# Tandem Hemiketal Formation-Intramolecular *Friedel-Crafts* Alkylation: A Facile Route to Hetero-Atom-Substituted Benzo-Fused Bicyclo[3.3.1]nonanes

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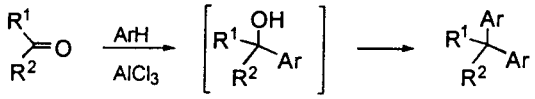
A previously unknown intramolecular *Friedel-Crafts* alkylation with *in situ* formed hemiketals as the electrophile is reported.

In the 120 years history of the *Friedel-Crafts* (*F-C*) reaction, ketones [1], either in the free carbonyl form or after being masked as ketals, have never been mainstay alkylating agents. This is presumably because, in the presence of a strong acid (a pre-requisite for most *F-C* reactions), ketones often undergo extensive side reactions leading to polymeric by-products. Also, as shown [2] by the examples available in the literature, alkylation of aromatics with ketones are normally difficult to stop at the monarylation (*i.e.*, with only one aromatic group attached to the carbonyl C-atom) stage. In most cases, the hydroxy compound formed in the first arylation reacts further with the aromatics to give diarylated products (*Scheme 1*). As for the *F-C* reactions of ketals, no case of preparative significance (to our knowledge) was known until recently, when we showed [3] that spiroketals may undergo intramolecular *F-C* alkylation in the presence of a *Brønsted* or *Lewis* acid. In this contribution, we wish to report on the first examples of synthetically significant *F-C* reactions with *in situ* formed hemiketals as alkylating agents. These results further extend the limits and scope of the well-established *F-C* reaction and exemplify new facile entries to the otherwise not easily accessible hetero-substituted benzo-fused bicyclo[3.3.1]nonane ring system.

*Scheme 1*




The precursors (open-chain hydroxy ketones) of cyclic hemiketals are prepared from corresponding aromatic aldehydes **1** in four steps as shown in *Scheme 2*. The aldol condensation of cyclopentanone with the aromatic aldehyde followed by elimination of $H_2O$ gave the intermediate $\alpha,\beta$-unsaturated ketones, which were directly hydrogenated

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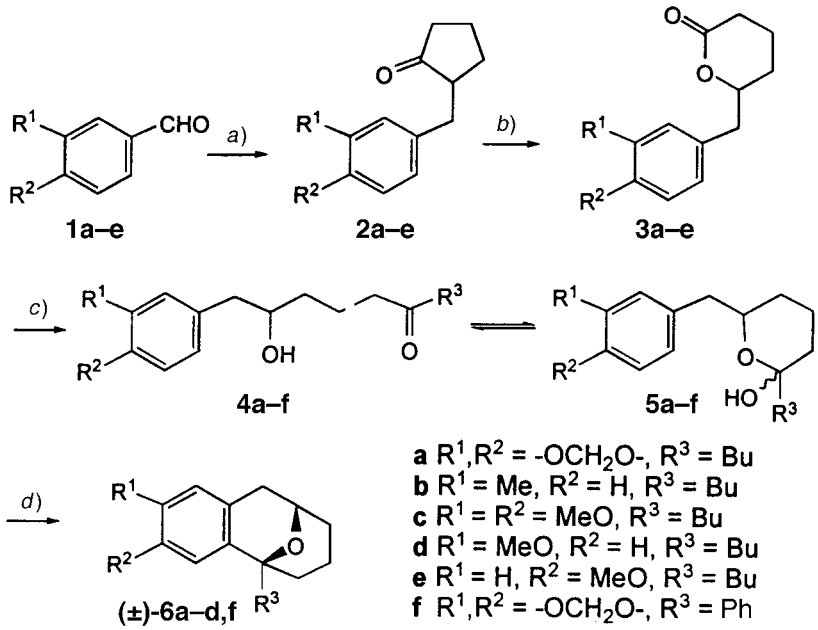
over 10% Pd/C to afford ketones **2**. The yields were generally good (60–86%), except for **2c** (39%; not optimized). The isolated ketones **2a**–**e** were subjected to *Bayer-Villiger* oxidation with 70% *m*-chloroperbenzoic acid (MCPBA) in $CH_2Cl_2$ with $NaHCO_3$ as buffer to give the corresponding lactones **3a**–**e** in 75–88% yields.

*Scheme 2*



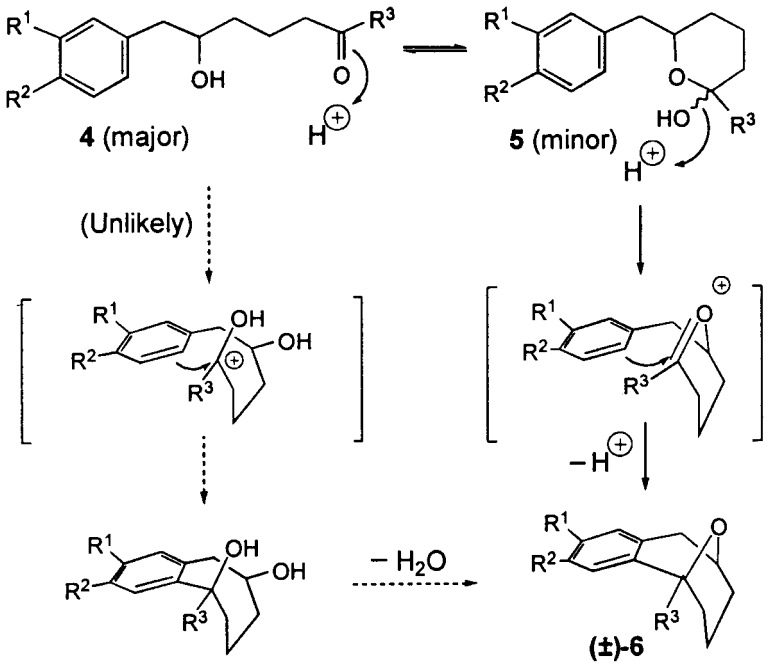

*a*) 1) 1N NaOH, cyclopentanone, 24 h, r.t.; 2) $H_2$, Pd/C, EtOH; 39–86% over two steps. *b*) MCPBA, $NaHCO_3$, r.t., $CH_2Cl_2$; 75–88%. *c*) BuLi (or PhLi), $Me_3SiCl$, THF, $-100°$; 44–76%. *d*) TsOH, PhH, reflux, 12–36 h or $BF_3 \cdot OEt_2$, THF, reflux, 12–36 h; 57–98%.

The lactone ring of **3a**–**e** was then opened with the most readily available organolithium, either BuLi or PhLi. To minimize the addition of a second alkyl group to the intermediate ketone, *Cooke*'s procedure [4] was applied. Thus, at $-100°$, with an excess $Me_3SiCl$ to intercept the intermediate hemiketal, the desired ketones could be obtained in good yields after removal of the termporary silyl-ether protecting group. Because of the existence of an equilibrium between the open-chain hydroxy ketone form **4a**–**f** and the cyclic hemiketal form **5a**–**f**, the isolated yields were sometimes lower than the genuine yields. This problem was particularly evident with **4f**/**5f**, where the hemiketal OH group was in a benzylic position; a substantial fraction of the product underwent a facile elimination of $H_2O$ to yield the corresponding cyclic enol ether. The unexpected enol ether, however, served equally well in the *F-C* cyclization as shown by subsequent experiments (see below).

The ensuing *F-C* reaction to give (±)-**6** presumably proceeds through the hemiketal **5** rather than the open-chain form **4**, although the $^1$H-NMR experiments clearly show that **4** represents, in most cases, the predominant form in solution. This is because the alternative route would involve an unfavorable eight-membered transition state

(*Scheme 3*). It is interesting to note that the OH group at the homobenzylic position plays a dual role in the *F-C* reaction. On one hand, it activates the ketone carbonyl group by forming a hemiketal (the OH may easily leave in the presence of an acid to generate an oxonium ion), and, on the other hand, the oxy 'bridge' effectively reduces the degree of rotational freedom of the side chain so that the unfavorable eight-membered transition state now becomes a favorable six-membered one.

*Scheme 3*




The *F-C* reaction of the hemiketals was probed with **5a** under several conditions. Apart from the previously employed HCl/MeOH and $BF_3 \cdot OEt_2$/THF recipes, we found that TsOH/PhH also worked well. Due to the convenience of handling the solid TsOH (monohydrate), the TsOH/PhH combination became the first choice. In fact, the new conditions often gave better yields. The results of the *F-C* cyclization are listed in the *Table*. As reported earlier for the spiroketals, the presence of an electron-donating group at the position *para* to the cyclization site facilitates the intramolecular *F-C* reaction. The best results were obtained with those compounds that contained an alkoxy group at the *para*-position. Replacing the alkoxy group with Me (weaker electron-donating group) reduced the yield significantly. The substitution position is also important. The same MeO group at the *meta*- instead of *para*-position had no facilitating effect at all; the reaction gave a complex product mixture.

We have also made a brief examination on the generation of the [3.2.1] system to see whether the procedure is applicable to five-membered hemiketals. Starting from the easily available levulinic acid (**7**), aldehyde **8** [5] was readily prepared in four steps (esterification in MeOH catalyzed by $H_2SO_4$, ketalization with ethylene glycol,

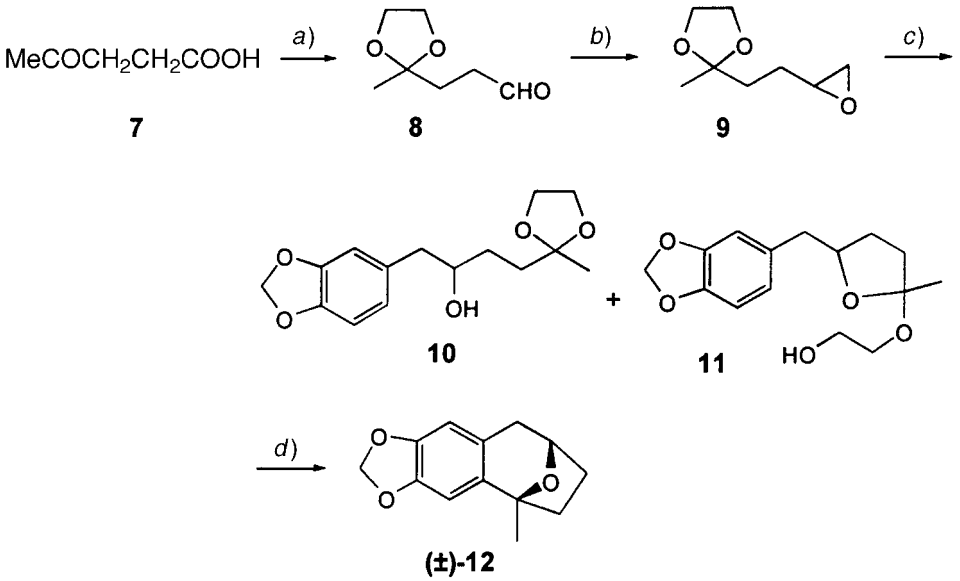
Table. F-C *Cyclization under Different Conditions*

| Starting Material | $R^1$ | $R^2$ | Main product | Isolated Yield [%] | |
|---|---|---|---|---|---|
| | | | | *Method A*[a]) | *Method B*[b]) |
| **4a/5a** | $-OCH_2O-$ | | **6a** | 93 | 93 |
| **4b/5b** | Me | H | **6b** | 63 | –[c]) |
| **4c/5c** | MeO | MeO | **6c** | 73 | 73 |
| **4d/5d** | MeO | H | **6d** | 98 | 88 |
| **4e/5e** | H | MeO | **6e** | –[c]) | –[c]) |
| **4f/5f** | $-OCH_2O-$ | | **6f** | 88 | 57 |

[a]) *Method A:* cat. TsOH, PhH, reflux. [b]) *Method B:* cat. $BF_3 \cdot OEt_2$, THF, reflux. [c]) A complex product mixture was obtained.

reduction with $LiAlH_4$, and *Swern* oxidation; *Scheme 4*). Treatment of **8** with dimethyloxosulfonium methylide [6] ($Me_2S(O)CH_2$) gave the corresponding epoxide **9** (20% yield for the *Swern* oxidation and the epoxidation; not optimized). Ring opening of the epoxide was realized in 66% yield with the aryllithium prepared from 5-bromo-1,3-benzodioxole [7] by lithium/halogen exchange with BuLi at $-40°$. The product **10** was often contaminated by small amounts of **11** (**10**/**11** 50 – 20 : 1). In the presence of an acidic catalyst, the content of **11** increased significantly, reflecting their relative stability.

*Scheme 4*



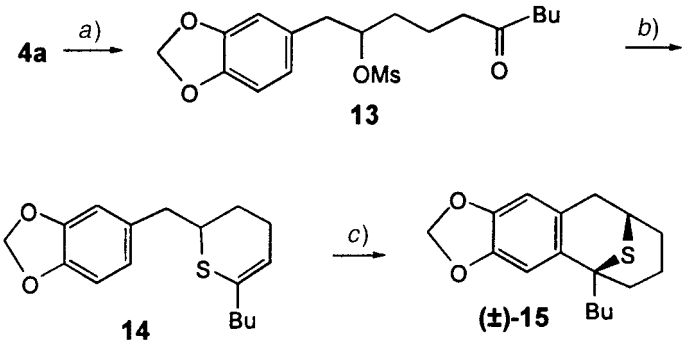

*a*) 1) MeOH, $H_2SO_4$; 60%; 2) $HOCH_2CH_2OH$, TsOH; 99%; 3) $LiAlH_4$; 90%; 4) *Swern* oxidation. *b*) DMSO/$Me_2S(O)CH_2$; 20% over two steps. *c*) $-78°$, ArLi, THF; 65%. *d*) HCl/MeOH, reflux, 12 h; 70%.

In an initial attempt to hydrolyze the ethylene glycol protecting group of **10**, it was noticed that some *F-C* product was already formed even before the starting ketal was

fully deprotected. With this insight, we reverted to the original HCl/MeOH procedure, which effectively combined the deprotection and the *F-C* reaction into one single step and gave the final *F-C* product (±)-**12** in 70% yield after reaction at reflux temperature for 12 h.

To examine whether thiohemiketals behave similarly, we next made an effort to prepare the thiol counterpart of **4a** by converting the OH group to mercapto group (*Scheme 5*). First, we tried to introduce the S-atom *via* reaction of the mesylate **13** of **4a** with potassium thioacetate [8]. None of the expected product was obtained, although formation of the mesylate did occur. Then, we tried to use the anion of benzenemethanethiol in place of the thioacetate. The substitution went well this time. However, removal of the benzyl protecting group to release the SH group encountered serious difficulties. Neither the Na/liq. $NH_3$ [9] nor the Li/naphthalene [10] procedure cleanly cleaved the benzyl group without yielding by-products. Finally, the problem was circumvented by using NaSH [11] as the nucleophile. The resulting mercapto ketone underwent facile thioacetalization, and the intermediate thiohemiketal easily lost one molecule of $H_2O$ to give the enthiol ether **14** as the product. In the subsequent *F-C* reaction, a major difference between the O- and S-substrate was observed. Unlike the enol ethers mentioned above (which undergo *F-C* cyclization as easily as the hemiketals), no cyclization took place with the S-analogue **14** under all the conditions so far employed. The desired cyclization to (±)-**15**, however, could be realized at 40° in $CHCl_3$ in nearly quantitative yields in the presence of trifluoromethanesulfonic acid (a stronger acid than TsOH, *etc.*).

*Scheme 5*




*a*) MsCl, $CH_2Cl_2$, $Et_3N$; 85%. *b*) NaSH, DMF; 91%. *c*) $CF_3SO_3H$, $CHCl_3$, 40°, 4 h; *ca.* 100%.

In brief, we have demonstrated a new sub-type of *F-C* reaction with hemiketals (formed *in situ* from the corresponding open-chain hydroxy ketones) acting as electrophiles. The reaction occurs easily when the *para*-position (with respect to the cyclization position) of the aromatic ring carries a strong electron-donating group. The reaction opens up a facile route to the interesting benzo-fused oxabicyclo[3.3.1]nonane system, which is otherwise not readily accessible. The corresponding oxabicyclo[3.2.1]octanes can also be prepared similarly. The S-analogues appear to need stronger acid to undergo the desired cyclization.

## Experimental Part

*General*. M.p.: Flash column chromatography (FC): silica gel *H* (10–40 μm), elution with petroleum ether (b.p. 60–90°) AcOEt. $^1$H-NMR Spectra: $CDCl_3$ solns. at 300 MHz, unless stated otherwise. Microanalyses were carried out in the Microanalytical Laboratory at the Shanghai Institute of Organic Chemistry.

*Aldol Condensation: General Procedure*. At r.t. aq. 1N NaOH (30 ml) was added to a mixture of the arom. aldehyde **1** (10 mmol) and cyclopentanone (15 mmol) with stirring. Stirring was continued for 24 h at r.t. Then, the mixture was extracted with $Et_2O$ (5 × 50 ml) and the combined org. extracts washed with brine (4 × 30 ml), dried ($MgSO_4$), and evaporated. The residue was dissolved in EtOH (99.5%; 100 ml) and hydrogenated under stirring over 10% Pd/C (50 mg) at 1 atm of $H_2$ for 12–24 h. The catalyst was filtered off, the filtrate evaporated, and the residue submitted to FC (hexanes/AcOEt 8:1): ketone **2**.

Baeyer-Villiger *Oxidation: General Procedure*. To ketone **2** (10 mmol) in $CH_2Cl_2$ (150 ml), 70% MCPBA (4.949 g; *ca*. 20 mmol) and powdered $NaHCO_3$ (*ca*. 29 mmol) were added in small portions. Then, the mixture was stirred at r.t. for 24 h. The solids were filtered off through *Celite* (washing with $CH_2Cl_2$). The filtrate and washings were washed twice with aq. sat. $NaHCO_3$ soln., dried ($MgSO_4$), and evaporated. The residue was submitted to FC: lactone **3**.

*Lactone Opening by Butyllithium: General Procedure*. To a soln. of **3** (3.5 mmol) in dry THF (50 ml) at −100° under $N_2$, $Me_3SiCl$ (1.78 g, 16.5 mmol) was added with stirring, followed by 1.6M/BuLi in hexanes (*ca*. 7.0 ml, added dropwise). The mixture was then stirred at −100° for another 20 min and at −78° for 30 min before the temp. was allowed to increase to 0°. EtOH (99.5%, *ca*. 0.5 ml) was added. After stirring for 5 min, the excess $Me_3SiCl$ and most of the THF were evaporated. $H_2O$ (2.0 ml) and 4M dil. HCl (4.0 ml) were added. The mixture was stirred for 10 min and then extracted with $Et_2O$ (4 × 30 ml). The extract was washed with sat. aq. $NaHCO_3$ soln. (2 × 15 ml) and brine (2 × 20 ml), dried ($Na_2SO_4$), and evaporated, and the residue was submitted to FC: ketone **4**, often contaminated with some ring-closed product **5**.

*Intramolecular* F-C *Reaction*. *Method A:* A soln. of the precursor **4** (20 mg) and TsOH (1–2 mg) in benzene (10 ml) was heated under reflux and $N_2$ for 12–36 h. After consumption of the starting material (TLC monitoring), the mixture was cooled to r.t. and diluted with $Et_2O$ (80 ml), the soln. washed with sat. aq. $NaHCO_3$ soln. (2 × 5 ml) and brine (2 × 10 ml), dried ($Na_2SO_4$), and evaporated, and the residue was submitted to FC: *F-C* product (±)-**6**.

*Method B:* As described in *Method A*, except that THF (10 ml) and $BF_3 \cdot OEt_2$ (1 small drop) were used in place of benzene and TsOH, resp.

*2-[(1,3-Benzodioxol-5-yl)methyl]cyclopentanone* (**2a**): M.p. 41.3–41.7°. Yield 63%. IR (KBr): 1740*s*, 1600*w*, 1580*s*, 1440*s*, 1240*s*, 1038*s*, 925*m*, 810*m*. $^1$H-NMR: 1.49–1.64 (*m*, 1 H); 1.69–1.83 (*m*, 1 H); 1.91–2.03 (*m*, 1 H); 2.04–2.19 (*m*, 2 H); 2.25–2.41 (*m*, 2 H); 2.50 (*dd*, *J* = 14, 8.2, 1 H); 3.06 (*dd*, *J* = 14, 4.3, 1 H); 5.94 (*s*, 2 H); 6.67 (*d*, *J* = 7.8, 1 H); 6.67 (br. *s*, 1 H); 6.73 (*d*, *J* = 7.8, 1 H). EI-MS: 218 (40, $M^+$), 162 (6), 135 (100), 136 (12), 122 (6), 77 (14). Anal. calc. for $C_{13}H_{14}O_3$: C 71.54, H 6.46; found: C 71.62, H 6.54.

*2-[(3-Methylphenyl)methyl]cyclopentanone* (**2b**): Yield 60%. IR (film): 1740*s*, 1605*m*, 1580*w*, 1150*m*, 780*m*, 740*m*, 695*m*. $^1$H-NMR: 1.49–1.64 (*m*, 1 H); 1.68–1.83 (*m*, 1 H); 1.92–2.04 (*m*, 1 H); 2.04–2.20 (*m*, 2 H); 2.28–2.42 (*m*, 2 H); 2.34 (*s*, 1 H); 2.50 (*dd*, *J* = 14, 9.5, 1 H); 3.13 (*dd*, *J* = 14, 3.8, 1 H); 6.97–7.04 (*m*, 3 H); 7.18 (*t*, *J* = 7.4, 1 H). EI-MS: 188 (36, $M^+$), 145 (15), 117 (43), 105 (100), 91 (31), 77 (23), 65 (12). Anal. calc. for $C_{13}H_{16}O$: C 82.94, H 8.66; found: C 83.12, H 8.51.

*2-[(3,4-Dimethoxyphenyl)methyl]cyclopentanone* (**2c**): Yield 39%. IR (film): 1735*s*, 1605*m*, 1590*s*, 1515*s*, 1260*s*, 1240*s*, 1050*s*, 1025*s*, 810*m*, 765*m*. $^1$H-NMR: 1.50–1.64 (*m*, 1 H); 1.65–1.81 (*m*, 1 H); 1.90–2.20 (*m*, 1 H); 2.03–2.18 (*m*, 2 H); 2.26–2.40 (*m*, 2 H); 2.53 (*dd*, *J* = 14, 9.1, 1 H); 3.06 (*dd*, *J* = 14, 4.3, 1 H); 3.859 (*s*, 3 H); 3.862 (*s*, 3 H); 6.67–6.72 (*m*, 2 H); 6.78 (*d*, *J* = 8.5, 1 H). EI-MS: 234 (29, $M^+$), 235 (5), 152 (11), 151 (100), 107 (8), 91 (7), 77 (6). Anal. calc. for $C_{14}H_{18}O_3$: C 71.77, H 7.74; found: C 71.85, H 7.84.

*2-[(3-Methylphenyl)methyl]cyclopentanone* (**2d**):Yield 86%. IR (film): 1735*s*, 1605*s*, 1590*s*, 1515*m*, 1260*m*, 1240*s*, 1050*m*, 1025*m*, 810*m*, 765*m*. $^1$H-NMR: 1.49–1.64 (*m*, 1 H); 1.67–1.80 (*m*, 1 H); 1.91–2.03 (*m*, 1 H); 2.05–2.19 (*m*, 2 H); 2.29–2.42 (*m*, 2 H); 2.52 (*dd*, *J* = 14, 9.3, 1 H); 3.14 (*dd*, *J* = 14, 4.0, 1 H); 3.81 (*s*, 3 H); 6.73 (*s*, 1 H); 6.75 (*d*, *J* = 7.7, 1 H); 6.73–6.78 (*m*, 3 H); 7.21 (*t*, *J* = 7.7, 1 H). EI-MS: 204 (99, $M^+$), 148 (100), 147 (52), 121 (72), 91 (45), 77 (27). Anal. calc. for $C_{13}H_{16}O_2$: C 76.44, H 7.90; found: C 76.47, H 7.97.

*2-[(4-Methoxyphenyl)methyl]cyclopentanone* (**2e**): Yield 63%. IR (film): 1735*s*, 1605*m*, 1590*w*, 1515*s*, 1240*s*, 1050*m*, 1025*m*, 810*m*. $^1$H-NMR: 1.49–1.63 (*m*, 1 H); 1.67–1.81 (*m*, 1 H); 1.89–2.02 (*m*, 1 H); 2.03–2.17 (*m*, 2 H); 2.26–2.40 (*m*, 2 H); 2.52 (*dd*, *J* = 14, 9.3, 1 H); 3.07 (*dd*, *J* = 14, 4.1, 1 H); 3.79 (*s*, 3 H); 6.83 (*d*, *J* = 8.7, 2 H); 7.09 (*t*, *J* = 8.7, 2 H). EI-MS: 204 (13, $M^+$), 147 (4), 122 (11), 121 (100), 91 (7), 77 (8). Anal. calc. for $C_{13}H_{16}O_2$: C 76.44, H 7.90; found: C 76.49, H 7.96.

*6-[(1,3-Benzodioxol-5-yl)methyl]tetrahydro-2*H*-pyran-2-one* (**3a**): M.p. 61.3–61.7°. Yield 83%. IR (KBr): 1730*s*, 1600*w*, 1500*s*, 1490*s*, 1240*s*, 1040*s*, 925*s*, 805*m*. $^1$H-NMR: 1.70–1.95 (*m*, 3 H); 2.36–2.49 (*m*, 1 H); 2.51–2.63 (*m*, 1 H); 2.79 (*dd*, *J* = 13.7, 6.7, 1 H); 2.99 (*dd*, *J* = 13.7, 5.8, 1 H); 4.38–4.49 (*m*, 1 H); 5.93 (*s*, 2 H); 6.67 (*dd*, *J* = 8.0, 1.6, 1 H); 6.72 (*d*, *J* = 1.6, 1 H); 6.75 (*d*, *J* = 8.0, 1 H). EI-MS: 234 (52, $M^+$), 135 (100), 99 (30), 77 (17), 71 (31), 55 (12), 43 (12). Anal. calc. for $C_{13}H_{14}O_4$: C 60.66, H 6.02; found: C 66.73, H 5.94.

*Tetrahydro-6-[(3-methylphenyl)methyl]-2*H*-pyran-2-one* (**3b**): Yield 88%. IR (film): 1730*s*, 1605*m*, 1584*w*, 1240*s*, 1040*s*, 925*m*, 780*m*. $^1$H-NMR: 1.46–1.58 (*m*, 1 H); 1.70–1.95 (*m*, 3 H); 2.33 (*s*, 3 H); 2.30–2.48 (*m*, 1 H); 2.51–2.62 (*m*, 1 H); 2.81 (*dd*, *J* = 13.7, 7.1, 1 H); 3.06 (*dd*, *J* = 13.7, 5.8, 1 H); 4.42–4.58 (*m*, 1 H); 7.01 (br. *d*, *J* = 7.7, 1 H); 7.02 (br. *s*, 1 H); 7.04 (br. *d*, *J* = 7.7, 1 H). EI-MS: 204 (26, $M^+$), 187 (11), 105 (45), 99 (100), 91 (14), 77 (20), 71 (100), 55 (26), 43 (27). Anal. calc. for $C_{13}H_{16}O_2$: C 76.44, H 7.90; found: C 76.34, H 7.92.

*6-[(3,4-Dimethoxyphenyl)methyl]tetrahydro-2*H*-pyran-2-one* (**3c**): M.p. 89.1–89.6°. IR (KBr): 1720*s*, 1600*w*, 1585*m*, 1240*s*, 1040*s*, 930*w*, 860*w*, 810*w*. Yield 75%. $^1$H-NMR: 1.40–1.58 (*m*, 1 H); 1.70–1.95 (*m*, 3 H); 2.34–2.47 (*m*, 1 H); 2.51–2.63 (*m*, 1 H); 2.31 (*dd*, *J* = 14.0, 6.6, 1 H); 3.01 (*dd*, *J* = 14.0, 5.5, 1 H); 3.86 (*s*, 3 H); 3.88 (*s*, 3 H); 4.42–4.53 (*m*, 1 H); 6.74–6.79 (*m*, 3 H); 6.81 (*d*, *J* = 8.5, 1 H). EI-MS: 250 (33, $M^+$), 233 (3), 151 (100), 109 (19), 99 (8), 91 (6), 71 (16). Anal. calc. for $C_{14}H_{18}O_4$: C 67.18, H 7.25; found: C 66.90, H 7.25.

*Tetrahydro-6-[(3-methoxyphenyl)methyl]-2*H*-pyran-2-one* (**3d**): M.p. 35.5–36.1°. IR (KBr): 1730*s*, 1600*m*, 1585*m*, 1250*s*, 1040*s*, 935*w*, 780*w*. Yield 80%. $^1$H-NMR: 1.43–1.62 (*m*, 1 H); 1.70–1.96 (*m*, 3 H); 2.35–2.48 (*m*, 1 H); 2.51–2.62 (*m*, 1 H); 2.83 (*dd*, *J* = 13.7, 7.1, 1 H); 3.06 (*dd*, *J* = 13.7, 5.8, 1 H); 3.79 (*s*, 3 H); 4.42–4.58 (*m*, 1 H); 6.80 (*d*, *J* = 7.7, 1 H); 6.78 (*d*, *J* = 7.7, 1 H); 6.76 (*s*, 1 H); 7.21 (*t*, *J* = 7.7, 1 H). EI-MS: 204 (26, $M^+$), 203 (20), 121 (31), 99 (81), 91 (27), 77 (21), 77 (100), 55 (27), 43 (30). HR-MS: 220.1095 ($C_{13}H_{16}O_3^+$; calc. 220.1099).

*Tetrahydro-6-[(4-Methoxyphenyl)methyl]-2*H*-pyran-2-one* (**3e**): M.p. 86.5–86.7°. Yield 83%. IR (KBr): 1720*s*, 1610*m*, 1580*w*, 1230*s*, 1160*m*, 1020*s*, 915*m*, 805*m*. $^1$H-NMR: 1.45–1.59 (*m*, 1 H); 1.70–1.95 (*m*, 4 H); 2.36–2.48 (*m*, 1 H); 2.52–2.64 (*m*, 1 H); 2.84 (*dd*, *J* = 14, 6.9, 1 H); 3.04 (*dd*, *J* = 14, 5.6, 1 H); 3.81 (*s*, 3 H); 4.49–4.52 (*m*, 1 H); 6.86 (*d*, *J* = 8.7, 2 H); 7.16 (*d*, *J* = 8.7, 2 H). EI-MS: 220 (22, $M^+$), 121 (100), 99 (13), 77 (8), 71 (17), 55 (8), 43 (8). Anal. calc. for $C_{13}H_{16}O_3$: C 70.89, H 7.23; found: C 70.67, H 7.00.

*10-(1,3-Benzodioxol-5-yl)-9-hydroxydecan-5-one* (**4a**): M.p. 50.8–51.4°. Yield 76%. IR (KBr): 3350*m*, 1715*s*, 1600*w*, 1240*s*, 930*s*, 800*m*. $^1$H-NMR: 0.92 (*t*, *J* = 7.3, 3 H); 1.20–1.90 (*m*, 10 H); 2.20–2.50 (*m*, 2 H); 2.54–2.65 (*m*, 1 H); 2.68–2.77 (*m*, 1 H); 3.78–3.82 (*m*, 1 H); 5.94 (*s*, 2 H); 6.66 (*dd*, *J* = 8.0, 1.7, 1 H); 6.72 (*d*, *J* = 1.7, 1 H); 6.76 (*d*, *J* = 8.0, 1 H). EI-MS: 292 (1, $M^+$), 157 (42), 135 (100), 113 (27), 57 (55), 41 (43).

*9-Hydroxy-10-(3-methylphenyl)decan-5-one* (**4b**): Yield 76%. IR (film): 3400*m*, 1715*s*, 1610*m*, 1590*m*, 1040*m*, 980*m*, 780*m*, 740*m*. $^1$H-NMR: 0.90 (*t*, *J* = 8.4, 3 H); 1.20–1.85 (*m*, 10 H); 2.33 (*s*, 3 H); 2.23–2.48 (*m*, 2 H); 2.56–2.68 (*m*, 1 H); 2.71–2.84 (*m*, 1 H); 3.72–3.86 (*m*, 1 H); 6.92–7.10 (*m*, 3 H); 7.19 (*t*, *J* = 8.0, 1 H). EI-MS: 263 (2, $M^+$), 157 (77), 113 (48), 105 (100), 91 (66), 57 (73), 41 (54).

*10-(3,4-Dimethoxyphenyl)-9-hydroxydecan-5-one* (**4c**): Yield 51%. IR (film): 3400*m*, 1715*s*, 1600*w*, 1520*s*, 1260*s*, 1240*s*, 1030*s*, 770*w*. $^1$H-NMR: 0.89 (*t*, *J* = 7.4, 3 H); 1.18–1.82 (*m*, 10 H); 2.30–2.50 (*m*, 2 H); 2.50–2.62 (*m*, 1 H); 2.70–2.81 (*m*, 1 H); 3.70–3.82 (*m*, 1 H); 3.85 (*s*, 3 H); 3.87 (*s*, 3 H); 6.72–6.73 (*m*, 2 H); 6.80 (*d*, *J* = 5.2, 1 H). EI-MS: 308 (5, $M^+$), 157 (35), 151 (100), 113 (21), 57 (47), 41 (43).

*9-Hydroxy-10-(3-methoxyphenyl)decan-5-one* (**4d**): Yield 55%. IR (film): 3450*m*, 1715*s*, 1600*m*, 1580*m*, 1260*s*, 1140*s*, 780*m*. $^1$H-NMR: 0.89 (*t*, *J* = 7.3, 3 H); 1.20–1.82 (*m*, 10 H); 2.30–2.48 (*m*, 2 H); 2.55–2.70 (*m*, 1 H); 2.70–2.85 (*m*, 1 H); 3.79 (*s*, 3 H); 3.70–3.86 (*m*, 1 H); 6.72–6.85 (*m*, 3 H); 7.21 (br. *t*, *J* = 8.0, 1 H). EI-MS: 278 (0.4, $M^+$), 157 (75), 122 (100), 121 (77), 113 (47), 57 (73), 41 (50).

*9-Hydroxy-10-(4-methoxyphenyl)decan-5-one* (**4e**): M.p. 51.3–51.8°. Yield 68%. IR (KBr): 3450*s*, 1715*s*, 1600*m*, 1580*w*, 1260*m*, 1140*m*, 780*m*. $^1$H-NMR: 0.89 (*t*, *J* = 7.4, 3 H); 1.20–1.80 (*m*, 10 H); 2.30–2.50 (*m*, 2 H); 2.50–2.64 (*m*, 1 H); 2.70–2.81 (*m*, 1 H); 3.70–3.82 (*m*, 1 H); 3.79 (*s*, 3 H); 6.84 (*d*, *J* = 8.5, 2 H); 7.12 (*d*, *J* = 8.5, 2 H). EI-MS: 278 (0.4, $M^+$), 157 (75), 122 (100), 121 (77), 113 (47), 57 (73), 41 (50).

*5-Butyl-5,6,7,8,9,10-hexahydro-5,9-epoxycycloocta[f]-1,3-benzodioxole* ((±)-**6a**): Yield 93% (*Method A*, reflux 12 h; or *Method B*, 8 h). IR (film): 2980*s*, 1500*s*, 1481*s*, 1240*s*, 1220*s*, 1040*s*, 940*m*, 850*m*, 830*m*, 800*m*. $^1$H-NMR: 0.87 (*t*, *J* = 7.1, 3 H); 1.08–1.58 (*m*, 8 H); 1.62–1.78 (*m*, 2 H); 1.82–2.00 (*m*, 2 H); 2.42 (*d*, *J* = 17, 1 H); 3.28 (*dd*, *J* = 17, 7.5, 1 H); 4.36 (*t*, *J* = 6.7, 1 H); 5.90 (*d*, *J* = 1.4, 1 H); 5.89 (*d*, *J* = 1.4, 1 H); 6.50 (*s*, 1 H); 6.56 (*s*, 1 H). EI-MS: 274 (10, $M^+$), 231 (100), 189 (12), 131 (7), 103 (6), 77 (5), 41 (6). Anal. calc. for $C_{17}H_{23}O_3$: C 74.42, H 8.08; found: C 74.58, H 8.19.

*5-Butyl-5,6,7,8,9,10-hexahydro-2-methyl-5,9-epoxybenzocyclooctene* ((±)-**6b**): Yield 63% (*Method A*, 12 h; *Method B* resulted in a complex mixture in this case). IR (film): 2930*s*, 1600*w*, 1500*m*, 1440*m*, 1080*m*, 1038*s*, 810*s*. $^1$H-NMR: 0.85 (*t*, *J* = 7.2, 3 H); 1.10–1.60 (*m*, 8 H); 1.65–185 (*m*, 2 H); 1.85–2.05 (*m*, 2 H); 2.30 (*s*, 3 H); 2.49 (*d*, *J* = 17, 1 H); 3.33 (*dd*, *J* = 17, 7.8, 1 H); 4.39 (*t*, *J* = 6.5, 1 H); 6.90 (*d*, *J* ≈ 8, 1 H); 6.90 (*s*, 1 H); 7.20

(*d*, $J \approx 8$, 1 H). EI-MS: 244 (13, $M^+$), 201 (100), 159 (24), 149 (26), 105 (15), 71 (21), 57 (37), 43 (22), 41 (22). Anal. calc. for $C_{17}H_{23}O_3$: C 74.42, H 8.08; found: C 74.58, H 8.19.

*5-Butyl-5,6,7,8,9,10-hexahydro-2,3-dimethoxy-5,9-epoxybenzocyclooctene* ((±)-**6c**): Yield 73% (*Method A* or *B*, 12 h). IR (film): 2850*s*, 1610*w*, 1515*s*, 1250*s*, 1030*m*, 850*w*, 760*w*. $^1$H-NMR: 0.86 (*t*, $J = 7.1$, 3 H); 1.10–1.60 (*m*, 8 H); 1.62–1.70 (*m*, 2 H); 1.72–2.00 (*m*, 2 H); 2.44 (*d*, $J = 17$, 1 H); 3.31 (*dd*, $J = 17, 7.8$, 1 H); 3.83 (*s*, 3 H); 3.85 (*s*, 3 H); 4.38 (*t*, $J = 6.5$, 1 H); 6.49 (*s*, 1 H); 6.58 (*s*, 1 H). EI-MS: 290 (20, $M^+$), 247 (100), 205 (15), 43 (6), 41 (10). Anal. calc. for $C_{18}H_{26}O_3$: C 74.45, H 9.02; found: C 74.37, H 9.17.

*5-Butyl-5,6,7,8,9,10-hexahydro-2-methoxy-5,9-epoxybenzocyclooctene* ((±)-**6d**): Yield 98% (*Method A*, 12 h) or 88% (*Method B*, 10 h). IR (film): 2930*s*, 1610*m*, 1580*w*, 1500*s*, 1270*m*, 1240*m*, 1030*m*, 840*m*, 800*m*. $^1$H-NMR: 0.86 (*t*, $J = 7.1$, 3 H); 1.10–1.58 (*m*, 8 H); 1.85–2.00 (*m*, 2 H); 2.50 (*d*, $J = 17$, 1 H); 3.35 (*dd*, $J = 17, 7.7$, 1 H); 3.78 (*s*, 3 H); 4.39 (*t*, $J = 6.6$, 1 H); 6.61 (br. *s*, 1 H); 6.70 (*d*, $J = 8$, 1 H); 6.91 (*d*, $J = 8$, 1 H). EI-MS: 260 (11, $M^+$), 217 (100), 175 (22), 147 (8), 91 (6), 41 (7). Anal. calc. for $C_{17}H_{24}O_2$: C 78.42, H 9.29; found: C 78.23, H 9.58.

*5,6,7,8,9,10-Hexahydro-5-phenyl-5,9-epoxycycloocta[*f*]-1,3-benzodioxole* ((±)-**6f**): Yield 88% (*Method A*, 24 h) or 57% (*Method B*, 36 h). IR (film): 2980*m*, 1505*m*, 1488*s*, 1235*s*, 1040*m*, 1020*w*, 930*w*, 830*m*, 760*m*. $^1$H-NMR: 1.40–1.78 (*m*, 2 H); 1.98–2.30 (*m*, 4 H); 2.58 (*d*, $J = 17$, 1 H); 3.52 (*dd*, $J = 17, 7.7$, 1 H); 4.54 (*t*, $J = 7.0$, 1 H); 5.85 (*d*, $J = 1.4$, 1 H); 5.83 (*d*, $J = 1.4$, 1 H); 6.00 (*s*, 1 H); 6.60 (*s*, 1 H). EI-MS: 294 (10, $M^+$), 215 (100), 189 (6), 165 (6), 152 (5), 77 (13). HR-MS: 294.1252 ($C_{19}H_{18}O_3^+$; calc. 294.1256).

*5-Butyl-6,7,8,9-tetrahydro-5,8-epoxy-5*H*-cycloocta[*f*]-1,3-benzodioxole* ((±)-**12**). Methyl levulinate (13.0 g; prepared from technical levulinic acid (**7**) by reaction with MeOH in the presence of $H_2SO_4$ in *ca.* 60% yield), ethylene glycol (9.3 g, 0.15 mmol), and TsOH (0.1 g) were stirred with heating in benzene with a *Dean-Stark* trap to remove the $H_2O$ formed in the reaction. When the distillate became clear, the mixture was cooled to r.t., poured into ice-water containing $Na_2CO_3$, extracted with $Et_2O$, washed with $H_2O$ (2 × 20 ml) and brine (2 × 20 ml), dried ($Na_2SO_4$), and evaporated: crude ketal ($^1$H-NMR homogeneous) in essentially quant. yield. The crude ketal was dissolved in dry THF (60 ml). With cooling (ice-water bath) and stirring, $LiAlH_4$ (1.63 g) was added within 15 min. The mixture was stirred at the same temp. for 30 min and then at r.t. for 3 h. A sufficient amount of $Na_2SO_4 \cdot n\,H_2O$ was added in small portions to decompose the excess $LiAlH_4$. The solids were filtered off, and the filter cake was washed with $Et_2O$. The combined filtrate and washing were washed with brine (20 ml), dried ($Na_2SO_4$), and evaporated: intermediate alcohol (5.80 g, 92%).

With stirring and cooling (−78°), DMSO (3.4 ml) was added (over 10 min) to a soln. of oxalyl chloride (2.0 ml) in dry $CH_2Cl_2$ (40 ml). The mixture was stirred for 20 min. A soln. of the intermediate alcohol (2.10 g) in $CH_2Cl_2$ (2 ml) was introduced. Stirring was continued at −78° for 1.5 h before $Et_3N$ (1.4 ml) was added. The bath was allowed to warm to r.t. over *ca.* 1 h, then $H_2O$ (30 ml) was added. The mixture was extracted with $Et_2O$ (4 × 40 ml), the combined org. phase washed with $H_2O$ (2 × 20 ml) and brine (20 ml), dried ($Na_2SO_4$), and evaporated to give the aldehyde **8** (2.01 g), which was directly used in the reaction with the sulfur ylide to prepare **9**.

NaH (0.90 g, 60% suspension in mineral oil) was washed with dry hexanes to remove oil. Dry DMSO (40 ml) was added, followed by $Me_3S(O)I$ (5.04 g) in small portions. After stirring at r.t. for 1 h, the crude aldehyde **8** (2.01 g) in DMSO (1 ml) was added. The mixture was stirred at r.t. for 5 min, then at 60° for another 3 h. The mixture was partitioned between $H_2O$ and $Et_2O$, the $Et_2O$ phase washed with brine, dried, and evaporated, and the residue was chromatographed: *2-methyl-2-[2-(oxiran-2-yl)ethyl]-1,3-dioxole* (**9**; 0.45 g, 20% over 2 steps). Oil which was used immediately in the next step. $^1$H-NMR (90 MHz): 1.33 (*s*, 3 H); 1.50–1.90 (*m*, 4 H); 2.50 (*dd*, $J = 5, 3$, 1 H); 2.77 (*t*, $J = 5$, 1 H); 2.97 (*m*, 1 H); 3.80–4.15 (*m*, 4 H). EI-MS: 158 (4, $M^+$), 156 (11), 101 (19), 87 (27), 83 (57), 55 (39), 43 (100).

To a soln. of 5-bromo-1,3-benzodioxole (1.6 g, 8 mmol) in dry THF (45 ml) stirred at −78° under $N_2$, 1.6M BuLi in hexane (5.0 ml) was added. The mixture was stirred at −40° for 1.5 h. The bath temp. was lowered to −78° and $BF_3 \cdot OEt_2$ (1.42 g, freshly distilled) was added, followed by **9** (0.80 g, 5 mmol) in THF (5 ml). After another 45 min at −78°, aq. $NaHCO_3$ soln. (5 ml) was added. The mixture was extracted with $Et_2O$ (3 × 50 ml), washed with brine (10 ml), dried ($MgSO_4$), and submitted to FC: *1-(1,3-benzodioxol-5-yl)-4-(2-methyl-1,3-dioxol-2-yl)butan-2-ol* (**10**, 0.92 g, 65%), containing small amounts of *2-{[5-[(1,3-benzodioxol-5-yl)methyl]tetrahydro-2-methylfuran-2-yl}oxy}ethanol* (**11**). Oil. $^1$H-NMR: 1.32 (*s*, 3 H); 1.50–1.78 (*m*, 2 H); 1.78–1.92 (*m*, 2 H); 2.22 (v.br. *s*, OH); 2.60 (*dd*, $J = 14, 8.2$, 1 H); 2.70 (*dd*, $J = 14, 4.7$, 1 H); 3.70–3.80 (*m*, 1 H); 3.88–3.98 (*m*, 4 H); 5.91 (*s*, 2 H); 6.64 (*dd*, $J = 8.0, 1.4$, 1 H); 6.70 (*d*, $J = 1.4$, 1 H); 6.73 (*d*, $J = 8.0$, 1 H).

A soln. of **10** (22 mg) in MeOH (5 ml) containing 36% HCl soln. (1 small drop) was heated to reflux for 12 h under $N_2$. The mixture was cooled to r.t., diluted with $Et_2O$ (50 ml), washed with aq. $NaHCO_3$ soln. (10 ml) and brine (10 ml), dried ($Na_2SO_4$), and submitted to give **12** (12 mg, 70%). Oil. IR (film): 2850*s*, 1500*m*, 1480*m*, 1230*m*, 1030*m*, 930*w*, 840*w*. $^1$H-NMR: 1.69 (*s*, 3 H); 1.68–1.90 (*m*, 2 H); 1.98–2.09 (*m*, 1 H); 2.18–2.31 (*m*, 1 H); 2.42 (*d*, $J = 16$, 1 H); 3.30 (*dd*, $J = 16, 5.2$, 1 H); 4.71 (*t*, $J = 6.3$, 1 H); 5.90 (*s*, 2 H); 6.54 (*s*, 1 H); 6.67

(*s*, 1 H). EI-MS: 218 (22, $M^+$), 203 (8), 189 (100), 175 (19), 115 (14), 91 (8), 77 (8). HR-MS: 218.0928 ($C_{13}H_{14}O_3^+$; calc. 218.0943).

*10-(1,3-Benzodioxol-5-yl)-9-[(methylsulfonyl)oxy]decan-5-one* (**13**). MsCl (39 mg, 1.5 equiv.) was added dropwise at 0° to a stirred soln. of **4a** (66 mg, 0.22 mmol) and $Et_3N$ (0.2 ml) in $CH_2Cl_2$ (5 ml). Stirring was continued at r.t. for 6 h. $Et_2O$ (50 ml) was added, before the mixture was washed with $H_2O$ (2 × 10 ml) and brine (15 ml), dried ($MgSO_4$), and evaporated to give the crude product, which was submitted to FC: **13** (71 mg, 85%). Gum. IR (film): 1720*s*, 1610*w*, 1500*s*, 1495*s*, 1350*s*, 1170*s*, 900*s*, 810*m*. $^1$H-NMR: 0.89 (*t*, *J* = 7.3, 3 H); 1.18–1.36 (*m*, 3 H); 1.46–1.62 (*m*, 3 H); 1.63–1.80 (*m*, 2 H); 2.37 (*t*, *J* = 7.5, 2 H); 2.38–2.48 (*m*, 2 H); 2.43 (*s*, 3 H); 2.89 (*d*, *J* = 6.3, 2 H); 4.70–4.82 (*m*, 1 H); 5.93 (*s*, 2 H); 6.66 (*d*, *J* = 8.0, 1.7, 1 H); 6.71 (*d*, *J* = 1.7, 1 H); 6.74 (*d*, *J* = 8.0, 1 H). EI-MS: 370 (6, $M^+$), 274 (18), 174 (100), 144 (20), 135 (78), 77 (21), 57 (19), 41 (19). Anal. calc. for $C_{18}H_{36}O_6S$: C 58.36, H 7.07; found: C 58.09, H 7.12.

*5-(6-Butyl-3,4-dihydro-2*H*-thiopyran-2-yl)-1,3-benzodioxole* (**14**). To a soln. of **13** (32 mg, 0.09 mmol) in DMF (5 ml) stirred at 0°, $NaSH \cdot n\ H_2O$ (220 mg, > 5 equiv.) was added. The mixture was stirred at 0° until the solids were well-dispersed. The mixture was then stirred at 40° for 4 h before being partitioned between $H_2O$ (5 ml) and AcOEt (30 ml). The aq. layer was extracted twice (2 × 30 ml). The combined org. phases were washed with $H_2O$ (2 × 10 ml) and brine (2 × 10 ml), dried ($MgSO_4$), and evaporated to give the crude oil. MeOH (10 ml) was added, followed by 6N HCl (0.5 ml). The mixture was then stirred at 40° for 30 min. MeOH was evaporated, the residue diluted with $Et_3O$ (50 ml), washed with $H_2O$ (10 ml), aq. sat. $NaHCO_3$ soln. (10 ml), and brine (2 × 10 ml), ($MgSO_4$), and evaporated, and the residue was submitted to FC: **14** (23 mg, 90%). Oil. IR (film): 1640*w*, 1600*w*, 1500*s*, 1490*s*, 1440*m*, 1245*s*, 1040*s*, 930*m*, 770*w*. $^1$H-NMR: 0.88 (*t*, *J* = 7.2, 3 H); 1.20–1.40 (*m*, 4 H); 1.40–1.65 (*m*, 4 H); 1.95–2.30 (*m*, 4 H); 2.78 (*dd*, *J* = 7.4, 3.6, 2 H); 3.18–3.30 (*m*, 1 H); 5.49 (*t*, *J* = 3.7, 1 H); 5.92 (*s*, 3 H); 6.67 (*d*, *J* = 8.0, 1 H); 6.69 (*s*, 1 H); 6.73 (*d*, *J* = 8.0, 1 H). EI-MS: 290 (34, $M^+$), 174 (62), 155 (100), 135 (39), 99 (33), 77 (33), 41 (21). HR-MS: 290.1314 ($C_{17}H_{22}O_2S^+$; calc. 290.1340).

*5-Butyl-5,6,7,8,9,10-hexahydro-5,9-epithiocycloocta[*f*]-1,3-benzodioxole* ((±)-**15**). To a soln. of **14** (6 mg) in $CH_2Cl_2$ (3 ml), $CF_3SO_3H$ (1 small drop) was added. The mixture was stirred at 40° for 4 h. Then AcOEt (40 ml) was added, the soln. washed with $H_2O$ (5 ml), aq. sat. $NaHCO_3$ soln. (10 ml), and brine (10 ml), dried ($MgSO_4$), and evaporated, and the residue was submitted to FC: (±)-**15** (*ca.* quant.). Oil. $^1$H-NMR: 0.92 (*t*, *J* = 7.0, 3 H); 1.20–1.80 (*m*, 10 H); 1.85–2.20 (*m*, 2 H); 2.84 (*d*, *J* = 17, 1 H); 3.19–3.25 (*m*, 1 H); 3.45 (*dd*, *J* = 17, 6.5, 1 H); 5.91 (*s*, 1 H); 5.92 (*s*, 1 H); 6.60 (*s*, 1 H); 6.69 (*s*, 1 H). EI-MS: 290 (14, $M^+$), 249 (5), 247 (71), 85 (52), 71 (69), 57 (100), 43 (77). HR-MS: 290.1355 ($C_{17}H_{22}O_2S^+$; calc. 290.1340).

This work was supported by the *Chinese Academy of Sciences* (*CAS* 'Knowledge Innovation' Project), the *Life Science Special Fund* of *CAS* Supported by the Ministry of Finance (Stz 98-3-03), the National '973' Project (G2000077502), the Ministry of Science and Technology of China (970211006-06), and the *National Natural Science Foundation of China* (29832020, 20025207).

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*Received July 28, 2000*