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Diels–Alder Reactions of Masked *p*-Benzoquinones

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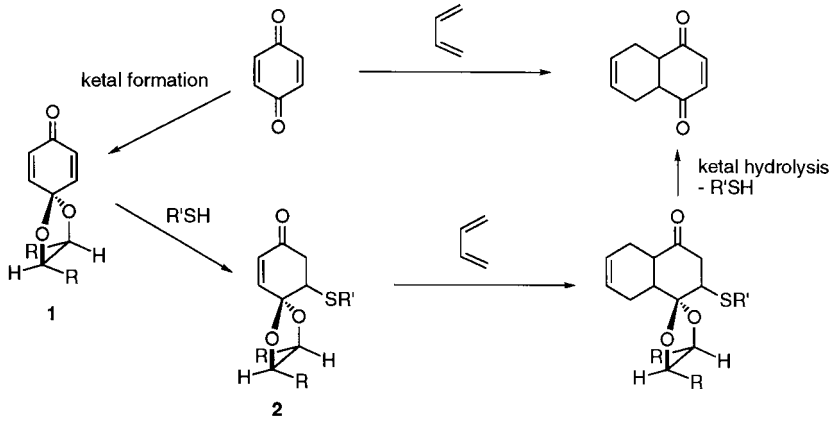
Abstract—Phenylthiomonoketal **3** works effectively as masked *p*-benzoquinone in Diels–Alder reactions. These cycloadditions may be performed with certain Lewis acid catalysts and give rise exclusively to *endo* adducts with a good to excellent *anti*-facial selectivity.

Introduction

p-Benzoquinone and its derivatives have been widely used in synthetic organic chemistry.[1] One particular feature of *p*-benzoquinone is its high symmetry. Although in some circumstances this characteristic may be an advantage, in most cases di-reaction can take place with consequent formation of product mixtures. Focusing our attention on this problem, we have recently prepared several compounds with general structures **1** and **2** (Scheme 1), which are synthetic equivalents of *p*-benzoquinone, having respectively one or both pairs of the originally identical functional groups differentiated.[2]

Monoketals of *p*-benzoquinone have acquired relevant importance because they have been used as starting materials for the synthesis of a wide range of bio-active natural products, including the antitumor antibiotic LL-C10037a,[3,4] several antibiotics of the manumycin family,[3,4b,5] bromoxone,[6] and aranorosin,[7] among others. All these compounds contain in their skeleton a highly functionalized cyclohexenone, as is also the case for **2**. In fact, we have tested the bio-activity of several compounds **1**, **2** and derivatives of both[2,8] and many of them present antituberculous activity.[9]

Recently, we have demonstrated the utility of compounds of type **2** as masked *p*-benzoquinone in 1,3-dipolar cycloadditions to nitrones.[2b,8] As a continuation of this work, and considering that *p*-benzoquinone and its derivatives have been used extensively in Diels–Alder reactions,[10] we decided to investigate the reactivity of **2** as dienophiles. We planned to use the strategy shown in Scheme 1, analogous to that previously developed for the cycloaddition to nitrones, consisting of masking one of each pair of equivalent functional groups of *p*-benzoquinone, and unmasking them after the cycloaddition.



Scheme 1.

Keywords: benzoquinones; Diels–Alder; acetals; stereocontrol.

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There are only a few precedents of Diels–Alder reactions with *p*-benzoquinone monoketals but none of these monoketals are chiral.[11] Diastereoselective Diels–Alder reactions using other kinds of enantiopure *p*-benzoquinone equivalents have been reported,[12] and there is also a work describing enantiopure *p*-benzoquinone adducts derived from chiral cyclopentadienes.[11f]

Our final goal was to prepare new compounds containing the 1,4-dioxaspiro[4,5]decan-2-one bicyclic system due to their bioactivity and to explore an alternative access to Diels–Alder adducts of *p*-benzoquinone derivatives in enantiopure form. The results are described herein.

Results and Discussion

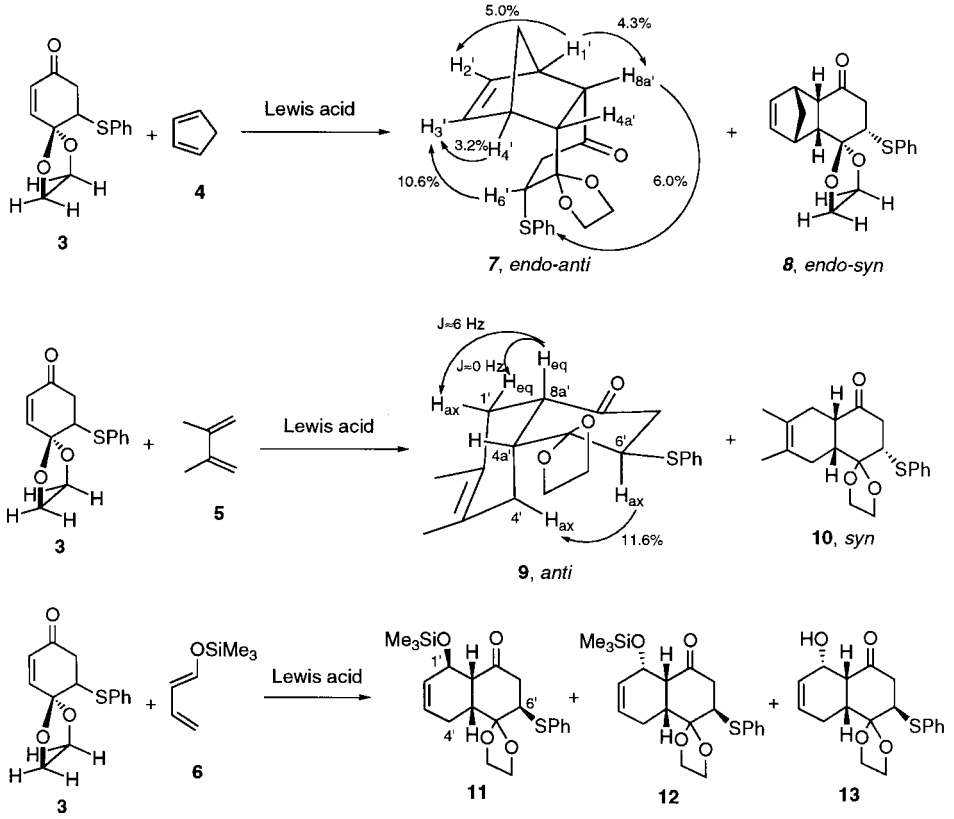
We investigated the reaction of racemic ketal **3**, which is also available in enantiopure form for both antipodes,[2b,c] with dienes **4**, **5** and **6** under different experimental conditions of temperature and Lewis acid catalysts (Table 1, Scheme 2). The reactions were controlled by ^{1}H NMR analysis of aliquots and were quenched when all the ketal **3** was consumed or the reaction mixture did not evolve further.

Compounds **3** and **4** did not react in the absence of Lewis acids (entry 1) and dimerization of the diene was exclusively

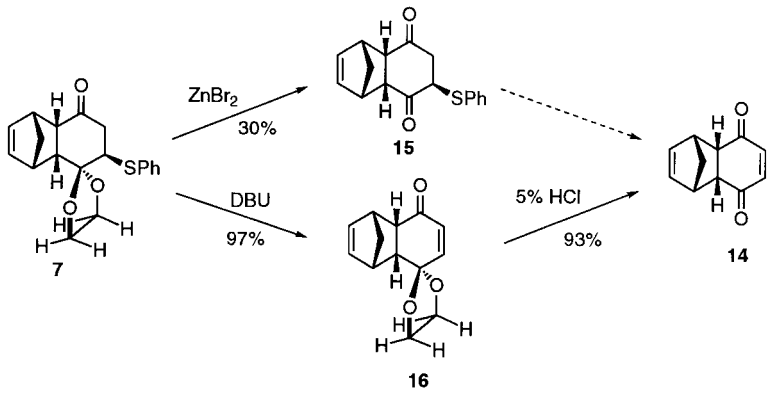
Table 1. Cycloadditions between ketal **3** and dienes **4–6**

Entry	Diene	Lewis acid	Conditions	Yield (%)	Adducts	Ratio
1	**4**	–	CH_2Cl_2, 60°C, 4 h	–	–	–
2	**4**	$BF_3{\cdot}Et_2O$	CH_2Cl_2, −42°C, 9 h	–	–	–
3	**4**	Et_2AlCl	CH_2Cl_2, 25°C, 8 days	–	–	–
4	**4**	$AlCl_3$	CH_2Cl_2, 25°C, 5 h	61	**7/8**	10:1
5	**4**	$TiCl_4$	Toluene, 25°C, 8 days	47[a]	**7/8**	33:1
6	**4**	SiO_2	–, 25°C, 7 days	92	**7/8**	88:1
7	**5**	–	–, 180°C, 18 h	–	–	–
8	**5**	SiO_2	–, 25°C, 5 months	64[a]	**9/10**	2:1[a]
9	**5**	$AlCl_3$	CH_2Cl_2, 25°C, 30 days	69	**9/10**	5:1
10	**6**	–	100°C, 7 days	96	**11/12/13**	1:11:20
11	**6**	SiO_2	CH_2Cl_2, 25°C, 5 h	–	–	–
12	**6**	$AlCl_3$	CH_2Cl_2, 25°C, 5 h	–	–	–

[a] Determined by ^{1}H NMR analysis.



Scheme 2.



Scheme 3.

observed. The addition of $BF_3{\cdot}Et_2O$ and Et_2AlCl to the reaction medium (entries 2 and 3) promoted only the decomposition of **3**, but $AlCl_3$, $TiCl_4$, and SiO_2 (entries 4–6) catalysed the Diels–Alder reaction and the cycloadducts **7**, *endo-anti*, and **8**, *endo-syn*, were isolated with a predominance of the *anti*-isomer in all the cases (Scheme 2). The best yield and diastereoselectivity was obtained with SiO_2 without solvent.

With the help of two-dimensional NMR spectra and nOe experiments all the proton and carbon signals of **7** could be assigned. The olefinic protons $H_{3'}$ and $H_{2'}$ appear as double doublets (dd) at δ 6.16 and 6.08, respectively, $H_{6'}$ as a double doublet at δ 3.43, and protons $H_{4a'}$ and $H_{8a'}$ as dd at δ 2.85 and 3.02, respectively. Comparison of the values of the coupling constants $J_{1',8a'}$=4.4 Hz, $J_{4',4a'}$=2.9 Hz, and $J_{4a',8a'}$=10.2 Hz with literature data,[13] shows that the major adduct **7** derives from an *endo* transition state. This stereochemistry is corroborated by the high nOe observed between $H_{6'}$ and $H_{3'}$, which also indicates that **7** derives from an *anti*-facial approach. The minor adduct **8** is also *endo*, as evidenced by the value of its diagnostic coupling constants, very similar to those of **7**; hence by exclusion **8** should educe from a *syn*-approach of the reactants.

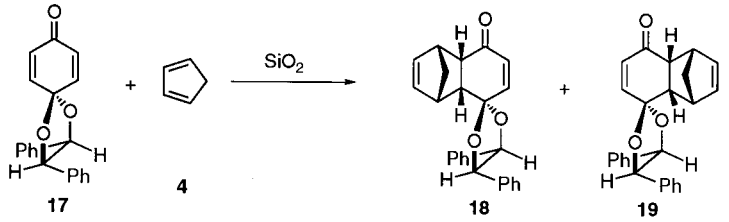
As expected, the uncatalysed reaction between ketal **3** and the less reactive dimethylbutadiene **5** did not proceed either (entry 7). For diene **5** the most effective catalyst was $AlCl_3$ (entry 9). In its presence, adducts **9** and **10** were obtained in 58 and 11% yield, respectively. Their stereochemistry was established by nOe. Irradiation of $H_{6'}$ caused enhancement of the signal corresponding to one proton $H_{4'}$ for **9**, while no nOe on protons $H_{4'}$ was observed for **10**. These experiments demonstrate that the major isomer **9** results from an *anti*-approach of the reactants in the transition state and that the main conformation is that shown in Scheme 2 with the thiophenyl group in an equatorial position. The coupling pattern of proton $H_{4a'}$ (J values of 12.4, 5.5 and 5.5 Hz) is consistent with a locked *trans*-diaxial relationship with one of the protons $H_{4'}$. In contrast, $H_{8a'}$ presents only two identical coupling constants of 5.8 Hz, and accordingly is assigned to an equatorial position related to the cyclohexene ring. A careful analysis of the ^{1}H NMR spectrum allowed us to infer that $^{cis}J_{1',8a'}$=5.8 Hz and $^{trans}J_{1',8a'}$=0 Hz. These data will be helpful for the stereochemical assignment of the adducts described below.

The uncatalysed reaction of ketal **3** with the silyl diene **6**, using the diene as solvent (entry 10) gave a mixture of three cycloaddition products **11**, **12** and **13**, which were isolated in 3, 33 and 60% yield, respectively, after column chromatography through silica gel. The high instability of the silyl cycloadducts **11** and **12** explains the predominance of the hydroxyketone **13** after chromatographic purification. In the presence of SiO_2 or $AlCl_3$ (entries 11 and 12) no cycloadducts were detected. Comparison of the significant chemical shifts and coupling constant values of **11**–**13** with those of **9** indicates that they all derive from an *anti*-approach and present the same preferred conformation. For the major product **13** a positive nOe observed on $H_{6'}$ when $H_{4'}$ was irradiated corroborates this assumption. The measured $J_{1',8a'}$ values of 0, 5.5 and 5.1 Hz in **11**, **12** and **13**, respectively, show that $H_{1'}$ and $H_{8a'}$ are *trans* in **11** and *cis* in **12** and **13** (vide supra). Since commercial diene **6** contains small amounts of the *cis* isomer, we cannot be sure whether **11** derives from an *exo-anti* transition state of *trans*-**6** or from an *endo-anti* approach of *cis*-**6**. We assume an *endo-anti* transition state of *trans*-**6** for the major adducts **12** and **13**.

As a summary of the above experiments, we concluded that in the Diels–Alder reactions of ketal **3** the thiophenyl group exerts good control of the facial diastereoselectivity and that the cycloaddition may be catalysed by several Lewis acids without decomposition of the ketal **3**.

To test the overall strategy of Scheme 1, we decided to unmask the functional groups of the original *p*-benzoquinone. With this aim the conversion of cycloadduct **7** into the unmasked equivalent **14**[10b] was undertaken (Scheme 3). The order of the required deprotections seemed unimportant and hydrolysis of the ketal was tried first. Nevertheless, all attempts to hydrolyse **7** under protic acidic conditions were unsuccessful and the new compound **15** could only be obtained in 30% yield after prolonged treatment of **7** with $ZnBr_2$. On the contrary, elimination of thiophenol by treatment of **7** with DBU followed by hydrolysis of **16**[11a] with 5% HCl proceeded in an overall 92% yield.

Next, we intended to apply the optimal cycloaddition conditions to enantiopure (+)-**3** and (−)-**3**. Unfortunately, the major adduct **7** isolated from the reactions of (+)- and (−)-**3**



Scheme 4.

with cyclopentadiene in the presence of SiO_2 did not present optical activity. We suspect that racemization of **3** had occurred under the reaction conditions, probably through an elimination–addition process.

As an alternative method of preparing *p*-benzoquinone related adducts in enantiopure form, we performed the cycloaddition of enantiopure ketal **17**[2a] with one equivalent of diene **4** in the presence of SiO_2 (Scheme 4). This reaction was sluggish, but after seven days at room temperature a mixture of diastereoisomeric cycloadducts **18** and **19** was obtained in an almost quantitative yield. We assume that **19** is the major component of the mixture with a ratio close to 2:1. All attempts to separate these compounds were unsuccessful.

In summary, we have demonstrated that the phenylthio-monoketal **3** works effectively as masked *p*-benzoquinone in Diels–Alder reactions. These cycloadditions may be performed under certain Lewis acid catalysts and give rise exclusively to *endo* adducts with good to excellent facial selectivity. The products may be converted efficiently into the formal cycloadducts of *p*-benzoquinone, but racemization of the starting ketal makes this methodology unsuitable to prepare enantiopure *p*-benzoquinone related Diels–Alder adducts. When the origin of chirality is in the dioxolane ring as in **17** the asymmetric induction is only moderate. All the new synthesized products present antituberculous activity and cytotoxicity assays are in progress.[9]

Experimental

Ketals **3**[2b,c] and **17**[2a] were prepared according to previously described methods. Reaction mixtures were stirred magnetically. The organic extracts were dried over anhydrous magnesium sulfate. Reaction solutions were concentrated using a rotary evaporator at 15–20 mmHg. Flash column chromatography was performed using Merck silica gel (230–400 mesh). Infrared spectra were recorded on a Nicolet 5 ZDX spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-250-WB instrument in $CDCl_3$ solutions. Mass spectra were performed on a Hewlett–Packard 5985B instrument at 70 eV; only peaks with higher intensity than 20% are reported, unless they belong to molecular ions or to significant fragments.

Reactions between ketal 3 and diene 4

SiO_2 as Lewis acid. A mixture of **3** (500 mg, 1.91 mmol), cyclopentadiene (630 μL, 7.62 mmol), and silica gel (5.0 g) was allowed to react at room temperature for 7 days. The silica gel was filtered off and washed with methylene chloride. Flash chromatography of the crude material (794 mg) using hexane–ethyl acetate (2:1) as eluent afforded the following fractions: (i) 7 mg (0.02 mmol, 1% yield) of (1′*RS*,4′*SR*,4a′*RS*,6′*SR*,8a′*SR*)-6′-phenylthio-1′,4′,4a′,6′,7′,8a′-hexahydrospiro{1,3-dioxolane-2,5′(8′*H*)-[1′,4′]-methanonaphthalen}-8′-one, **8**, *endo-syn*, as a colorless oil; (ii) 549 mg (1.67 mmol, 88% yield) of its (1′*RS*,4′*SR*,4a′*RS*,6′*RS*,8a′*SR*)-isomer, **7**, *endo-anti*, as a white solid; and (iii) 16 mg (0.06 mmol, 3%) of **3**. **7**: mp 80–82°C (AcOEt–hexane); IR (KBr): 3002, 2959, 2889, 1701, 1476, 1307, 1251, 1159, 1061 cm^{-1}; ^{1}H NMR: δ 7.40–7.30 (m, 2H), 7.25–7.10 (m, 3H), 6.16 (dd, $J_{3',2'}$=5.9 Hz, $J_{3',4'}$=2.9 Hz, 1H:$H_{3'}$), 6.08 (dd, $J_{2',3'}$=5.9 Hz, $J_{2',1'}$=2.9 Hz, 1H:$H_{2'}$), 4.20–4.00 (m, 4H:2H_4, 2H_5), 3.43 (dd, $J_{6',7'}$=10.2 Hz, $J_{6',7'}$=5.1 Hz, 1H:$H_{6'}$), 3.30 (br s, 1H:$H_{1'}$), 3.10 (br s, 1H:$H_{4'}$), 3.02 (dd, $J_{8a',4a'}$=10.2 Hz, $J_{8a',1'}$=4.4 Hz, 1H:$H_{8a'}$), 2.85 (dd, $J_{4a',8a'}$=10.2 Hz, $J_{4a',4'}$=2.9 Hz, 1H:$H_{4a'}$), 2.61 (dd, $J_{7',7'}$=17.5 Hz, $J_{7',6'}$=10.2 Hz, 1H:$H_{7'}$), 2.49 (dd, $J_{7',7'}$=17.5 Hz, $J_{7',6'}$=5.1 Hz, 1H:$H_{7'}$), 1.43 (br d, J=8.8 Hz, 1H:CH_2), 1.29 (br d, J=8.8 Hz, 1H:CH_2); ^{13}C NMR: δ 209.8 ($C_{8'}$), 136.2/136.0 ($C_{2'}$/$C_{3'}$), 135.2/131.4/128.9/126.9 (C_{Ar}), 109.9 (C_2), 66.3/65.0 (C_4/C_5), 51.8 ($C_{8a'}$), 49.9 ($C_{6'}$), 49.8 (CH_2), 48.0 ($C_{4a'}$), 47.3 ($C_{1'}$), 45.5 ($C_{4'}$), 45.3 ($C_{7'}$); MS (*m*/*z*): 328 (M^+, 21), 219 (49), 153 (28), 126 (100), 99 (23), 98 (58), 91 (32), 66 (30), 65 (22), 55 (29). Anal. Calcd for $C_{19}H_{20}O_3S$: C, 69.49; H, 6.14; S, 9.76. Found: C, 69.45; H, 6.28; S, 9.64. **8**: IR (film): 3065, 2952, 2924, 2854, 1708, 1476, 1441, 1258, 1202, 1181, 1082, 1026 cm^{-1}; ^{1}H NMR: δ 7.40–7.30 (m, 2H), 7.25–7.10 (m, 3H), 6.08 (m, 2H:$H_{3'}$, $H_{2'}$), 4.30–4.00 (m, 4H:2H_4, 2H_5), 3.67 (dd, $J_{6',7'}$=13.1 Hz, $J_{6'7'}$=6.2 Hz, 1H:$H_{6'}$), 3.22 (br s, 1H:$H_{1'}$), 3.04 (dd, $J_{8a'4a'}\approx$ 11.3 Hz, $J_{8a',1'}\approx$4.0 Hz, 1H:$H_{8a'}$), 2.98 (br s, 1H:$H_{4'}$), 2.90 (dd, $J_{4a',8a'}$=11.3 Hz, $J_{4a',4'}\approx$2.9 Hz, 1H:$H_{4a'}$), 2.65 (dd, $J_{7',7'}$=18.7 Hz, $J_{7',6'}$=6.2 Hz, 1H:$H_{7'}$), 2.35 (dd, $J_{7',7'}$=18.7 Hz, $J_{7',6'}$=13.1 Hz, 1H:$H_{7'}$), 1.43 (br d, J=8.4 Hz, 1H:CH_2), 1.27 (br d, J=8.4 Hz, 1H:CH_2); HRMS (EI) (M^+) calcd for $C_{19}H_{20}O_3S$ 328.1133, found 328.1148.

$AlCl_3$ as Lewis acid. A mixture of **3** (49 mg, 0.19 mmol) and $AlCl_3$ (11 mg, 0.08 mmol) in anhydrous methylene chloride (1.5 mL) under nitrogen atmosphere was stirred for 10 min. Cyclopentadiene (33 μL, 0.40 mmol) was added and the reaction mixture was allowed to react at room temperature for 5 h. The mixture was washed with saturated $NaHCO_3$ solution, neutralized with aqueous 5% HCl and washed with water. Flash chromatography of the crude material (51 mg) using hexane–ethyl acetate (2:1) as eluent afforded 37 mg of a 10:1 mixture of **7** and **8** (61% yield) as a white solid.

$TiCl_4$ as Lewis acid. Toluene (1 mL), **3** (50 mg, 0.19 mmol), and $TiCl_4$ (1 mL of a 0.08 M solution in toluene, 0.08 mmol) were introduced in a 5 mL Schlenk reactor at −78°C. The mixture was stirred at room temperature for 15 min, **4** (32 μL, 0.39 mmol) was added, and the mixture was maintained at the same temperature for 8 days. ^1H NMR analysis revealed the formation of only 47% of a 33:1 mixture of **7** and **8**, along with unreacted **3**.

Reactions between ketal 3 and diene 5

$AlCl_3$ as Lewis acid. A mixture of **3** (100 mg, 0.38 mmol) and $AlCl_3$ (31 mg, 0.23 mmol) in anhydrous methylene chloride (3 mL) was stirred for 30 min under nitrogen atmosphere. Butadiene **5** (150 μL, 1.33 mmol) was added and the reaction mixture was allowed to react at room temperature for 30 days. The mixture was washed with saturated $NaHCO_3$ solution, neutralized with aqueous 5% HCl and washed with water. Flash chromatography of the crude material (159 mg) using hexane–ethyl acetate (4:1) as eluent afforded the following fractions: (i) 51 mg (0.15 mmol, 39% yield) of (4a′*RS*,6′*RS*,8a′*SR*)-2′,3′-dimethyl-6′-phenylthio-1′,4′,4a′,6′,7′,8a′-hexahydrospiro-[1,3-dioxolane-2,5′(8′*H*)-naphthalen]-8′-one, **9**, *anti*, as a white solid; (ii) 10 mg (0.03 mmol, 8% yield) of its (4a′*RS*,6′*SR*,8a′*SR*)-isomer, **10**, *syn*, as a yellow oil; and (iii) 31 mg (0.12 mmol, 31%) of **3**. With respect to recovered **3**, adducts **9** and **10** are isolated in 58 and 11% yield, respectively. **9**: 114–117°C (AcOEt–hexane); IR (KBr): 2966, 2910, 1715, 1581, 1476, 1441, 1370, 1138, 1120, 1047, 745 cm^{-1}; ^1H NMR: δ 7.45–7.35 (m, 2H), 7.25–7.10 (m, 3H), 4.36–4.26 (m, 2H:$2H_4$/$2H_5$), 4.14–4.03 (m, 2H:$2H_4$/$2H_5$), 3.78 (dd, $J_{6',7'}$=12.4 Hz, $J_{6',7'}$=6.6 Hz, 1H:$H_{6'}$), 3.08 (br t, J≈5.8 Hz, 1H:$H_{8a'}$), 2.76 (t, $J_{7',7'}$≈$J_{7',6'}$≈13.0 Hz, 1H:$H_{7'}$), 2.67 (dd, $J_{7',7'}$≈13.0 Hz, $J_{7',6'}$=6.6 Hz, 1H:$H_{7'}$), 2.45 (br d, $J_{1',1'}$≈17.5 Hz, 1H:$H_{1'}$), 2.34 (dt, $J_{4a',4'}$≈12.4 Hz, $J_{4a',4'}$=$J_{4a',8a'}$=5.5 Hz, 1H:$H_{4a'}$), 2.08 (br d, $J_{4',4'}$=16.8 Hz, 1H:$H_{4'}$), 1.88 (very br d, $J_{1',1'}$≈17.5 Hz, 1H:$H_{1'}$), 1.64 (br d, $J_{4',4'}$=16.8 Hz, 1H:$H_{4'}$), 1.61 (br s, 3H:CH_3), 1.54 (br s, 3H:CH_3); ^{13}C NMR: δ 207.4 ($C_{8'}$), 135.2/131.8/128.9/127.2 (C_{Ar}), 123.9/122.5 ($C_{2'}$/$C_{3'}$), 110.1 (C_2), 66.3/66.1 (C_4/C_5), 52.6 ($C_{6'}$), 46.5 ($C_{7'}$), 45.0 ($C_{8a'}$), 43.5 ($C_{4a'}$), 30.8 ($C_{4'}$), 29.1 ($C_{1'}$), 19.1/18.6 ($2CH_3$); MS (*m*/*z*): 344 (M^+, 16), 235 (11), 179 (100), 107 (20), 55 (24). Anal. Calcd for $C_{20}H_{24}O_3S$: C, 69.74; H, 7.02; S, 9.31. Found: C, 69.75; H, 7.12; S, 9.20. **10**: IR (film): 2966, 2910, 2850, 1715, 1476, 1441, 1293, 1138, 1096, 1026, 962, 745 cm^{-1}; ^1H NMR: δ 7.43–7.30 (m, 2H), 7.30–7.10 (m, 3H), 4.20–3.90 (m, 4H:$2H_4$, $2H_5$), 3.58 (dd, $J_{6',7'}$=4.5 Hz, $J_{6',7'}$=2.6 Hz, 1H:$H_{6'}$), 3.00 (dd, $J_{7',7'}$=14.6 Hz, $J_{7',6'}$=4.5 Hz, 1H:$H_{7'}$), 2.65–2.35 (m, 3H:$H_{4a'}$, $H_{7'}$, $H_{8a'}$), 2.30–1.90 (m, 4H:$2H_{1'}$, $2H_{4'}$), 1.54 (br s, 6H:$2CH_3$); ^{13}C NMR: δ 208.2 ($C_{8'}$), 133.7/129.1/127.8 (C_{Ar}), 124.0/123.8 ($C_{2'}$/$C_{3'}$), 109.6 (C_2), 65.9/65.6 (C_4/C_5), 52.7 ($C_{6'}$), 47.3 ($C_{8a'}$), 43.6 ($C_{7'}$), 41.3 ($C_{4a'}$), 31.2/30.8 ($C_{1'}$/$C_{4'}$), 19.0/18.7 (2 CH_3); MS (*m*/*z*): 344 (M^+, 9), 179 (100); HRMS (EI) (M^+) calcd for $C_{20}H_{24}O_3S$ 344.1446, found 344.1448.

SiO_2 as Lewis acid. In a sealed reactor, a mixture of **3** (106 mg, 0.40 mmol), **5** (175 μL, 1.52 mmol), and silica gel (1.08 g) was allowed to react at room temperature for 5 months. ^1H NMR analysis revealed the formation of only 64% of a mixture ca 2:1 of **9** and **10**, along with unreacted **3**.

Reaction between ketal 3 and diene 6

In a sealed reactor, a mixture of **3** (528 mg, 2.01 mmol) and **6** (3.50 μL, 19.55 mmol) was allowed to react at 100°C for 7 days. Flash chromatography of the crude material (2.97 g) using hexane–ethyl acetate (4:1) as eluent afforded the following fractions: (i) 23 mg (0.06 mmol, 3% yield) of (1′*RS*,4a′*RS*,6′*RS*,8a′*RS*)-1′-trimethylsilyloxy-6′-phenylthio-1′,4′,4a′,6′,7′,8a′-hexahydrospiro[1,3-dioxolane-2,5′(8′*H*)-naphthalen]-8′-one, **11**, as a colorless oil; (ii) 267 mg (0.66 mmol, 33% yield) of its (1′*RS*,4a′*SR*,6′*SR*,8a′*SR*)-isomer, **12**, as a colorless oil; and (iii) 401 mg (1.21 mmol, 60% yield) of (1′*RS*,4a′*SR*,6′*SR*,8a′*SR*)-1′-hydroxy-6′-phenylthio-1′,4′,4a′,6′,7′,8a′-hexahydrospiro[1,3-dioxolane-2,5′(8′*H*)-naphthalen]-8′-one, **13**. **11**: IR (film): 3037, 2959, 2924, 1722, 1258, 1145, 1124, 1054, 1019 cm^{-1}; ^1H NMR: δ 7.40–7.30 (m, 2H), 7.25–7.05 (m, 3H), 5.70–5.50 (m, 2H:$H_{2'}$, $H_{3'}$), 4.45 (d, $J_{1',2'}$=4.0 Hz, 1H:$H_{1'}$), 4.30–3.90 (m, 4H:$2H_4$, $2H_5$), 3.62 (dd, $J_{6',7'}$=13.2 Hz, $J_{6',7'}$=5.8 Hz, 1H:$H_{6'}$), 2.99 (br d, $J_{8a',4a'}$=5.5 Hz, 1H:$H_{8a'}$), 2.70 (td, $J_{7',7'}$=$J_{7',6'}$=13.2 Hz, $J_{7',8a'}$=1.1 Hz, 1H:$H_{7'}$), 2.55 (dd, $J_{7',7'}$=13.2 Hz, $J_{7',6'}$=5.8 Hz, 1H:$H_{7'}$), 2.45 (dt, $J_{4a',4'}$=12.4 Hz, $J_{4a',4'}$=$J_{4a',8a'}$=5.5 Hz, 1H:$H_{4a'}$), 2.21 (dt, $J_{4',4'}$=18.6 Hz, $J_{4',3'}$≈$J_{4',4a'}$≈5.0 Hz, 1H:$H_{4'}$), 1.54 (br dd, $J_{4',4'}$=18.6 Hz, $J_{4',4a'}$=12.4 Hz, 1H:$H_{4'}$), 0.00 (s, 9H:$3CH_3$); ^{13}C NMR: δ 207.0 ($C_{8'}$), 135.0/132.0/129.0 (C_{Ar}), 127.6/127.2/127.0 (C_{Ar}/$C_{2'}$/$C_{3'}$), 109.6 (C_2), 66.2/66.0 (C_4/C_5), 62.0 ($C_{1'}$), 53.2/52.7/46.5/38.7/24.5 ($C_{4'}$/$C_{4a'}$/$C_{6'}$/$C_{7'}$/$C_{8a'}$), 0.0 (CH_3); HRMS (EI) (M^+) calcd for $C_{21}H_{28}O_4SSi$ 404.1478, found 404.1484. **12**: IR (film): 3030, 2959, 2924, 2854, 1708, 1258, 1145, 1117, 1047, 1019 cm^{-1}; ^1H NMR: δ 7.40–7.28 (m, 2H), 7.22–7.05 (m, 3H), 5.57 (br d, $J_{2',3'}$=10.0 Hz, 1H:$H_{2'}$), 5.41 (ddt, $J_{3',2'}$=10.0 Hz, J'=4.8 Hz, J''=J'''=2.5 Hz, 1H:$H_{3'}$), 4.30–4.12 (m, 3H:$2H_4$/$2H_5$, $H_{1'}$), 4.08–3.90 (m, 2H:$2H_4$/$2H_5$), 3.65 (dd, $J_{6',7'}$=13.2 Hz, $J_{6',7'}$=5.8 Hz, 1H:$H_{6'}$), 3.26 (br t, $J_{8a',4a'}$≈$J_{8a',1'}$≈5.5 Hz, 1H:$H_{8a'}$), 2.71 (t, $J_{7',7'}$=$J_{7',6'}$=13.2 Hz, 1H:$H_{7'}$), 2.52 (dd, $J_{7',7'}$=13.2 Hz, $J_{7',6'}$=5.8 Hz, 1H:$H_{7'}$), 2.34 (dt, $J_{4a',4'}$≈11.0 Hz, $J_{4a',4'}$≈$J_{4a',8a'}$≈5.5 Hz, 1H:$H_{4a'}$), 2.14 (br d, $J_{4',4'}$=18.6 Hz, 1H:$H_{4'}$), 1.65 (ddq, $J_{4',4'}$=18.6 Hz, $J_{4',4a'}$≈11.8 Hz, $J_{4',3'}$≈$J_{4',2'}$≈$J_{4',1'}$≈3.5 Hz, 1H:$H_{4'}$), 0.00 (s, 9H:$3CH_3$); ^{13}C NMR: δ 203.5 ($C_{8'}$), 134.8/132.0/130.8/128.9 (C_{Ar}), 127.1/123.9 ($C_{2'}$/$C_{3'}$), 109.3 (C_2), 67.4/66.2/66.1 (C_4/C_5/$C_{1'}$), 53.8/50.4/47.6/44.2/24.4 ($C_{4'}$/$C_{4a'}$/$C_{6'}$/$C_{7'}$/$C_{8a'}$), 0.0 (CH_3); MS (*m*/*z*): 404 (M^+, 1), 183 (24), 167 (20), 149 (20), 142 (25), 99 (21), 79 (24), 75 (63), 73 (100), 70 (20), 69 (21), 55 (23); HRMS (EI) (M^+) calcd for $C_{21}H_{28}O_4SSi$ 404.1478, found 404.1468. **13**: mp 137–139°C (methylene chloride–pentane); IR (KBr): 3492, 2892, 1697, 1413, 1151, 1117, 1044, 1021, 692 cm^{-1}; ^1H NMR: δ 7.50–7.35 (m, 2H), 7.30–7.15 (m, 3H), 5.74 (br d, $J_{2',3'}$=10.2 Hz, 1H:$H_{2'}$), 5.58 (ddt, $J_{3',2'}$=10.2 Hz, J'=4.8 Hz, J''≈J'''≈2.3 Hz, 1H:$H_{3'}$), 4.40–4.15 (m, 2H:$2H_4$/$2H_5$), 4.15–4.00 (m, 3H:$2H_4$/$2H_5$, $H_{1'}$), 3.77 (dd, $J_{6',7'}$=13.5 Hz, $J_{6',7'}$=6.2 Hz, 1H:$H_{6'}$), 3.72 (d, $J_{OH,1'}$=12.1 Hz, 1H:OH), 3.47 (br t, $J_{8a',4a'}$≈$J_{8a',1'}$≈5.1 Hz, 1H:$H_{8a'}$), 2.81 (td, $J_{7',7'}$=$J_{7',6'}$=13.5 Hz, J=1.1 Hz, 1H:$H_{7'}$), 2.66 (dd, $J_{7',7'}$=13.5 Hz, $J_{7',6'}$=6.2 Hz, 1H:$H_{7'}$), 2.43 (dt, $J_{4a',4'}$=11.3 Hz, $J_{4a',4'}$≈$J_{4a',8a'}$=5.6 Hz, 1H:$H_{4a'}$), 2.27 (br d, $J_{4',4'}$=18.6 Hz, 1H:$H_{4'}$), 1.76 (ddq, $J_{4',4'}$=18.6 Hz, $J_{4',4a'}$=11.5 Hz, $J_{4',3'}$≈$J_{4',2'}$≈$J_{4',1'}$≈3.5 Hz, 1H:$H_{4'}$); ^{13}C NMR: δ

210.1 ($C_{8'}$), 134.9/132.0/131.2/129.1 (C_{Ar}), 127.4/124.7 ($C_{2'}$/$C_{3'}$), 109.3 (C_2), 67.8/66.4/66.3 (C_4/C_5/$C_{1'}$), 52.9/49.2/47.3/43.7/24.6 ($C_{4'}$/$C_{4a'}$/$C_{6'}$/$C_{7'}$/$C_{8a'}$); MS (*m/z*): 332 (M^+, 6), 167 (100), 149 (26), 99 (39), 73 (21), 55 (46). Anal. Calcd for $C_{18}H_{20}O_4S$: C, 65.04; H, 6.06; S, 9.64. Found: C, 64.85; H, 6.05; S, 9.68.

(1*RS*,4*SR*,4a*RS*,6*RS*,8a*SR*)-6-Phenylthio-1,4,4a,6,7,8a-hexahydro[1,4]methanonaphthalen-5,8-dione, 15. A suspension of **7** (103 mg, 0.31 mmol) and $ZnBr_2$ (150 mg, 0.67 mmol) in methylene chloride (4 mL) was stirred at room temperature for 3 months. Water was added and the mixture was extracted with methylene chloride. Flash chromatography of the crude material (58 mg) using hexane–ethyl acetate (4:1) as eluent afforded **15** (27 mg, 0.09 mmol, 30% yield) as a colorless oil: IR (KBr): 2995, 2966, 2931, 2875, 1708, 1581, 1476, 1441, 1258, 1068, 737 cm^{-1}; ^1H NMR: δ 7.35–7.15 (m, 5H), 6.18 (dd, J=5.5 Hz, J'=2.9 Hz, 1H:H_2/H_3), 6.01 (dd, J=5.5 Hz, J'=2.2 Hz, 1H:H_2/H_3), 3.75 (dd, $J_{6,7}$=4.4 Hz, $J_{6,7}$=3.7 Hz, 1H:H_6), 3.45–3.30 (m, 4H:H_1, H_4, H_{4a}, H_{8a}), 2.66 (dd, $J_{7,7}$=17.2 Hz, $J_{7,6}$=3.7 Hz, 1H:H_7), 2.52 (dd, $J_{7,7}$=17.2 Hz, $J_{7,6}$=4.4 Hz, 1H:H_7), 1.44 (br d, J=8.8 Hz, 1H:CH_2), 1.32 (br d, J=8.8 Hz, 1H:CH_2); ^{13}C NMR: δ 207.6/204.5 (C_5/C_8), 137.9/135.1/132.0/131.6/129.3/128.4 (C_2/C_3/C_{Ar}), 52.5/50.9/49.4/48.72/48.68/46.1/42.7 (C_1/C_4/C_{4a}/C_6/C_7/C_{8a}/CH_2); MS (*m/z*): 284 (M^+, 31), 218 (41), 175 (21), 136 (51), 135 (44), 110 (34), 109 (100), 91 (46), 66 (50), 65 (27), 55 (26). Anal. Calcd for $C_{17}H_{16}O_2S$: C, 71.80; H, 5.67; S, 11.27. Found: C, 71.54; H, 5.64; S, 11.23.

(1′*RS*,4′*SR*,4a′*RS*,8a′*SR*)-1′,4′,4a′,8a′-Tetrahydrospiro-{1,3-dioxolane-2,5′(8′H)-[1′,4′]methanonaphthalen}-8′-one, 16. A solution of **7** (449 mg, 1.37 mmol) and DBU (410 μL, 2.75 mmol) in methylene chloride (5 mL) was kept at room temperature for 20 min. The organic phase was washed with aqueous 1% HCl and water. Flash chromatography of the crude material (477 mg) using hexane–ethyl acetate (2:1) as eluent afforded compound **16**[11a] (289 mg, 1.32 mmol, 97% yield) as a colorless oil: ^1H NMR: δ 6.27 (dd, $J_{6',7'}$=10.2 Hz, $J_{6',4a'}$=1.5 Hz, 1H:$H_{6'}$), 6.02 (dd, $J_{3',2'}$=5.8 Hz, $J_{3',4'}$=2.9 Hz, 1H:$H_{3'}$), 5.89 (d, $J_{7',6'}$=10.2 Hz, 1H:$H_{7'}$), 5.84 (dd, $J_{2',3'}$=5.8 Hz, $J_{2',1'}$=2.2 Hz, 1H:$H_{2'}$), 4.10–3.90 (m, 4H:$2H_4$, $2H_5$), 3.29 (br s, 1H:$H_{1'}$), 3.16 (br s, 1H:$H_{4'}$), 2.98 (dd, $J_{8a',4a'}$=8.8 Hz, $J_{8a',1'}$=4.0 Hz, 1H:$H_{8a'}$), 2.81 (dd, $J_{4a',8a'}$=8.8 Hz, $J_{4a',4'}$=4.0 Hz, 1H:$H_{4a'}$), 1.39 (br d, J=8.8 Hz, 1H:CH_2), 1.28 (br d, J=8.8 Hz, 1H:CH_2); ^{13}C NMR: δ 200.1 ($C_{8'}$), 145.2 ($C_{6'}$), 135.4/133.9/132.2 ($C_{2'}$/$C_{3'}$/$C_{7'}$), 104.0 (C_2), 65.5/64.3 (C_4/C_5), 49.7/48.6/47.5/46.6/46.0 ($C_{1'}$/$C_{4'}$/$C_{4a'}$/$C_{8a'}$/CH_2).

(1*RS*,4*SR*,4a*RS*,8a*SR*)-1,4,4a,8a-Tetrahydro[1,4]methanonaphthalen-5,8-dione, 14. A solution of **16** (288 mg, 1.32 mmol) in aqueous 5% HCl (30 mL) was left at room temperature for 1 h. The solution was extracted with ether and after conventional work up yielded **14** as a yellow solid (214 mg, 1.23 mmol, 93% yield). Mp: 76–77°C (ethyl acetate–hexane). Lit.[10b] mp 76–78.5°C.

Reaction between ketal 17 and diene 4

A mixture of **17** (257 mg, 0.84 mmol), cyclopentadiene (70 μL, 0.85 mmol), and silica gel (2.57 g) was allowed to react at room temperature for 6 days. The silica gel was filtered off and washed with methylene chloride. Flash chromatography of the crude material (330 mg) using toluene–methylene chloride (5:1) as eluent afforded the following fractions: (i) 115 mg (0.38 mmol, 45%) of **17**; (ii) 167 mg (0.45 mmol, 54% yield) of a 1:2 (or 2:1) mixture of (4*R*,5*R*,1′*R*,4′*S*,4a′*R*,8a′*S*)-4,5-diphenyl-1′,4′,4a′,8a′-tetrahydrospiro[1,3-dioxolane-2,5′(8′*H*)-[1,4]methanonaphthalen]-8′-one and its (4*R*,5*R*,1′*S*,4′*R*,4a′*S*,8a′*R*)-isomer, **18** and **19**, as a white solid. With respect to recovered **17** the yield is 97%. Mixture **18** and **19**: mp 101–105°C; IR (KBr): 3050, 3036, 2931, 2878, 1744, 1670, 1260, 1127, 755, 678 cm^{-1}; ^1H NMR (M: major isomer; m: minor isomer): δ 7.35–7.05 (m, 10H), 6.62 (d, $J_{6',7'}$=10.2 Hz, 1H:$H^m_{6'}$), 6.51 (d, $J_{6',7'}$=10.2 Hz, 1H:$H^M_{6'}$), 6.04 (m, 1H:$H_{3'}$), 5.97 (d, $J_{7',6'}$=10.2 Hz, 1H:$H_{7'}$), 5.85 (m, 1H:$H_{2'}$), 4.85 (d, $J_{4,5}$=8.4 Hz, 1H:H^m_4/H^m_5), 5.73 (d, $J_{4,5}$=8.4 Hz, 1H:H^m_4/H^m_5), 4.71 (s, 2H:H^M_4, H^M_5), 3.50 (br s)+3.40–3.20 (m)+3.15–3.00 (m) (total: 4H:$H_{1'}$, $H_{4'}$, $H_{4a'}$, $H_{8a'}$), 1.50–1.30 (m, 2H:CH_2); ^{13}C NMR: δ 136.0–125.0 (C_{Ar}, $C_{2'}$, $C_{3'}$, $C_{7'}$), M: 200.2 ($C_{8'}$), 145.1 ($C_{6'}$), 104.5 (C_2), 85.7/84.4 (C_4/C_5), 50.1/48.9/47.5/47.3/46.9 ($C_{1'}$/$C_{4'}$/$C_{4a'}$/$C_{8a'}$/CH_2), m: 199.7 ($C_{8'}$), 146.5 ($C_{6'}$), 104.4 (C_2), 86.1/85.8 (C_4/C_5), 49.4/48.4/47.9/47.4/46.3 ($C_{1'}$/$C_{4'}$/$C_{4a'}$/$C_{8a'}$/CH_2); MS (*m/z*, CI/NH_3): 388 (M^++18, 8), 371 (M^++1, 46), 214 (100), 196 (44). Anal. Calcd for $C_{25}H_{22}O_3$: C, 81.06; H, 5.99. Found: C, 81.04; H, 6.09.

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References

1. Swenton, J. S. In *The Chemistry of the Quinonoid Compounds*, Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1988; Vol. 2, pp 899–962.
2. (a) de March, P.; Escoda, M.; Figueredo, M.; Font, J.; Alvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1995**, *60*, 3895–3897. (b) de March, P.; Escoda, M.; Figueredo, M.; Font, J. *Tetrahedron Lett.* **1995**, *36*, 8665–8668. (c) de March, P.; Escoda, M.; Figueredo, M.; Font, J.; Medrano, J. *An. Quím. Int. Ed.* **1997**, *93*, 81–87. (d) de March, P.; Figueredo, M.; Font, J.; Medrano, J. *Tetrahedron* **1999**, *55*, 7907–7914.
3. Taylor, R. J. K.; Alcaraz, L.; Kapfer-Eyer, I.; Macdonald, G.; Wei, X.; Lewis, N. *Synthesis* **1998**, 775 and references cited therein.
4. (a) Wipf, P.; Kim, Y. *J. Org. Chem.* **1994**, *59*, 3518–3519. (b) Wipf, P.; Kim, Y.; Jahn, H. *Synthesis* **1995**, 1549–1561.
5. Alcaraz, L.; Macdonald, G.; Ragot, J. P.; Lewis, N.; Taylor, R. J. K. *J. Org. Chem.* **1998**, *63*, 3526–3527.
6. (a) Gautier, E. C. L.; Lewis, N. J.; McKillop, A.; Taylor, R. J. K. *Tetrahedron Lett.* **1994**, *35*, 8759–8760. (b) Johnson, C. R.; Miller, M. W. *J. Org. Chem.* **1995**, *60*, 6674–6675.
7. McKillop, A.; McLaren, L.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1385–1393.
8. de March, P.; Escoda, M.; Figueredo, M.; Font, J.; Alvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1997**, *62*, 7781–7787.
9. Unpublished results. Antimycobacterial data were provided by

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10. For some examples see: (a) Lora-Tamayo, M.; Leon, J. L. *J. Chem. Soc.* **1948**, 1499–1501. (b) Marchand, A. P.; Allen, R. W. *J. Org. Chem.* **1974**, *39*, 1596. (c) Chiba, K.; Tada, M. *J. Chem. Soc., Chem. Commun.* **1994**, 2485–2486. (d) Chung, W.-S.; Wang, J.-Y. *J. Chem. Soc., Chem. Commun.* **1995**, 971–972. (e) Levin, J. I. *Tetrahedron Lett.* **1996**, *37*, 3079–3082. (f) Cuerva, J. M.; Echavarren, A. M. *Synlett* **1997**, 173–174. (g) Brimble, M. A.; Elliott, R. J. R. *Tetrahedron* **1997**, *53*, 7715–7730.

11. (a) Carreño, M. C.; Fariña, F.; Galán, A.; García Ruano, J. L. *J. Chem. Res., Synop.* **1979**, 296–297; *J. Chem. Res., Miniprint* **1979**, 3443–3467. (b) Swenton, J. S. *Acc. Chem. Res.* **1983**, *16*, 74–81. (c) Russell, R. A.; Evans, D. A. C.; Warrener, R. N. *Aust. J. Chem.* **1984**, *37*, 1699–1707. (d) Carreño, M. C.; Fariña, F.; García Ruano, J. L.; Puebla, L. *J. Chem. Res., Synop.* **1984**, 288–289. (e) Jarvo, E. R.; Boothroyd, S. R.; Kerr, M. A. *Synlett* **1996**, 897–899. (f) Gerstenberger, I.; Hansen, M.; Mauvais, A.; Wartchow, R.; Winterfeldt, E. *Eur. J. Org. Chem.* **1998**, 643–650.

12. (a) Carreño, M. C.; García Ruano, J. L.; Urbano, A.; Hoyos, M. A. *J. Org. Chem.* **1996**, *61*, 2980–2985 and references cited therein. (b) Carreño, M. C.; Mahugo, J.; Urbano, A. *Tetrahedron Lett.* **1997**, *38*, 3047–3050. (c) Carreño, M. C.; García Ruano, J. L.; Remor, C. Z.; Urbano, A.; Fischer, J. *Tetrahedron Lett.* **1997**, *38*, 9077–9080. (d) Carreño, M. C.; González, M. P.; Houk, K. N. *J. Org. Chem.* **1997**, *62*, 9128–9137.

13. Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. In *Tabellen zur Strukturaufklärung organischer Verbindungen mit spektroskopischen Methoden*, Springer: Berlin, 1976.