%. Yellow crystals. M.p. 221°. R_f (hexane/AcOEt 1:1) 0.43. UV/VIS (EtOH): See *Table 1*. IR (KBr): 3255*s* (OH), 3061*w*, 3040*m*, 1641*w*, 1599*s*, 1555*s*, 1449*s*, 1412*m*, 1334*m*, 1217*s*, 1165*s*, 1130*s*, 852*m*, 776*m*, 744*m*, 723*s*, 682*m*, 644*s*, 555*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): See *Table 2*. ^{13}C-NMR (150 MHz, $CDCl_3$): See *Table 3*. EI-MS: 391 (23, $[M+1]^+$), 390 (100, $M^{+\bullet}$), 375 (12, $[M-Me]^+$), 364 (33), 350 (13), 234 (8), 189 (16), 178 (15), 165 (21), 152 (15).

Table 1. *UV Spectra of the 3-(X-Sulfonyl)benzo[a]heptalene-2,4-diols* **5**[a])

Benzo[*a*]heptalene[b])	λ_{max} [nm] (log ε)	λ_{min} [nm] (log ε)
5c	216 (4.49) 242 (4.39) 263 (4.40) 318 (4.03) 401 (sh, 3.01)	209 (4.48) 236 (4.39) 251 (4.38) 299 (3.96)
5c′	223 (4.49) 262 (4.37) 317 (4.06) 397 (sh, 3.04)	245 (4.31) 296 (3.95)
5d	217 (4.46) 240 (4.38) 263 (4.41) 314 (3.99) 389 (sh, 3.01)	207 (4.45) 235 (4.38) 250 (4.36) 300 (3.96)
5d′	224 (4.49) 262 (4.39) 313 (4.04) 389 (sh, 2.99)	245 (4.32) 296 (3.96)

[a]) Spectra in EtOH. [b]) X = Ph for **5c** and **5d**, X = morpholino for **5c′** and **5d′**.

2.1.4. *12-Methyl-3-(morpholinosulfonyl)benzo[a]heptalene-2,4-diol* (**5c′**). According to *GP*, methyl morpholino sulfone (0.930 g, 5.63 mmol) was reacted with BuLi soln. (2.5 ml, 6.2 mmol) and **15c** (0.320 g, 1.13 mmol) in THF (20 ml). After addition of another amount of BuLi soln. (1.81 ml, 4.52 mmol) at $-5°$, the mixture was stirred at r.t. for 2 h. CC (silica gel; hexane/AcOEt 4:1) and crystallization from Et_2O/CH_2Cl_2/hexane yielded pure **5c′** (0.158 g, 35%). Yellow crystals. M.p. 164°. R_f (hexane/AcOEt 1:1) 0.35. UV/VIS (EtOH): See *Table 1*. IR (KBr): 3356*s* (OH), 3191*s*, 3012*w*, 2969*m*, 2927*m*, 2861*m*, 1792*w*, 1699*w*, 1593*s*, 1559*s*, 1426*s*, 1382*s*, 1338*m*, 1304*m*, 1262*s*, 1171*m*, 1097*s*, 961*s*, 871*m*, 730*s*, 643*s*, 566*m*, 512*m*. ^{1}H-NMR (600 MHz, $CDCl_3$): See *Table 2*. ^{13}C-NMR (150 MHz, $CDCl_3$): See *Table 3*. EI-MS: 400 (23, $[M+1]^+$), 399 (100, $M^{+\bullet}$), 256 (9), 248 (26, $[M-(C_4H_8NO_3S+H)^+]$), 222 (12), 220 (12), 208 (20), 189 (9), 178 (10), 165 (14), 123 (17), 105 (13), 85 (14), 83 (21). Anal. calc. for $C_{21}H_{21}NO_5S$ (399.47): C 63.14, H 5.30, N 3.51, S 8.03; found: C 63.09, H 5.37, N 3.38, S 7.70.

2.1.5. *7,12-Dimethyl-3-(phenylsulfonyl)benzo[a]heptalene-2,4-diol* (**5d**). According to *GP*, $MeSO_2Ph$ (0.394 g, 2.52 mmol) was reacted with BuLi soln. (1.11 ml, 2.78 mmol) and **15d** (0.148 g, 0.496 mmol) in THF

Table 2. *^{1}H-NMR Data of the 3-(X-Sulfonyl)benzo[a]heptalene-2,4-diols* **5**[a])

Position of H-atoms and/or Me groups	δ [ppm] (J [Hz])[b])			
	5c	**5c′**	**5d**	**5d′**
H–C(1)	6.22 (*s*)	6.28 (*d*, ^5J = 0.4)	6.21 (*s*)	6.26 (*s*)
HO–C(2)	8.64 (*s*)	8.21 (*s*)	8.62 (*s*)	8.21 (*s*)
XSO_2–C(3)	7.96 (*dd*, ^3J = 7.4, *o*-H); 7.66 (*t*-like, ^3J = 7.6, *p*-H); 7.55 (*dd*, ^3J = 7.6, ^4J = 1.7, *m*-H)	3.78, 3.14 (2*m*)	7.97 (*m*, ^3J = 7.7, *o*-H), 7.66 (*m*, ^3J = 7.3, *p*-H), 7.55 (*m*, ^3J = 7.5, *m*-H)	3.78, 3.14 (2*m*)
HO–C(4)	9.24 (*s*)	8.78 (*s*)	9.23 (*s*)	8.77 (*s*)
H–C(5)	7.06 (*d*, ^3J = 11.8)	7.07 (*d*, ^3J = 11.8)	7.04 (*d*, ^3J = 11.9)	7.04 (*d*, ^3J = 11.8)
H–C(6)	6.32 (*dd*, ^3J = 11.8, 5.9)	6.34 (*m*, ^3J = 11.6, 6.1)	6.22 (*d*, ^3J = 11.8)	6.24 (*d*, ^3J = 11.8)
H- or Me–C(7)	5.45 (*dd*, ^3J = 5.8, ^4J = 1.3)	5.50 (*dd*, ^3J = 5.8, ^4J = 1.4)	1.687 (*s*)	1.733 (*s*)
H–C(8)	5.98 (*d*, ^3J = 10.4)	6.04 (*dd*, ^3J = 10.4, ^4J = 0.6)	5.90 (*d*, ^3J = 10.3)	5.96 (*d*, ^3J = 10.2)
H–C(9)	6.15 (*dd*, ^3J = 10.4, 6.1)	6.19 (*m*, ^3J = 10.4, 6.8, ^4J = 0.8)	6.22 (*dd*, ^3J = 10.3, 5.7)	6.25 (*dd*, ^3J = 10.3, 5.7)
H–C(10)	6.35 (*dd*, ^3J = 11.6, 6.2)	6.37 (*m*, ^3J = 11.6, 6.1)	6.38 (*dd*, ^3J = 11.5, 5.6)	6.38 (*dd*, ^3J = 11.4, 5.7)
H–C(11)	6.43 (*d*, ^3J = 11.7)	6.45 (*d*, ^3J = 11.8)	6.44 (*d*, ^3J = 11.7)	6.40 (*d*, ^3J = 11.4)
Me–C(12)	1.686 (*s*)	1.715 (*s*)	1.679 (*s*)	1.711 (*s*)

[a]) Spectra at 600 MHz; $CDCl_3$, C*H*Cl_3 at 7.260 ppm. [b]) X = Ph for **5c** and **5d**; X = morpholino for **5c′** and **5d′**.

Table 3. *^{13}C-NMR Data of the 3-(X-Sulfonyl)benzo[a]heptalene-2,4-diols* **5**[a])[b])

Position of C-atoms and Me groups	δ [ppm]			
	5c	**5c′**	**5d**	**5d′**
C(1)	110.16	109.96	109.82	109.60
C(2)	156.96	156.77	156.66	156.47
C(3)	108.28	103.34	108.07	103.10
C(4)	153.35	153.09	153.42	152.98
C(4a)	120.43	120.32	119.75	119.60
C(5)	125.68	125.72	125.38	125.46
C(6)	127.40	127.46	132.22	132.29
C(7)	125.17	125.24	129.50	129.48
C(7a)	138.11	138.12	132.01	132.26
C(8)	129.83	129.92	128.06	128.14
C(9)	129.69	129.69	128.41	128.39
C(10)	130.86	130.88	130.58	130.60
C(11)	136.98	136.98	136.24	136.23
C(12)	133.98	133.95	132.41	132.38
C(12a)	132.64	132.51	132.63	132.68
C(12b)	145.73	145.07	146.41	145.80
Me–C(7)	–	–	16.60	16.88
Me–C(12)	20.37	20.39	19.91	19.92
X–SO_2–C(3)	141.12 (C(1)); 134.42 (*p*-C); 129.62 (*m*-C); 126.16 (*o*-C)	65.72, 45.63	141.20 (C(1)); 135.38 (*p*-C); 129.60 (*m*-C); 126.19 (*o*-C)	65.72, 45.61

[a]) Spectra at 150 MHz; $CDCl_3$, *C*DCl_3 at 77.00 ppm. [b]) Assignments of all C-signals *via* HSQC and HMBC spectra; X = Ph for **5c** and **5d**; X = morpholino for **5c′** and **5d′**.

(9 ml). After addition of another amount of BuLi soln. (0.79 ml, 1.98 mmol) at −5°, the mixture was stirred at r.t. for 5 h. The usual workup, CC (silica gel; hexane/AcOEt 4:1) and crystallization from Et_2O/hexane yielded pure **5d** (0.042 g, 21%). Yellow crystals. M.p. 194°. R_f (hexane/AcOEt 1:1) 0.45. UV/VIS (EtOH): See *Table 1*. IR (KBr): 3370*m* (OH), 3191*m*, 2975*w*, 1598*s*, 1549*w*, 1446*m*, 1364*m*, 1258*m*, 1127*s*, 1066*m*, 871*w*, 787*w*, 742*m*, 685*w*, 633*s*, 567*m*, 469*w*. ^{1}H-NMR (600 MHz, $CDCl_3$): See *Table 2*. ^{13}C-NMR (150 MHz, $CDCl_3$): See *Table 3*. EI-MS: 405 (24, $[M+1]^+$), 404 (100, $M^{+\cdot}$), 389 (53, $[M-Me]^+$), 378 (18), 364 (52), 248 (15, $[M-(PhSO_2+Me)^+]$), 247 (15), 219 (12), 202 (11), 189 (28), 178 (21), 165 (32), 152 (14), 77 (6, $[Ph]^+$). Anal. calc. for $C_{24}H_{20}O_4S$ (404.49): C 71.23, H 4.98, S 7.93; found: C 70.90, H 4.79, S 7.84.

2.1.6. *7,12-Dimethyl-3-(morpholinosulfonyl)benzo[*a*]heptalene-2,4-diol* (**5d′**). According to *GP*, methyl morpholino sulfone (0.413 g, 2.50 mmol) was reacted with BuLi soln. (1.10 ml, 2.75 mmol) and **15d** (0.149 g, 0.499 mmol) in THF (11 ml). After addition of another amount of BuLi soln. (0.80 ml, 2.00 mmol) at −5°, the mixture was stirred at r.t. for 5 h. The usual workup, CC (silica gel; hexane/AcOEt 3:1) and crystallization from Et_2O/CH_2Cl_2/hexane gave **5d′** (0.085 g, 41%). Yellow crystals. M.p. 219°. R_f (hexane/AcOEt 1:1) 0.37. UV/VIS (EtOH): See *Table 1*. IR (KBr): 3202*s* (OH), 3014*w*, 2981*m*, 2936*m*, 2911*m*, 2872*m*, 1946*w*, 1769*w*, 1600*s*, 1566*s*, 1505*w*, 1436*s*, 1388*s*, 1363*s*, 1300*m*, 1258*s*, 1174*m*, 1106*s*, 1066*m*, 1005*w*, 946*s*, 870*m*, 849*w*, 738*s*, 703*s*, 632*m*, 558*m*, 516*m*, 470*w*. ^{1}H-NMR (600 MHz, $CDCl_3$): See *Table 2*. ^{13}C-NMR (150 MHz, $CDCl_3$): See *Table 3*. EI-MS: 414 (25, $[M+1]^+$), 413 (100, $M^{+\cdot}$), 373 (9), 262 (16, $[M-(C_4H_8NO_3S+H]^+$), 247 (9), 236 (11), 234 (10), 222 (22), 189 (11), 165 (9). Anal. calc. for $C_{22}H_{23}NO_5S$ (413.49): C 63.90, H 5.61, N 3.39, S 7.75; found: C 64.41, H 6.69, N 3.26, S 7.55.

3. [^{13}C]-Labelling Experiments. – 3.1. *Formation of [^{13}C]H_3SO_2Ph.* According to a procedure of *Wildeman* and *van Leusen* [16], a suspension of $PhSO_2Na$ (1.22 g, 7.43 mmol) in 1,2-dimethoxyethane (9 ml) was reacted with [^{13}C]H_3I (99 atom-% ^{13}C; 1.00 g, 7.00 mmol) and Bu_4NBr (0.12 g, 0.37 mmol). The mixture was stirred under N_2 at 40° for 8 h. Thereafter, it was poured on ice and extracted with Et_2O (3 × 50 ml). The org. phase was washed with H_2O and with brine, and dried ($MgSO_4$). After removal of the solvent in a rotatory evaporator, the residue was crystallized from Et_2O/hexane to give [^{13}C]H_3SO_2Ph (0.812 g, 5.17 mmol, 74%). White crystals. M.p. 88.0–88.5°. R_f (Et_2O/hexane 3:1) 0.32. ^{1}H-NMR ($CDCl_3$): 3.05 (*d*, ^1J = 138.2, [^{13}C]H_3). ^{13}C-NMR ($CDCl_3$): 140.63 (*d*, ^2J = 8.9, C(1) of Ph); 44.46 ([^{13}C]H_3).

3.2. *Methyl 9-Isopropyl-1,6-dimethyl-3-[2-(phenylsulfonyl)[2-^{13}C]acetyl]heptalene-4-carboxylate* (**19a***). BuLi soln. (1.62 ml, 4.05 mmol) was slowly added at −5° to a soln. [^{13}C]H_3SO_2Ph (24.9 atom-% ^{13}C; 0.67 g, 4.28 mmol) in dry THF (30 ml). After stirring at −5° for 30 min, a white precipitate had been formed. The mixture was cooled to −78°, and a soln. of **15a** (0.915 g, 2.69 mmol) [11] in THF (5 ml) was added dropwise. After stirring for 1 h at −70°, the mixture was acidified with 1N aq. HCl soln. and extracted with Et_2O (3 × 100 ml). The org. phase was washed with H_2O (3 × 200 ml) and with brine (1 × 200 ml), and dried ($MgSO_4$). The solvent was removed, and the residue was chromatographed (silica gel (250 g); Et_2O/hexane 1:1). Crystallization from Et_2O/hexane gave **19a*** (0.622 g, 1.34 mmol, 50%) as yellow crystals. In addition, **20a**** (0.092 g, 0.16 mmol, 6%) and starting material **15a** (0.356 g, 1.05 mmol, 39%) were isolated.

Data of **19a***: M.p. 140–141°. R_f (hexane/AcOEt 2:1) 0.30. ^{1}H-NMR ($CDCl_3$): 8.08 (*dt*, ^3J = 7.0, ^4J = 1.7, H_o of Ph); 7.62 (*m*, H_p of Ph); 7.53 (*m*, H_m of Ph); 7.44 (*dd*, ^3J = 6.5, ^5J = 0.9, H–C(3)); 6.28 (*d*, ^3J = 6.6, H–C(8)); 6.24 (*dd*, ^3J = 6.4, ^4J = 1.3, H–C(7)); 6.15 (*dd*, ^3J = 6.5, ^4J = 1.4, H–C(2)); 5.84 (*s*, H–C(10)); 4.66/4.64 (*AB*, J_{AB} = 17.9, [^{12}C]H_2SO_2; *ABX*, J_{AB} = 17.9, $J_{AX}=J_{BX}$ = 136.5, [^{13}C]H_2SO_2); 3.51 (*s*, MeOCO); 2.49 (*sept.*, *J* = 6.9, Me_2CH); 2.049 (*t*, $^4J \approx {}^5J$ = 1.1, Me–C(1)); 1.821 (*s*, Me–C(6)); 1.090/1.059 (2*d*, ^3J = 6.9, 6.8, Me_2CH); ^{13}C-NMR ($CDCl_3$): 194.10 (*s*, O=*C*–C(5)); 166.86 (*s*, O=*C*–C(4)); 150.26/144.39 (2*s*); 141.60 (*d*); 139.94, 139.48 (2*s*); 133.55 (*d*); 132.07, 131.97, 130.81 (3*s*); 129.43, 129.04, 128.70 (3*d*); 127.91 (*s*); 125.86, 125.68, 124.78 (3*d*); 65.15 (enhanced *t*, CH_2SO_2); 52.01 (*q*, *Me*OCO); 35.71 (*d*, Me_2CH); 25.15, 23.69, 23.01, 22.60 (4*q*).

*Data of 8-Isopropyl-6,11-dimethyl-2-(phenylsulfonyl)-3-[(phenylsulfonyl)[^{13}C]methyl][2-^{13}C]cyclopenta[*a*]heptalen-1(1*H*)-one* (**20a****): M.p. 221–222° (dec.). R_f (hexane/AcOEt 2:1) 0.18. ^{1}H-NMR ($CDCl_3$): 8.24 (*dt*, ^3J = 7.0, ^4J = 1.5, H_o of $PhSO_2$–C(2)); 8.08 (*dt*, ^3J = 7.1, ^4J = 1.5, H_o of $PhSO_2CH_2$–C(3)); 7.70 (*tt*, ^3J = 7.4, ^4J = 1.4, H_p of $PhSO_2CH_2$–C(3)); 7.59 (*m*, H_p of $PhSO_2$–C(2), H_m of $PhSO_2CH_2$–C(3)); 7.51 (*tt*, ^3J = 7.4, ^4J = 1.6, H_m of $PhSO_2$–C(2)); 6.88 (*d*, ^3J = 7.0, H–C(4)); 6.40 (*dd*, ^3J = 7.0, ^4J = 1.2, H–C(10)); 6.27 (*dd*, ^3J = 7.2, ^4J = 1.2, H–C(5), H–C(9)); 6.15 (*d*, ^4J = 1.1, H–C(7)); 5.25/5.14 (*AB*, J_{AB} = 12.7, [^{12}C]H_2–C(3); *ABX*, J_{AB} = 12.7, $J_{AX}=J_{BX}$ = 141.7, [^{13}C]H_2–C(3)); 2.49 (*sept.*, ^3J = 6.8, Me_2CH); 2.145 (*d*, ^4J = 0.6, Me–C(6)); 2.132 (*s*, Me–C(11)); 1.109, 1.091 (2*d*, ^3J = 6.9, 6.8, Me_2CH); ^{13}C-NMR ($CDCl_3$): 180.24 (*s*, C=O); 152.27, 148.57, 144.48, 140.59, 140.20, 139.55, 138.22 (7*s*); 137.79 (enhanced *s*, C(2)); 134.32, 133.71 (2*d*); 132.63 (*s*); 131.85 (*d*); 131.51 (*s*); 129.69, 129.44, 129.27, 128.66, 128.45, 126.71, 126.63 (7*d*); 125.18 (*s*); 52.34 (enhanced *t*, CH_2SO_2); 35.91 (*d*, Me_2CH); 25.84, 24.39, 22.99, 22.87 (4*q*).

3.3. *Formation of 9-Isopropyl-7,12-dimethyl-3-(phenylsulfonyl)-[1-^{13}C]benzo[a]heptalene-2,4-diol* (**5a***). $MeSO_2Ph$ (0.255 g, 1.63 mmol) was dissolved in dry THF (10 ml). The mixture was cooled to $-5°$, and BuLi soln. (0.65 ml, 1.63 mmol) was added slowly. While stirring at $-5°$, a white precipitate was formed. After 30 min, the mixture was cooled to $-78°$, and a soln. of **19a*** (0.150 g, 0.322 mmol) in THF (5 ml) was added. The temp. was raised within 2 h to $-5°$. Additional BuLi soln. (0.51 ml, 1.28 mmol) was added, and the mixture was allowed to warm up to r.t. After 30 min, the reaction was quenched by addition of 1N aq. HCl soln. The products were extracted with Et_2O (3×30 ml). The org. phase was washed with H_2O (3×50 ml) and with brine (1×50 ml), and dried ($MgSO_4$). The solvent was distilled off, and the residue was chromatographed (silica gel (100 g); Et_2O/hexane 1:1). Diol **5a*** (0.009 g, 6%) and **20a*** (0.019 g, 10%) were isolated. Unreacted $MeSO_2Ph$ was recovered as a third component.

Data of **5a***: Identical with those reported in [7]. ^{1}H-NMR ($CDCl_3$): 6.22 (75% *s* and 25% *d*, $^1J = 165.7$, H–C(1)). ^{13}C-NMR ($CDCl_3$): 109.79 (enhanced *d*, C(1)).

Data of **20a***. ^{1}H-NMR ($CDCl_3$): As above. Clear *AB* for $PhSO_2CH_2$–C(3). ^{13}C-NMR ($CDCl_3$): As above; however, no enhanced *t* for $PhSO_2CH_2$–C(3), but strongly enhanced *s* for C(2).

Recovered $MeSO_2Ph$: ^{1}H- and ^{13}C-NMR ($CDCl_3$) showed at the Me group no ^{13}C incorporation above the natural level.

REFERENCES

[1] K. Nakanishi, T. Goto, S. Itô, S. Natori, S. Nozoe, 'Natural Products Chemistry', Kodansha Ltd., Academic Press, Inc., Tokyo, 1975, Vol. 2, p. 349 ff.
[2] M. G. Banwell, *Aust. J. Chem*. **1991**, *44*, 1.
[3] K. Hafner, G. L. Knaup, H. J. Lindner, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 155.
[4] Y. Chen, R. W. Kunz, P. Uebelhart, R. H. Weber, H.-J. Hansen, *Helv. Chim. Acta* **1992**, *75*, 2447.
[5] K. Abou-Hadeed, H.-J. Hansen, *Helv. Chim. Acta* **2000**, *83*, in preparation.
[6] a) P. Uebelhart, P. Mohler, R.-A. Fallahpour, H.-J. Hansen, *Helv. Chim. Acta* **1995**, *78*, 1437; b) C. Hörndler, H.-J. Hansen, *Helv. Chim Acta* **1997**, *80*, 2520.
[7] K. Abou-Hadeed, H.-J. Hansen, *Helv. Chim. Acta* **1997**, *80*, 2535.
[8] M. Lutz, A. Linden, K. Abou-Hadeed, H.-J. Hansen, *Helv. Chim. Acta* **1999**, *82*, 372.
[9] P. Uebelhart, H.-J. Hansen, *Helv. Chim. Acta* **1992**, *75*, 2493.
[10] P. Göksaltik, diploma thesis, University of Zurich, 2000.
[11] R. H. Weber, P. Brügger, T. Jenny, H.-J. Hansen, *Helv. Chim. Acta* **1987**, *70*, 742.
[12] R. H. Weber, P. Brügger, W. Arnold, P. Schönholzer, H.-J. Hansen, *Helv. Chim. Acta* **1987**, *70*, 1439.
[13] S. El Houar, H.-J. Hansen, *Helv. Chim. Acta* **1997**, *80*, 253.
[14] K. Abou-Hadeed, H.-J. Hansen, *Helv. Chim. Acta* **2000**, *83*, in preparation.
[15] K. Hafner, H. Weldes, *Liebigs Ann. Chem*. **1957**, *606*, 90; K. Hafner, C. Bernbhard, *Liebigs Ann. Chem.* **1959**, *625*, 108.
[16] J. Wildeman, A. M. van Leusen, *Synthesis* **1979**, 733.

Received June 22, 2000