Note

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c00909 • Publication Date (Web): 17 Jul 2020

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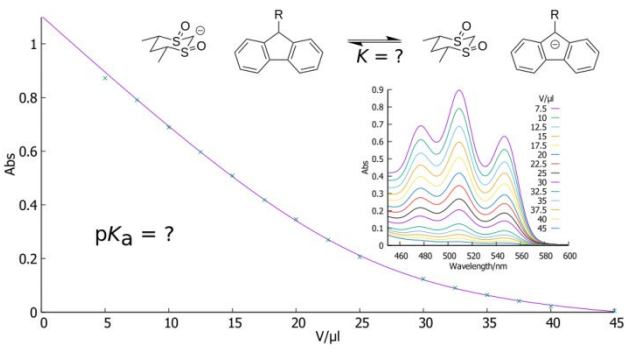


Abstract: Two methods for the determination of pK_a values of weak acids are described, a direct titration with dimsyl potassium in the presence of an indicator and a back titration in which an analyte/indicator mixture is deprotonated and then titrated with ammonium chloride. Both methods have been validated by measuring pK_a values of compounds, for which values had been determined previously. The back titration methods was applied to the measuring of pK_a values of two 1,3-dithiane-derived bissulfoxides and a monosulfone.

Keywords: C–H acidity / pK_a values / Titration / UV absorption / Dithianes

A precise knowledge of pK_a values significantly facilitates the understanding of organic reactions including their thermodynamics, kinetics, their reaction mechanisms, and the resulting selectivities.[1]

During our continuous efforts in the investigation of stereoelectronic effects in sulfur-based functional groups,[2-9] we measured and calculated pK_a values[6] of thiane- and dithiane-derived sulfide, sulfoxide, and sulfone anions.[4] Herein we present a simple and general method for the measurement of pK_a values of weakly C–H-acidic compounds.

Only a small fraction of organic acids (AH) show strong acidities which can be determined in aqueous solution. Since the early 1930s efforts were made to expand the acidity scales beyond pK_a = 14. In their seminal work Conant and Wheland presented the definition of relative pK_a values not dependent on the proton concentration; they can be expressed without explicit consideration of the used solvent. The pK_a value is here calculated relative to the known pK_a value of an indicator (IndH).[10]

The balance between an indicator and a base (A^-) leads to an equation allowing for the calculation of the conjugate acid's (AH) pK_a value from the (known) indicator's pK_a value and the equilibrium constant K. (A stepwise deviation of the relevant equations is given in the Supporting Information.)

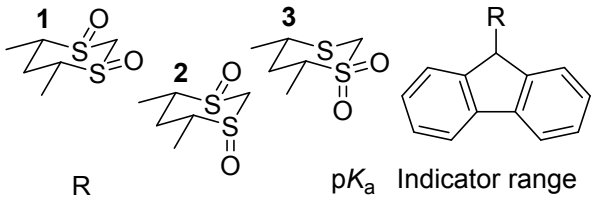
$$Ind^- + AH \overset{K}{\rightleftharpoons} IndH + A^-$$

$$pK_a\,(AH) = pK_a\,(IndH) - \log(K)$$

Determination of pK_a values is thus possible by measuring of the equilibrium concentrations of the conjugate acids and bases of the analyte and an indicator with known pK_a. Although the solvent does not appear in these equations, it has an influence on the absolute and relative pK_a values of acids. Depending on the charge states of the acids and conjugate bases, the polarity of the solvent and the ability to act as hydrogen bond acceptor or donor can shift the pK_a values for several orders of magnitude. For this reason pK_a values of weak acids have been determined

in various solvents, mostly in DMSO,[1] in acetonitrile,[11] in *N*,*N*-dimethylformamide (DMF),[12] and in cyclohexylamine.[13] An excellent overview on this work has been given by Leito et al.[14]

The determination of weak acids' pK_a values was dominated by the tremendous amount of work finished by Bordwell et al., who determined the acidity in DMSO of more than 1000 compounds.[1] They used indicators whose deprotonated anions show absorbance in UV/Vis spectra, allowing a spectroscopic measurement of their concentrations according to the Beer–Lambert law. An indicator can only be used for pK_a value determinations in a range of ±2 units around its own pK_a value. After the pK_a scale in DMSO was established with the first measured compounds, it could be expanded by the utilization of new indicators overlapping in its applicable pK_a range with the respective ranges of previously used indicators (Figure 1).[15] This strategy is now known as the overlapping or bracketing indicator method.[16]



R		pK_a	Indicator range
Me	MFH (**4**)	22.3	20.3–24.3
*t*Bu	*t*BuFH (**5**)	24.4	22.4–26.4
CH_2tBu	NpFH (**6**)	20.3	18.3–22.3
Ph	PhFH (**7**)	17.9	15.9–19.9

Figure 1. Investigated Compounds **1**–**3**. The Indicators **4**–**7** are Applicable in the Given pK_a Ranges.

Unfortunately, Bordwell's method is (to the best of our knowledge) documented rather sparsely in their publications. The possibly most detailed description is given in Ref. [15] and a short summary hereof is given in the Supporting Information. A key feature of Bordwell's method is its generality. Any substance that can be deprotonated in equilibrium and being transparent at the observed wavelengths can be measured. As the concentration of the analyte is smaller than the concentration of the indicator, the rates of side reactions and effects of homoconjugation (homoassociation)[17] are reduced.

Alternative procedures have been reported by O'Donoghue[18] and Leito.[11, 19-24] Nevertheless, these procedures were either not used for the determination of very high pK_a values or the analyte (anion) needs to show UV absorption. Furthermore, we considered the necessity of performing the respective measurements in a glove box[22-24] an inconvenient limitation.

Our own efforts to reproduce the protocol of Bordwell by using a quartz cell with a Schlenk stopcock and gas-tight syringes ran more than disappointing. It turned out that gravimetric determination of volumes gave erratic results due to variable argon pressures. Furthermore, each removal from the argon line caused small contaminations with air. Even the very simple punching of a needle trough the septum led to a significant decrease of absorbance, obviously

due to introduction of oxygen. Another issue was a contamination of all DMSO solutions (except for the DimK solution) with tiny amounts of ubiquitous acid. (Leito similarly reported the presence of acidic contaminations in acetonitrile.[23]) Consequently, we envisioned a protocol mostly avoiding these detrimental issues, allowing pK_a measurements of very weak acids using conventional laboratory equipment.

Direct Titration of Analyte/Indicator Mixtures. If a DimK solution of known concentration is successively added to an analyte/indicator mixture, the acid dissociation constant K can be calculated from the increase of absorbance. Ubiquitous acid contaminations do not interfere, as long as the pK_a values of these acids are considerably smaller than the analyte's pK_a value. A small fraction of the initially added DimK solution neutralizes these contaminants before the analyte/indicator equilibration is reached. As the base is added via syringe, its amount can be measured volumetrically. No connecting/disconnecting of any part is necessary and a possible contamination with oxygen is minimized. To reduce weighing errors in the alignment of the analyte/indicator ratio we always used 1:1 mixtures. Each addition results in a data point, allowing the calculation of a value for K. The instability of the DimK solution made an independent determination of its concentration impractical; its concentration was instead obtained by a curve fitting process if a sufficient number of data points is available. Four data

points are the minimum number to fit the four parameters used in the final equation, while an error can only be estimated with eight data points. Even more data points are preferable, especially when the pK_a value difference between analyte and indicator is large. Deviation of the relevant equations is given in the Supporting Information.

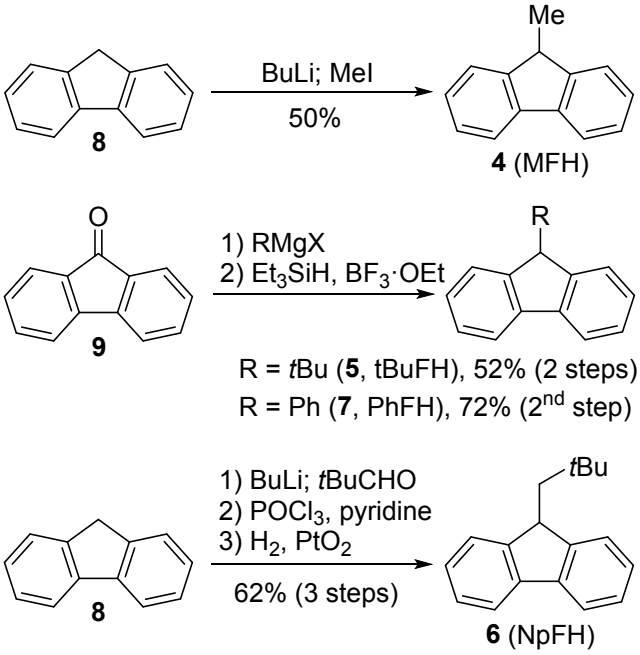
As indicators we used fluorene derivatives **4**–**7**, for which pK_a values were provided by Bordwell et al.[15, 25] With MFH (**4**) as indicator, the published pK_a value of indole was reproduced with good accuracy (deviation <0.1 units). However, a significant attrition of the glass syringes used for addition of DimK solution was observed. Following each addition of base, no further change of the equilibrium was observed after 30–60 seconds, which allowed a rapid acquisition of data points. With pyrrole, dithiane derivatives **1**–**3**, and other compounds it lasted more than three minutes to reach the respective equilibria. In these cases non-satisfying fits were obtained due to a decrease of the DimK concentration during the experiment. For these compounds an alternative procedure was developed.

Back Titration of Analyte/Indicator Mixtures. A mixture of quantitatively deprotonated indicator and analyte can be stored without deterioration much longer in the quartz cell than the DimK solution can be kept in the syringe. Firstly, quartz is considerably less sensitive towards alkaline solutions than the syringe's glass and secondly, the conjugated bases are thermodynamically

less basic and thus more stable than the dimsyl anion. This alternative protocol is initiated by rapid addition of DimK solution to the analyte/indicator mixture until maximum absorbance is reached. The actual measurement is then performed by portionwise addition of a proton source, where we used an ammonium chloride solution. This proton donor is transparent in its protonated and deprotonated states and seems to be not prone to detrimental side reactions. The relevant equations are again given in the Supporting Information.

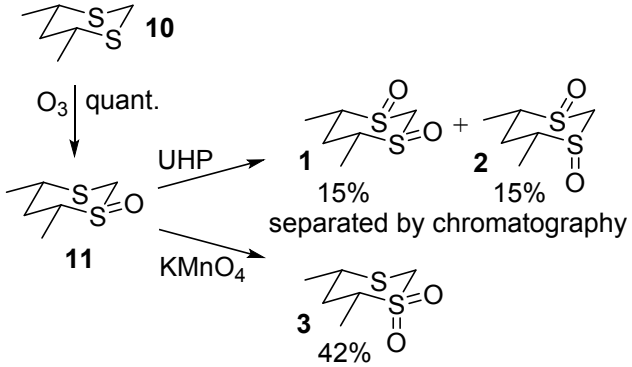
MFH (**4**), tBuFH (**5**), and PhFH (**7**) were synthesized by slight modification of published protocols;[26-27] particularly the purification processes were improved to obtain compounds of high purity (Scheme 1). The published synthesis of 9-neopentylfluorene (NpFH, **6**) required harsh conditions and gave low yields.[28] We considered a method published by Katz et al. for the synthesis of similar compounds more useful:[29] Condensation of fluorene (**8**) with pivaldehyde and subsequent hydrogenation furnished NpFH (**6**) with high purity.

Scheme 1. Synthesis of Indicators.



The synthesis of the isomeric 1,3-dithiane dioxides **1**, **2** and **3** has already been reported by us[5] and others.[30-31] Here we present a simpler method for the synthesis of monoxide **11** (Scheme 2): Oxidation of 1,3-dithiane **10** with ozone afforded sulfoxide **11** with virtually quantitative yield and high purity.

Scheme 2. Synthesis of Dithiane Dioxides.



We validated the herein presented methods by determining the pK_a values of compounds for which data had already been published. The methods were established and optimized using indole as analyte and MFH or tBuFH, respectively, as indicators. We additionally determined the pK_a values of indole, pyrrole, diphenylamine, and benzyl phenyl sulfone with the back titration method; the obtained values turned out to be in good agreement with the published data (Table 1). Nevertheless, titrations of 2,2,2-trifluoroethanol and acetophenone were not successful. No stationary absorbance was observed after addition of the base, possibly due to side reactions: Trifluoroethanolate is prone to fragmentation into formaldehyde and the CF_3^- anion, while acetophenone is most likely undergoing an aldol reaction. The latter reaction probably was a negligible problem with Bordwell's protocol, since the analyte's concentration was there kept lower, thus decreasing the rate constant of intermolecular side reactions. Fluorene (FH) can be used with reservations as indicator in the direct titration, but turned out to be not applicable in the back titration, since a side reaction was observed at high concentrations of the base leading to additional UV/Vis absorptions. (Problems with fluorene as indicator had already been reported in the literature.[32]) Substituted fluorenes show different behavior in the presence of excess base: Methylfluorene (MFH) shows an irreversible decrease of absorbance when additional DimK is added, while *tert*-butylfluorene (tBuFH) turned out to be stable even at high base concentrations

and is thus ideally suited for titrations with strong bases (see Supporting Information: titration of pyrrole with MFH and tBuFH). To suppress adverse effects, it is recommended to avoid a distinct overtitration and the presence of high base concentrations.

Table 1. Measured pK_a values.

Compound	pK_a (Indicator)	Previously published pK_a values
indole	21.0 (MFH)	20.95[33]
pyrrole	22.7 (MFH)	23.05[33]
	23.0 (tBuFH)	
diphenylamine	25.0 (tBuFH)	24.95[34]
benzyl phenyl sulfone	23.4 (tBuFH)	23.4[1]
acetophenone	failed	24.7[15]
2,2,2-trifluoroethanol	failed	23.45[1]
bissulfoxide (eq/eq) **1**	23.4 (MFH)	25.4 (26.8)[a]
	23.4 (tBuFH)	
bissulfoxide (eq/ax) **2**	24.9 (tBuFH)	24.1 (25.5)[a]
sulfone **3**	25.4 (tBuFH)	23.4 (25.5)[a]

[a] Values predicted on DFT level, MP2 level is given in parenthesis. These values have been calculated by us previously.[6]

Fitting of the data is usually possible with an error below 0.1 pK_a units, which is in accordance with deviations in independent experiments. The protocol is very simple to perform and could be reproduced even by undergraduate students after a short instruction.

We have previously published calculated and provisional experimental pK_a values[6] for 1,3-dithiane dioxide isomers **1**–**3** to correlate these values with stereoelectronic effects operative in dithiane derivatives.[3-5, 7] pK_a values of these compounds could be successfully determined with the new protocol. Identical pK_a values for bissulfoxide **1** were determined with MFH and tBuFH as indicators. Systematic deviations between experimental and calculated pK_a values can be expected; they are intrinsic possibilities with the method applied in the calculations. Possible explanations for the discrepancies could be ion pairing or homoconjugation, i.e., the association of protonated and deprotonated species, or of specific stabilizing interactions of the anions with solvent molecules. These effects are not included in the solvent correction used for the quantum chemical prediction of pK_a values.

We developed a simple and robust protocol for the determination of pK_a values, where a simple Schlenk line is sufficient; a glove box is not required. An accuracy of ~0.1 pK_a units, which had already been reported by Bordwell et al. could be reproduced with our methods, provided that no side reactions occur with the analyte or indicator. Though we used indicator/analyte

ratios of 1:1 to reduce weighing errors, the methods are not limited to that ratio. Variations of this ratio could possibly be useful for the investigation of homoconjugation and ion pairing. The upper limit for pK_a measurements with the indicators used by us is ~26.4. Bordwell stated for his original method that acids with pK_a ranges of 32–35 are difficult to measure in DMSO (pK_a = 35) due to leveling effects of the solvent.[1]

It is likely that our protocols could be adapted for measurements in other solvents, especially to the quite similar solvent acetonitrile, but our experience from the optimization of our protocols leads one to assume that some alterations in detail would be necessary.

Experimental Section

General. Tetrahydrofuran (THF) and pentane were distilled from sodium benzophenone ketyl radical prior to use. DMSO was distilled as described in the text. All moisture-sensitive reactions were carried out under oxygen-free argon using oven-dried glassware and a vacuum line (Schlenk technique). Liquids were handled with gas-tight syringes. Ozone was generated with an ozone generator 300.5 (Erwin Sander Elektroapparatebau) from dry air. Flash column chromatography was carried out using Merck silica gel 60 (230–400 mesh) and thin-layer chromatography was carried out by using commercially available Merck F_{254} pre-coated sheets. Spots were detected by fluorescence quenching and staining in an iodine chamber. NMR

spectra were recorded on Bruker Avance AV 300, Bruker Avance 400, or Bruker Avance III HD 500 spectrometers. ^{13}C NMR spectra were recorded with broad band decoupling and signals were assigned by HSQC experiments. The spectra were calibrated using the residual solvent signals. IR spectra were recorded on a Bruker FT-IR spectrometer 'Alpha' (Bruker) using ATR on diamond. EI and FAB mass spectra were recorded with a Finnigan MAT-95 and APCI spectra were recorded with a Q Exactive Orbitrap (Thermo Fisher). UV/Vis spectra were measured with a Cary 60 UV-Vis (Agilent) spectrometer. We used a quartz cell with septum screw cap and a UV/Vis spectrometer with a thermostatted holder for the measurements. Melting points were measured with an Optimelt MPA100 apparatus and are not corrected. Most syntheses have been performed according to literature procedures; these are only included in the supporting information.

9-Methyl-9*H*-fluorene (MFH, 4). The compound was synthesized in slight modification of a published procedure.[26] BuLi (2.5 M in hexanes, 9.40 mL, 23.5 mmol) was added dropwise at –78 °C to a solution of fluorene (3.00 g, 18.0 mmol) in THF (60 mL). The mixture was warmed to rt to dissolve the precipitate and cooled again to –78 °C. MeI (1.70 mL, 3.85 g, 27.1 mmol) was added dropwise. The mixture was allowed to warm to rt and concentrated at reduced pressure. The residue was partitioned between CH_2Cl_2 (100 mL) and H_2O (50 mL) and the organic layer

was washed with half-concentrated brine (50 mL), dried (Na_2SO_4), concentrated at reduced pressure, dissolved in MeOH (25 mL) and stored overnight at –18 °C. The precipitated crystals were filtered off and dried at reduced pressure to yield the product (1.63 g, 9.05 mmol, 50%) as a colorless fine crystalline solid. m. p. 43–44 °C (MeOH) (44–46 °C).[35] ^{1}H NMR (300 MHz, acetone-d_6): δ = 1.49 (d, ^3J = 7.4 Hz, 3 H, CH_3), 3.94 (q, ^3J = 7.29 Hz, 1 H, 9-H), 7.27–7.40 (m, 4 H, Ar-H), 7.52–7.59 (m, 2 H, Ar-H), 7.80–7.85 (m, 2 H, Ar-H); the spectroscopic data are in full agreement with reported data.[26]

9-(*tert*-Butyl)-9*H*-fluoren-9-ol. The compound was synthesized in slight modification of a published procedure.[27] *t*BuMgCl (1.0 M in THF, 10.0 mL, 10.0 mmol) was added dropwise within 20 min at 0 °C to a solution of fluorenone (1.00 g, 5.55 mmol) in THF (40 mL). The mixture was warmed to rt within 3 h, quenched with H_2O (10 mL), diluted with EtOAc (100 mL), and washed with saturated NH_4Cl solution (3×50 mL). The combined aqueous layers were extracted with EtOAc (2×50 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), concentrated at reduced pressure, and purified by column chromatography (silica gel, cyclohexane/EtOAc, 30:1) to yield the product (743 mg, 3.12 mmol, 56%) as a colorless viscous oil. R_f = 0.22 (cyclohexane/EtOAc, 20:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 [s, 9 H, $C(CH_3)_3$],

1.93 (br s, 1 H, OH), 7.23 (dd, $^3J \approx {}^3J \approx 7.9$ Hz, 2 H, Ar-H), 7.34 (dd, $^3J \approx {}^3J \approx 7.5$ Hz, 2 H, Ar-H), 7.55–7.62 (m, 4 H, Ar-H).

9-(*tert*-Butyl)-9*H*-fluorene (tBuFH, 5). The compound was synthesized in slight modification of a published procedure.[27] $BF_3{\cdot}OEt_2$ (0.7 mL, 800 mg, 5.64 mmol) was added dropwise at 0 °C to a solution of 9-(*tert*-butyl)-9*H*-fluoren-9-ol (672 mg, 2.82 mmol) and Et_3SiH (0.9 mL, 656 mg, 5.64 mmol) in CH_2Cl_2 (6.5 mL) and the mixture was stirred for 1 h at 0 °C. Saturated aqueous Na_2CO_3 solution (2 mL) and half-concentrated brine (10 mL) were added, the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried (Na_2SO_4), concentrated at reduced pressure, and purified by column chromatography (silica gel, cyclohexane) to yield the product (583 mg, 2.62 mmol, 93%) as a colorless solid. m. p. 101–103 °C (cyclohexane). R_f = 0.45 (cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 [s, 9 H, $C(CH_3)_3$], 3.77 (s, 1 H, 9-H), 7.23 (dd, $^3J \approx {}^3J \approx 7.3$ Hz, 2 H, Ar-H), 7.35 (dd, $^3J \approx {}^3J \approx 7.4$ Hz, 2 H, Ar-H), 7.60 (d, $^3J = 7.5$ Hz, 2 H, Ar-H), 7.73 (d, $^3J = 7.5$ Hz, 2 H, Ar-H); the spectroscopic data are in full agreement with reported data.[36]

9-(2,2-Dimethylpropylidene)-9*H*-fluorene. The compound was synthesized according to a published method.[29] BuLi (2.5 M in hexanes, 3.6 mL, 9.15 mmol) was added dropwise at 0 °C to a solution of fluorene (1.52 g, 9.14 mmol) in Et_2O (10 mL) and the mixture was stirred at 0 °C

for 5 min, then at rt for 5 min and then cooled again to 0 °C. A solution of *t*BuCHO (1.0 mL, 790 mg, 9.14 mmol) in Et_2O (4.0 mL) was added and the mixture was stirred at 0 °C for 5 min and was allowed to warm to rt. Saturated aqueous NH_4Cl solution (30 mL) was added, the organic layer was separated and the aqueous layer was extracted with EtOAc (30 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and concentrated at reduced pressure. The crude mixture (2.36 g) of the title compound and 1-(fluoren-9-yl)-2,2-dimethylpropane-1-ol (TLC) was dissolved in pyridine (25 mL). A mixture of $POCl_3$ (13 mL) and pyridine (13 mL) was added at 0 °C and the resulting mixture was stirred for 2 h at 100 °C. After cooling to rt the mixture was poured onto ice water (150 mL) while a vivid exothermic reaction was observed. The mixture was extracted with EtOAc (3×100 mL). The combined organic layers were washed with aqueous $CuSO_4$ solution (0.5 M, 2×100 mL), saturated aqueous $NHCO_3$ solution (100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated at reduced pressure to yield the product (2.04 g, 8.71 mmol, 95%) as a yellow oil, which was used in the next step without further purification. R_f = 0.48 (cyclohexane, EtOAc, 100:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.59 [s, 9 H, $C(CH_3)_3$], 6.95 (s, 1 H, =CH), 7.26–7.42 (m, 4 H, Ar-H), 7.66–7.81 (m, 3 H, Ar-H), 8.04–8.10 (m, 1 H, Ar-H); the spectroscopic data are in full agreement with reported data.[37]

9-Neopentyl-9*H*-fluorene (NpFH, 6). The compound was synthesized using a published protocol.[29] A suspension of 9-(2,2-dimethylpropylidene)-9*H*-fluorene (2.00 g, 8.53 mmol) and $PtO_2 \cdot H_2O$ (100 mg, 0.408 mmol) in Et_2O (25 mL) was stirred at rt for 3 h under an atmosphere of H_2 (balloon). Solid material was removed by passing the mixture through a pad of Celite® and washing with Et_2O. The mixture was concentrated at reduced pressure and the remnant was dissolved in a minimum amount of hot EtOH, filtered hot and crystallized upon cooling to yield the product (1.31 g, 5.55 mmol, 65%) as long colorless needles. m. p. 75–78 °C (EtOH) (79–80 °C).[28, 38] R_f = 0.52 (cyclohexane/EtOAc, 100:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 [s, 9 H, $C(CH_3)_3$], 2.02 (d, ^3J = 4.1 Hz, 2 H, CH_2), 3.91 (t, ^3J = 4.0 Hz, 1 H, 9-H), 7.33–7.41 (m, 4 H, 2-H, 3-H, 6-H, 7-H), 7.57 (br d, ^3J = 7.5 Hz, 2 H, 1-H, 8-H or 4-H, 5-H), 7.78 (br d, ^3J = 7.4 Hz, 2 H, 4-H, 5-H or 1-H, 8-H); ^{13}C NMR (126 MHz, $CDCl_3$) : δ = 30.5 [C(CH_3)$_3$], 31.4 [C(CH_3)$_3$], 44.7 (C-9), 47.6 (CH_2), 119.7 (C-4, C-5 or C-1, C-8), 124.5 (C-1, C-8 or C-4, C-5), 126.7 (C-2, C-7 or C-3, C-6), 127.2 (C-3, C-6 or C-2, C-7), 140.7 (C_{quart}-Ar), 150.17 (C_{quart}-Ar); IR (ATR): $\tilde{\upsilon}$ = 3062, 3040, 2949, 2929, 2861, 1908, 1464, 1445, 1393, 1364, 1281, 1235, 1152, 1099; MS (APCI): *m/z* (%) = 252.1 (19), 251.1 (100), 235.1 (60), 179.1 (34), 121.1 (35); HRMS (APCI): *m/z* calcd for $C_{18}H_{19}$ ($M–H^+$): 235.1481; found 235.1478.

9-Phenyl-9*H*-fluoren-9-ol. The compound was synthesized in slight modification of a published procedure.[27] PhBr (0.5 mL, 0.748 g, 4.76 mmol) was added to a suspension of magnesium (turnings, 2.43 g, 100 mmol) in Et_2O (50 mL). The reaction was initiated by addition of I_2 (a small grain) then further PhBr (10.0 mL, 15.0 g, 95.2 mmol) in Et_2O (50 mL) was added dropwise within 20 min. The mixture was heated for 80 min under reflux, then cooled to 0 °C. A solution of fluorenone (**9**, 15.0 g, 83.3 mmol) in THF (50 mL) was added at 0 °C within 10 min. The mixture was allowed to warm to rt and poured into saturated aqueous NH_4Cl solution (300 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3×150 mL). The combined organic layers were washed with H_2O (2×150 mL) and brine (150 mL), dried (Na_2SO_4), and concentrated at reduced pressure. A fraction of the crude product was purified by column chromatography (silica gel, cyclohexane/EtOAc, 30:1) to yield the product as a highly viscous oil. Despite a prolonged drying (5 h) at high vacuum, the product contained 9% residual EtOAc (NMR). Nevertheless, the substance could be used in the next step without adverse effects. R_f = 0.35 (cyclohexane, EtOAc, 10:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.47 (s, 1 H, OH), 7.19–7.42 (m, 11 H, Ar-H), 7.68 (br d, ^3J = 7.5 Hz, 2 H, Ar-H); the spectroscopic data are in full agreement with reported data.[39]

9-Phenyl-9*H*-fluorene (PhFH, 7). The compound was synthesized in slight modification of a published procedure.[27] $BF_3{\cdot}OEt_2$ (0.9 mL, 1.01 g, 7.11 mmol) was added dropwise at 0 °C to a solution of 9-phenyl-9*H*-fluoren-9-ol (purity: 91%; 918 mg, 3.55 mmol) and Et_3SiH (1.1 mL, 826 mg, 7.11 mmol) in CH_2Cl_2 (8 mL) and the mixture was stirred at 0 °C for 40 min. Saturated aqueous Na_2CO_3 solution (1 mL) and half-concentrated brine (20 mL) were added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were dried (Na_2SO_4), concentrated at reduced pressure, and purified by column chromatography (silica gel, cyclohexane) and by recrystallization (cyclohexane/hexanes, 1:1) to yield the title compound (617 mg, 2.55 mmol, 72%) as colorless needles. m. p. 148 °C (cyclohexane/hexanes). R_f = 0.18 (cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.09 (s, 1 H, 9-H), 7.10–7.16 (m, 2 H, Ar-H), 7.23–7.46 (m, 9 H, Ar-H), 7.84 (br d, ^3J = 7.6 Hz, 2 H, Ar-H); the spectroscopic data are in full agreement with reported data.[27]

***meso*-2,4-Bis(4-toluenesulfonyloxy)pentane.** The compound was synthesized in slight modification of a published procedure.[40] A solution of 2,4-pentanediol (mixture of isomers, 50.0 g, 480 mmol) in pyridine (100 mL) was added dropwise within 3 h at –10 °C to a solution of *p*-TsCl (186 g, 974 mmol) in pyridine (500 mL). The mixture was stirred for 3 d at rt, then poured onto a mixture of ice (300 g) and concentrated HCl (200 mL). The mixture was extracted with

CH_2Cl_2 (3×250 mL). The combined organic layers were washed with 1 M HCl (3×100 mL), aqueous Cu_2SO_4 solution (10%, 3×100 mL), and half-concentrated brine (100 mL), concentrated at reduced pressure, dissolved in CH_2Cl_2 (100 mL), washed with 1 M HCl (3×100 mL) and half-concentrated brine (100 mL) to remove residual pyridine, dried (Na_2SO_4), concentrated at reduced pressure, and recrystallized repeatedly (5×, cyclohexane/EtOAc, 3:1) to yield the product (26.5 g, 64.2 mmol, 13%) as voluminous colorless crystals. The mother liquors were concentrated and combined to be used in further crystallizations. Repeated recrystallization afforded additional product. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (d, ^3J = 6.3 Hz, 6 H, 1-H, 5-H), 1.69 (dt, ^2J = 14.4 Hz, ^3J = 6.3 Hz, 1 H, 3-H), 2.04 (dt, ^2J = 14.2 Hz, ^3J = 7.0 Hz, 1 H, 3-H'), 2.45 (s, 6 H, Ar-CH_3), 4.57 (ddq, $^3J \approx {}^3J \approx {}^3J \approx$ 6.4 Hz, 2 H, 2-H), 7.33 (d, ^3J = 8.0 Hz, 4 H, Ar-H), 7.75 (d, ^3J = 8.3 Hz, 4 H, Ar-H).

***meso*-Pentan-2,4-dithiol.** The compound was synthesized in slight modification of a published procedure.[41] $Na_2S{\cdot}9H_2O$ (16.3 g, 67.8 mmol) was added portionwise within 15 min to a suspension of S_8 (4.50 g, 17.6 mmol) in DMF (375 mL). The mixture was stirred for 20 min at rt and *meso*-2,4-bis(4-toluenesulfonyloxy)pentane (55.9 g, 136 mmol) was added. The mixture was stirred for 3 d at 95 °C and poured onto ice (160 g). Concentrated HCl (10 mL) was added and the mixture was extracted with cyclohexane (5×150 mL). The combined organic layers were

washed with H_2O (2×150 mL), dried (Na_2SO_4), and concentrated at reduced pressure (40 °C, p > 50 mbar). Residual cyclohexane was removed by co-evaporation with acetone (30 mL) and pentane (30 mL). The crude mixture of trithiane (7.72 g, 46.4 mmol, 34%) and dithiolane (10.2 g, 75 mmol, 56%) was used in the next step without further purification or separation.

The mixture (17.9 g) was dissolved in Et_2O (150 mL) and added at 0 °C within 45 min to a suspension of $LiAlH_4$ (4.40 g, 116 mmol) in Et_2O (75 mL). The mixture was allowed to warm to rt and stirred at rt for 2.5 h. H_2O (30 mL) and H_2SO_4 (10%, 250 mL) were added carefully. After stirring at rt overnight the organic layer was separated and the aqueous phase was extracted with Et_2O (5×100 mL). The combined organic layers were washed with H_2O (100 mL), dried (Na_2SO_4), concentrated at reduced pressure, and distilled at reduced pressure (65–70 °C, 11 mbar). The distillate was dissolved in Et_2O (100 mL) and the solvent was extracted with aqueous KOH solution (20%, 3×100 mL). The combined aqueous layers were cooled, acidified with half-concentrated H_2SO_4 (100 mL), and extracted with Et_2O (3×100 mL). The combined organic layers were washed with H_2O, dried (Na_2SO_4), and concentrated at reduced pressure to yield the product (4.23 g [6% Et_2O], 29.2 mmol, 25%; 23% over 2 steps) as a yellow oil. Residual Et_2O cannot be removed without significant losses of the product. Nevertheless, it could be used without prejudice in the next step.

For future experiments it is recommended to perform the acid/base extraction before the distillation. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (d, ^3J = 6.7 Hz, 6 H, 1-H, 5-H), 1.49 (d, ^3J = 6.7 Hz, 2 H, SH), 1.77 (t, ^3J = 7.3 Hz, 2 H, 3-H), 3.08 (dtq, $^3J \approx {}^3J \approx {}^3J \approx$ 6.9 Hz, 2 H, 2-H, 4-H); the spectroscopic data are in full agreement with reported data.[42]

***meso*-4,6-Dimethyl-1,3-dithiane (10).** The compound was synthesized in adaption of a published procedure.[43] A solution of *meso*-pentan-2,4-dithiol (4.22 g, 31.0 mmol) and dimethoxymethane (2.7 mL, 2.36 g, 31.1 mmol) in $CHCl_3$ (100 mL) was heated to reflux and a solution of $BF_3{\cdot}OEt_2$ (7.7 mL, 8.80 g, 62.0 mmol) in $CHCl_3$ (100 mL) was added dropwise within 1 h. The mixture was stirred for 1 h at reflux, then cooled to rt, and quenched by addition of H_2O (150 mL). The organic layer was washed with saturated aqueous Na_2CO_3 solution (3×100 mL) and H_2O (50 mL), dried (Na_2SO_4), concentrated at reduced pressure, and purified by distillation (100 °C, 15 mbar) to yield the product (3.75 g, 25.3 mmol, 82%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (d, ^3J = 6.9 Hz, 6 H, 4-CH_3, 6-CH_3), 1.32 (dt, ^2J = 13.9 Hz, ^3J = 11.4 Hz, 1 H, 5-H_{ax}), 2.07 (dt, ^2J = 14.2 Hz, ^3J = 2.2 Hz, 1 H, 5-H_{eq}), 2.81 (dqd, ^3J = 11.4 Hz, ^3J = 6.8 Hz, ^3J = 2.2 Hz, 2 H, 4-H, 6-H), 3.53 (d, ^2J = 14.1 Hz, 1 H, 2-H_{eq}), 4.06 (d, ^2J = 14.1 Hz, 1 H, 2-H_{ax}).

***rac*-(1*S*,4*S*,6*R*)-4,6-Dimethyl-1,3-dithiane-1-oxide (11).** A stream of ozone (~160 mg, 3.32 mmol) was bubbled for 5 min at –40 °C through a solution of dithiane **10** (492 mg, 3.32 mmol) in CH_2Cl_2 (100 mL). The volatiles were removed at reduced pressure to yield the title compound (547 mg, 3.32 mg, quant.) as a colorless solid, which was used in the next steps without additional purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (d, ^3J = 6.8 Hz, 3 H, 4-CH_3), 1.44 (d, ^3J = 6.8 Hz, 3 H, 6-CH_3), 1.92 (ddd, ^2J = 15.0 Hz, $^3J \approx {}^3J \approx$ 11.9 Hz, 1 H, 5-H_{ax}), 2.27 (ddd, ^2J = 15.0 Hz, $^3J \approx {}^3J \approx$ 2.3 Hz, 1 H, 5-H_{eq}), 2.69 (dqd, ^3J = 12.1 Hz, ^3J = 6.8 Hz, ^3J = 2.3 Hz, 1 H, 6-H), 3.05 (dqd, ^3J = 11.4 Hz, ^3J = 6.8 Hz, ^3J = 2.2 Hz, 1 H, 4-H), 3.78 (d, ^2J = 12.7 Hz, 1 H, 2-H_{eq}), 3.98 (d, ^2J = 12.7 Hz, 1 H, 2-H_{ax}); the spectroscopic data are in full agreement with reported data.[5]

***meso*-(1*S*,3*R*,4*S*,6*R*)-4,6-Dimethyl-1,3-dithiane-1,3-dioxide (1) and *rac*-(1*R*,3*R*,4*S*,6*R*)-4,6-Dimethyl-1,3-dithiane-1,3-dioxide (2).** The compounds were synthesized in slight modification of a published procedure.[5] Finely ground urea hydrogen peroxide (UHP; 952 mg, 10.1 mmol) was added to a solution of sulfoxide **11** (1.51 g, 9.20 mmol) in AcOH (50 mL). The mixture was stirred at rt overnight and concentrated at reduced pressure. The residue was partitioned between CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ solution (80 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4×50 mL). The combined organic

phases were concentrated at reduced pressure and purified by flash chromatography (silica gel, CH_2Cl_2/MeOH, 50:1→30:1) to yield the bissulfoxides **1** (250 mg, 1.38 mmol, 15%) and **2** (256 mg, 1.42 mmol, 15%) as colorless solids. **1**: m. p. 209–212 °C, decomp. (CH_2Cl_2/MeOH) (Lit: 199–210°C).[5] R_f = 0.41 (CH_2Cl_2/MeOH, 10:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (d, ^3J = 6.9 Hz, 6 H, 4-CH_3, 6-CH_3), 1.42–1.57 (m, 1 H, 5-H_{ax}), 2.20 (dtd, ^2J = 17.1 Hz, ^3J = 2.4 Hz, ^5J = 0.7 Hz, 1 H, 5-H_{eq}), 2.90 (dqd, ^3J = 12.4 Hz, ^3J = 6.8 Hz, ^3J = 2.4 Hz, 2 H, 4-H, 6-H), 3.89 (br d, ^2J = 10.9 Hz, 1 H, 2-H_{eq}), 4.74 (d, ^2J = 10.9 Hz, 1 H, 2-H_{ax}). The spectroscopic data are in agreement with those reported in literature.[5] **2**: m. p. 200–202 °C, decomp. (CH_2Cl_2/MeOH) (Lit: 196–200°C).[5] R_f = 0.47 (CH_2Cl_2/MeOH 10:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (d, ^3J = 7.0 Hz, 3 H, 4-CH_3 or 6-CH_3), 1.53 (d, ^3J = 6.8 Hz, 3 H, 6-CH_3 or 4-CH_3), 1.98 (ddd, ^2J = 16.0 Hz, ^3J ≈ ^3J ≈ 2.3 Hz, 1 H, 5-H_{eq}), 2.58 (ddd, ^2J = 16.0 Hz, ^3J ≈ ^3J ≈ 12.1 Hz, 1 H, 5-H_{ax}), 2.90 (partly covered, dqd, ^3J = 12.0 Hz, ^3J = 7.1 Hz, ^3J = 2.4 Hz, 1 H, 4-H or 6-H), 2.99 (partly covered, dqd, ^3J = 12.4 Hz, ^3J = 6.9 Hz, ^3J = 2.1 Hz, 1 H, 6-H or 4-H), 3.52 (d, ^2J = 13.0 Hz, 1 H, 2-H_{eq}), 4.66 (d, ^2J = 13.0 Hz, 1 H, 2-H_{ax}). The spectroscopic data are in agreement with those reported in literature.[5]

***rac*-(4*S*,6*R*)-4,6-Dimethyl-1,3-dithiane-1,1-dioxide (3).** The compound was synthesized in slight modification of a published procedure.[5] A solution of $KMnO_4$ (441 mg, 2.79 mmol) in H_2O

(20 mL) was added dropwise at rt over 15 min to a solution of sulfoxide **11** (305 mg, 1.86 mmol) in acetone (30 mL). After stirring overnight at rt the mixture was decolorized by addition of saturated aqueous $NaHSO_3$ solution and extracted with CH_2Cl_2 (4×50 mL). The combined organic layers were washed with half-concentrated brine (40 mL), dried (Na_2SO_4), concentrated at reduced pressure, and purified by two subsequent flash chromatographies (first: silica gel, $CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH, 10:1; second: silica gel, CH_2Cl_2/Et_2O, 5:1) and a recrystallization (cyclohexane/EtOAc) to yield the product (142 mg, 0.788 mmol, 42%) as colorless woolly crystals. m. p. 197–198 °C (cyclohexane/EtOAc) (198–200 °C).[5] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (d, ^3J = 6.8 Hz, 3 H, 4-CH_3), 1.37 (d, ^3J = 6.8 Hz, 3 H, 6-CH_3), AB signal (partly covered, δ_A = 2.31, δ_B = 2.23, J_{AB} = 14.6 Hz; A part additional split: dd, $^3J \approx {}^3J \approx$ 11.2 Hz; B part additional split: dd, $^3J \approx {}^3J \approx$ 3.3 Hz, 2 H, 5-H), 3.10 (dqd, ^3J = 11.3 Hz, ^3J = 7.1 Hz, ^3J = 4.2 Hz, 1 H, 6-H), 3.19 (partly covered, dqd, ^3J = 10.3 Hz, ^3J = 6.9 Hz, ^3J = 3.3 Hz, 1 H, 4-H), 3.69 (d, ^2J = 14.6 Hz, 1 H, 2-H_{eq}), 4.12 (d, ^2J = 14.6 Hz, 1 H, 2-H_{ax}). The spectroscopic data are in full agreement with those reported in literature.[5]

Supporting Information Available: Experimental details, spectra and scripts. This material is available free of charge via the Internet at http://pubs.acs.org.

Acknowledgment. We thank Marcel Schendel and Tobias C. Bentzel for their help within the advanced lab courses.

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