DMSO-d_6) see Table I; (5:1 $CDCl_3/CD_3OD$) δ 6.83 (br s, 1 H, H-2'), 6.81 (br s, 2 H, H-5' and H-6'), 6.54 (br s, H-5), 5.99 (s, 2 H, H_2-7'), 4.14 (t, 2 H, J = 6.5 Hz, H_2-16), 4.07 (br s, 2 H, H_2-14), 3.75 (s, 3 H, Me-12), 3.28 (s, 3 H, Me-13), 3.20 (t, 2 H, J = 6.5 Hz, H_2-17); ^{13}C NMR ($CDCl_3$/DMSO-d_6) see Table I; HRFABMS obsd m/z = 449.1236 (MH^+, $C_{18}H_{21}N_6O_6S$ requires 449.1243); CIMS m/z 341 [$MH^+ - (CH_2CH_2SO_3H)$], 232 (100).

Methylation of (9*E*)-Clathridine 9-*N*-(2-Sulfoethyl)imine (2). A stirred solution of **2** (3.0 mg) in methanol (1 mL) was treated with excess ethereal diazomethane solution for 2 h. The excess reagent was destroyed by adding 1% aqueous acetic acid, and then chloroform (2 mL) was added. The organic layer was washed with H_2O (3 × 2 mL) and dried over Na_2SO_4, and the solvent was removed to obtain a yellow oil (3.2 mg) that was purified by reversed-phase HPLC (C_{18} column, 7:3 MeOH/H_2O) to obtain the methyl ester **3** (2.0 mg): ^1H NMR ($CDCl_3$) δ 6.79 (d, 1 H, J = 7.6 Hz, H-5'), 6.66 (dd, 1 H, J = 7.6, 2 Hz, H-6'), 6.65 (br s, 1 H, H-2'), 6.36 (s, 1 H, H-5), 5.98 (s, 2 H, H-7'), 4.04 (t, 2 H, J = 7.2 Hz, H-16), 3.90 (s, 3 H, SO_3Me), 3.80 (br s, 2 H, H-14), 3.51 (s, 3 H, Me-12), 3.43 (t, 2 H, J = 7.2 Hz, H2-17), 3.38 (s, 3 H, NMe-3), 3.14 (s, 3 H, Me-13); ^{13}C NMR ($CDCl_3$) δ 165.3 (s), 163.4(s), 159.9 (s), 148.2 (s), 147.0 (s), 146.5 (s), 128.8 (s), 128.3 (s), 121.7 (d), 115.3 (d), 108.8 (d), 108.7 (d), 101.3 (t), 55.7 (q), 50.8 (t), 42.6 (t), 34.5 (q), 31.2 (q), 30.4 (t), 25.6 (q).

Reduction of Methyl Ester 3. Sodium borohydride (3.0 mg) was added to a solution of **3** (1.8 mg) in methanol (0.5 mL), and the solution was stirred for 30 min at room temperature, after which time the excess reagent was destroyed with dilute acetic acid. The solvent was evaporated, and the product was extracted with chloroform (3 × 2 mL) and purified by reversed-phase HPLC (C_{18} column, 1:1 MeOH/H_2O) to obtain **4** (0.9 mg): ^1H NMR (10:1 $CDCl_3/CD_3OD$) δ 6.79 (d, 1 H, J = 8 Hz, H-5'), 6.66 (br d, 1 H, J = 8 Hz, H-6'), 6.65 (br s, 1 H, H-2'), 6.47 (s, 1 H, H-5), 5.99 (s, 2 H, H-7'), 5.25 (s, 1 H, H-11), 4.00 (m, 2 H, H-16), 3.83 (br s, 2 H, H-14), 3.61 (m, 1 H, H-17), 3.30 (m, 1 H, H-17), 3.54 (s, 3 H, Me-12), 3.38 (s, 3 H, NMe-3), 3.06 (s, 3 H, Me-13); HRFABMS obsd m/z 465.1559 (MH^+), $C_{19}H_{25}N_6O_6S$ requires 465.1556.

Single Crystal X-ray Diffraction Analysis of (9*E*)-Clathridine 9-*N*-(2-Sulfoethyl)imine (2). (9*E*)-Clathridine 9-*N*-(2-sulfoethyl)imine (**2**) crystallized as yellow blocks, and a single crystal with dimensions 0.4 × 0.4 × 0.4 mm was selected for further analysis. Preliminary photographs displayed orthorhombic symmetry with accurate lattice constants, determined by a least-squares fit of 25 diffractometer-measured 2θ values in the range $30° \leq 2\theta \leq 45°$, of a = 8.363 (2), b = 10.586 (2), and c = 22.800 (3) Å. Systematic absences indicated space group $P2_12_12_1$, and density considerations required one molecule of $C_{18}H_{20}N_6O_6S$ for the asymmetric unit. A total of 1621 reflections with $2\theta \leq 116°$ were measured using a variable speed θ:2θ scan. Periodically monitored check reflections showed no significant decomposition. After correction for Lorentz, polarization, and background effects, a total of 1552 (97%) reflections were judged observed ($|F_o| \geq 3\sigma|F_o|$). The structure was solved using the SHELXTL library of programs. Full-matrix least-squares refinements with anisotropic non-hydrogen atoms and fixed riding hydrogens have converged to a conventional crystallographic discrepancy index of R = 0.046 and R_w = 0.067 with $w = \sigma^2(F + 0.0005F^2)$. The final difference electron density map was essentially featureless with ±0.38 eÅ^3. Additional crystallographic details are available as supplementary material.

Acknowledgment. The sponge was collected by Drs. Brad Cartê and Steve Bobzin and was identified by Dr. Rob van Soest (Amsterdam). The research was supported by grants from the National Institutes of Health (CA 49084 and CA 24487) and by the California and New York Sea Grant Programs.

Supplementary Material Available: Tables of crystal data, data collection, solution and refinement, fractional coordinates, bond distances, bond angles, and thermal factors for (9*E*)-clathridine 9-*N*-(sulfoethyl)imine (**2**) (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

ω-Heteroatom Effect on the Nickel-Catalyzed Reactions of Benzylic Thioethers with Grignard Reagents

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Received October 8, 1991 (Revised Manuscript Received January 4, 1992)

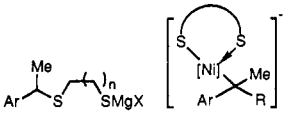
The nickel-catalyzed cross-coupling reactions of aryl, vinylic, and allylic organosulfur compounds with the Grignard reagent are well-documented.[1] It is noted that simple benzylic thioethers are relatively unreactive under these conditions.[2] To illustrate, the reaction of α-thiomethoxytoluene with PhMgBr in the presence of $NiCl_2L_2$ (L = Ph_3P or dppp) afforded diphenylmethane in only 9% yield and over 70% of the starting material was recovered. The impediment may arise from the difficulty in achieving an intermolecular oxidative addition process cleaving the carbon–sulfur bond. We recently reported that benzylic dithioacetals react with Grignard reagents in the presence of the nickel catalyst to give the corresponding styrenes[3,4] or geminal dialkylated products[3,5] in good yields. Occasionally, the reaction can proceed at room temperature. The involvement of intermediate **1** has been speculated (Scheme I).[4] Although **1** is a benzylic thioether, an appropriately located anionic sulfur moiety may effectively coordinate to the nickel catalyst to form a chelation complex which may undergo a smooth *intramolecular* oxidative addition across the benzylic carbon–sulfur bond. In order to test the validity of this conjecture, we have carried out a systematic study to investigate the effect of different ω-heteroatoms in the thioether chain on the reactivity of the benzylic carbon–sulfur bond in the nickel-catalyzed reactions.

Results and Discussion

As just mentioned, **1** is the key intermediate for the olefination reaction of the benzylic dithioacetal with the Grignard reagent and can readily proceed a formal elimination process to give an olefin.[4] We have therefore synthesized various benzylic thioethers **2** (see Experimental Section) for comparison.

At room temperature, **2** was treated with 4 equiv of MeMgI in the presence of 5 mol % of $NiCl_2(PPh_3)_2$ for 18 h. The results are compiled in Table I. Both the chain length connecting the benzylic sulfur atom to the ω-heteroatom and the nature of the heteroatom affect the reactivity of **2**.

Under the reaction conditions, **2a–e** rapidly react with the Grignard reagent to generate the corresponding thiolate anion **4**, which would associate with the nickel to give intermediate **1** (X = S). Further intramolecular oxidative addition across the benzylic carbon–sulfur bond gives **5**,



4 **5**

(1) For reviews, see: (a) Luh, T.-Y.; Ni, Z.-J. *Synthesis* **1990**, *89*. (b) Fiandanese, V. *Pure Appl. Chem.* **1990**, *62*, 1987. (c) Naso, F. *Pure Appl. Chem.* **1988**, *60*, 79.

(2) Okamura H.; Takei, H. *Tetrahedron Lett.* **1979**, 3425.

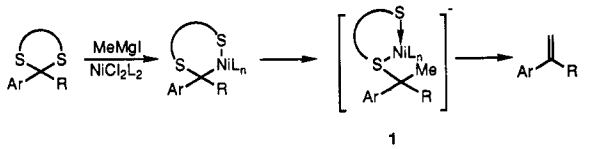
(3) For a review, see: Luh, T.-Y. *Acc. Chem. Res.* **1991**, *24*, 257.

(4) Ni, Z.-J.; Mei, N.-W.; Shi, X.; Wang, M. C.; Tzeng, Y.-L.; Luh, T.-Y. *J. Org. Chem.* **1991**, *56*, 4035 and references therein.

(5) Tzeng, Y.-L.; Yang, P.-F.; Mei, N.-W.; Yuan, T.-M.; Yu, C. C.; Luh, T.-Y. *J. Org. Chem.* **1991**, *56*, 5289 and references therein.

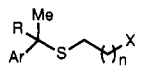
0022-3263/92/1957-2178$03.00/0

Scheme I



1

Table I. $NiCl_2(PPh_3)_2$-Catalyzed Reaction of Thioethers 2 with MeMgI



2

3a Ar = 2-Np R = H
b Ar = 1-Np R = H
c Ar = Ph R = Ph

substr	Ar	R	X	n	3 (% yield)	% yield of recovd 2
2a	2-Np	H	SH	1	**3a** (69)[a]	
2b		H	SH	2	**3a** (65)	
2c		H	SH	3	**3a** (61)	
2d	1-Np	H	SH	1	**3b** (81)[b]	
2e	2-Np	H	SH	5	**3a** (5)	91
2f		H	SMe	1	**3a** (0)	82
2g		H	SMe	2	**3a** (0)	91
2h		H	OH	1	**3a** (10)	78
2i		H	OH	2	**3a** (4)	87
2j		H	NH_2	1	**3a** (77)	
2k	Ph	Ph	NH_2	1	**3c** (56)[c]	

[a] Reference 10. [b] Reference 11. [c] Reference 12.

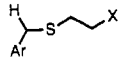
which undergoes a formal β-elimination process to afford **3**. As can be seen from Table I, the yields of the corresponding styrenes **3** from **2a–d** are much higher than that from **2e**. Apparently, the chelation of ω-thiolate anion to the nickel like **1** plays an important role on the reactivity of these nickel-catalyzed reactions, the formation of such a chelation intermediate **1** being expectedly highly unfavorable for the reaction with **2e** due to the ring constraint.

Interestingly, **2f** and **2g** are inert under the reaction conditions, starting materials being recovered. This observation indicates that the terminal X group should be able to give an anionic moiety which may give a more stable chelation intermediate in **1**, leading to further reaction. Indeed, it is known that a mercaptide anion ligand is more strongly bound to the central metal atom than a thioether group.[6] When X was a hydroxy group such as in **2h** and **2i**, **3** was obtained in poor yield and most of the starting materials were recovered. On the other hand, the terminal amino group promotes the smooth cleavage of the benzylic carbon–sulfur bond (**2j** and **2k**). Again, the ability to form the chelation complex **1** plays a key role on the reactivity of the C–S bond cleavage in **2**.

The aforementioned benzylic thioethers have β-hydrogen(s); therefore, an intermediate like **1** would rapidly undergo β-hydride elimination to give **3**. Compounds **6** contain no such hydrogen. As such, either a cross-coupling reaction with the Grignard reagent or homolytic cleavage of the nickel–carbon bond could occur. The former process will give the corresponding displacement product **7**. The latter step will lead to the formation of an organic radical which may dimerize to give the corresponding dimeric product **8**. The chain connecting the benzylic sulfur atom to the heteroatom in **6** was chosen to be an ethylene bridge because, according to the results shown in Table I, this chain length could yield optimal five-membered chelation to the nickel atom which resulted in the facile cleavage of the benzylic carbon–sulfur bond. It is well documented

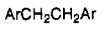
(6) Murray, S. G.; Hartley, F. R. *Chem. Rev.* **1981**, *81*, 365.

Table II. $NiCl_2$(dppe)-Catalyzed Reaction of Thioethers 6 with MeMgI



6

7



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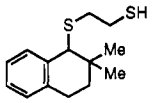


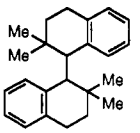
9

substr	Ar	X	7 (% yield)	8 (% yield)	% yield of recovd 6
a	1-Np	SH	**7a** (64)[a]	**8a** (18)[b]	
b	2-Np	SH	**7b** (85)[c]		
c	4-MePh	SH	**7c** (58)[d]	**8c** (13)[e]	
d	3-OMePh	SH	**7d** (50)[f]	**8d** (31)[f]	
e	4-OMePh	SH	**7e** (75)[d]		
f	2-MePh	SH		**8f** (80)[e]	
g	1-Np	NH_2	**7a** (70)	*g*	8
h		OH	**7a** (28)	**8a** (3)	38
i		H	**7a** (23)	*g*	70

[a] Reference 13. [b] Reference 14. [c] Reference 15. [d] Reference 16. [e] Reference 17. [f] Reference 18. [g] Trace amount of **8a**.

that the presence of a bidendate ligand in the nickel catalyst will facilitate the reductive elimination step, which will lead to carbon–carbon bond formation.[7] Accordingly, $NiCl_2$(dppe) was chosen as the catalyst for this purpose. Thus, **6** was allowed to react with 4 equiv of MeMgI in the presence of 5 mol % $NiCl_2$(dppe) at 46 °C for 18 h followed by the usual workup. This reaction temperature was chosen to slightly accelerate the reaction. The results are tabulated in Table II.

As shown in Table II, both ω-mercapto and ω-amino groups apparently enhanced the reactivity of the benzylic carbon–sulfur bond in **6**. Thioethers **6a–e** afforded the coupling products **7a–e** in moderate to good yields. Occasionally, the dimeric products **8** were also obtained in small amounts. The yield of **8** seemed to increase with an increase in steric hindrance around the reaction center and with the stability of the corresponding benzylic radicals. Thus, **6a** gave **8a** in 18% yield in addition to 64% of **7a**. Interestingly, **6f** yielded exclusively **8f**. The highly sterically hindered **9** was inert under the reaction conditions. However, at refluxing benzene temperature, **9** afforded **10** as the sole product in 84% yield. Whereas the diphenylmethyl radical is quite stable, the reaction of **11** afforded **12** in 74% yield. Similar to the reactions with **2h** and **2i**, when X is a hydroxyl group as in **6h**, the reaction proceeded poorly.



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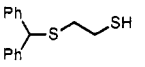

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12

In summary, we have addressed two interesting features in the nickel-catalyzed reactions of the Grignard reagent with benzylic thioethers in which an ω-heteroatom is present in the leaving group. Our results furnish a new insight in the design of an appropriate leaving group in the metal-catalyzed reactions. In addition, a pertinent rationale for the facile nickel-catalyzed cross-coupling reactions of dithioacetals with Grignard reagents[4] can be obtained.

Experimental Section

General Procedure for the Preparation of Benzylic Thioether 2 or 6 from Benzyl Alcohol.[8] To a suspension of

(7) (a) Trost, B. M.; Ornstein, P. L. *J. Org. Chem.* **1982**, *47*, 748. (b) Tiecco, M.; Tingoli, M.; Wenkert, E. *J. Org. Chem.* **1985**, *50*, 3828.

ZnI_2 (0.5–1.0 equiv) and benzyl alcohol in CH_2Cl_2 was added thiol (2 equiv), and the mixture was stirred at room temperature for 8 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried ($MgSO_4$). The filtrate was evaporated in vacuo to give the crude thioether, which was purified by chromatography on silica gel (EtOAc/hex = 1/50).

4-(2-Naphthyl)-3-thiapentane-1-thiol (2a). In a manner similar to that described in the general procedure, the reaction of 1-(2-naphthyl)ethanol (516 mg, 3.0 mmol), ZnI_2 (957 mg, 3.0 mmol), and 1,2-ethanedithiol (0.5 mL, 6.0 mmol) in CH_2Cl_2 (6 mL) gave **2a** as an oil (400 mg, 54%): IR (neat) 3051, 2965, 2620, 1049, 948, 892, 857, 819, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.57 (t, J = 8 Hz, 1 H), 1.64 (d, J = 6 Hz, 3 H), 2.51–2.58 (m, 4 H), 4.15 (q, J = 8 Hz, 1 H), 7.43–7.84 (m, 7 H); ^{13}C NMR δ 22.5, 24.6, 35.3, 44.4, 125.2, 125.8, 125.9, 126.2, 127.7, 128.6, 132.8, 133.1, 140.9; MS m/z (rel intensity) 248 (M, 12), 155 (M – 93, base peak); HRMS calcd for $C_{14}H_{16}S_2$ 248.0693, found 248.0694. Anal. Calcd: C, 67.69; H, 6.49. Found: C, 67.49; H, 6.47.

5-(2-Naphthyl)-4-thiahexane-1-thiol (2b). In a manner similar to that described in the general procedure, the reaction of 1-(2-naphthyl)ethanol (516 mg, 3 mmol), ZnI_2 (958 mg, 3 mmol), and 1,3-propanedithiol (0.6 mL, 6 mmol) in CH_2Cl_2 (6 mL) afforded colorless oil **2b** (409 mg, 52%): IR (neat) 3051, 2963, 2628, 1065, 948, 892, 857, 819, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.22 (t, J = 8 Hz, 1 H), 1.63 (d, J = 8 Hz, 3 H), 1.75 (quint., J = 8 Hz, 2 H), 2.32–2.57 (m, 4 H), 4.08 (q, J = 8 Hz, 1 H), 7.40–7.83 (m, 7 H); ^{13}C NMR δ 22.5, 23.4, 29.5, 33.1, 44.4, 125.3, 125.8, 126.2, 127.7, 128.5, 132.7, 133.1, 141.2; MS m/z (rel intensity) 262 (M, 12), 155 (M – 107, base peak), 106 (M – 156, 48); HRMS calcd for $C_{15}H_{18}S_2$ 262.0850, found 262.0850. Anal. Calcd: C, 68.65; H, 6.91. Found: C, 68.80; H, 6.76.

6-(2-Naphthyl)-5-thiaheptane-1-thiol (2c). In a manner similar to that described in the general procedure, the reaction of 1-(2-naphthyl)ethanol (516 mg, 3 mmol), ZnI_2 (958 mg, 3 mmol), and 1,4-butanedithiol (0.7 mL, 6 mmol) in CH_2Cl_2 (6 mL) gave **2c** as an oil (331 mg, 40%): IR (neat) 3051, 2962, 2566, 1052, 1018, 948, 892, 857, 750, 684, 615 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25 (t, J = 8 Hz, 1 H), 1.56 (m, 4 H), 1.64 (d, J = 6 Hz, 3 H), 2.24–2.47 (m, 4 H), 4.10 (q, J = 8 Hz, 1 H), 7.43–7.84 (m, 7 H); ^{13}C NMR δ 22.5, 24.1, 27.8, 30.6, 33.0, 44.3, 125.3, 125.7, 126.1, 127.6, 128.5, 132.7, 133.1, 141.3; MS m/z (rel intensity) 276 (M, 9), 155 (M – 121, base peak), 120 (M – 156, 22); HRMS calcd for $C_{16}H_{20}S_2$ 276.1006, found 276.1004. Anal. Calcd: C, 69.51; H, 7.29. Found: C, 69.37; H, 7.56.

4-(1-Naphthyl)-3-thiapentane-1-thiol (2d). In a manner similar to that described in the general procedure, the reaction of 1-(1-naphthyl)ethanol (1.03 g, 6 mmol), ZnI_2 (1.92 g, 6 mmol), and 1,2-ethanedithiol (1.0 mL, 12 mmol) in CH_2Cl_2 (12 mL) gave **2d** as an oil (833 mg, 56%): IR (neat) 3047, 2965, 2558, 1593, 1447, 1370, 1205, 1164, 799 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.58 (t, J = 6.6 Hz, 1 H), 1.76 (d, J = 7 Hz, 3 H), 2.49–2.69 (m, 4 H), 4.87 (q, J = 7 Hz, 1 H), 7.43–8.23 (m, 7 H); ^{13}C NMR δ 22.5, 24.7, 35.3, 39.5, 122.9, 124.4, 125.4, 125.6, 126.0, 127.8, 129.0, 130.9, 133.9, 138.7; MS m/z (rel intensity) 248 (M, 12), 155 (M – 93, base peak); HRMS calcd for $C_{14}H_{16}S_2$ 248.0693, found 248.0695. Anal. Calcd: C, 67.69; H, 6.49. Found: C, 67.99; H, 6.58.

8-(2-Naphthyl)-7-thianonane-1-thiol (2e). In a manner similar to that described in the general procedure, the reaction of 1-(2-naphthyl)ethanol (860 mg, 5 mmol), ZnI_2 (1.6 g, 5 mmol), and 1,6-hexanedithiol (1.5 mL, 10 mmol) in CH_2Cl_2 (10 mL) produced **2e** as an oil (320 mg, 21%): IR (neat) 3052, 2925, 2567, 1019, 948, 892, 857, 819, 749, 615 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.21–1.56 (m, 9 H), 1.63 (d, J = 6 Hz, 3 H), 2.12–2.47 (m, 4 H), 4.08 (q, J = 8 Hz, 1 H), 7.35–7.83 (m, 7 H); ^{13}C NMR δ 22.5, 24.5, 27.8, 28.2, 29.1, 31.1, 33.8, 44.3, 125.4, 125.7, 126.1, 127.7, 128.4, 132.7, 133.2, 141.4; MS m/z (rel intensity) 304 (M, 42), 155 (M – 149, base peak); HRMS calcd for $C_{18}H_{24}S_2$ 304.1319, found 304.1316. Anal. Calcd: C, 68.65; H, 6.91. Found: C, 68.68; H, 6.95.

1-Hydroxy-4-(2-naphthyl)-3-thiapentane (2h). In a manner similar to that described in the general procedure, the reaction of 1-(2-naphthyl)ethanol (516 mg, 3 mmol), ZnI_2 (479 mg, 1.5 mmol), and 2-hydroxyethanethiol (0.25 mL, 3.6 mmol) in CH_2Cl_2 (6 mL) gave crude **2h**, which was chromatographed on silica gel (EtOAc/hex = 3/7) to afford pure **2h** as an oil (576 mg, 83%): IR (neat) 3382, 3052, 2964, 1172, 948, 893, 858, 684, 615 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.64 (d, J = 8 Hz, 3 H), 2.09 (t, J = 6 Hz, 1 H), 2.50 (t, J = 6 Hz, 2 H), 3.51–3.61 (m, 2 H), 4.15 (q, J = 8 Hz, 1 H), 7.43–7.84 (m, 7 H); ^{13}C NMR δ 22.6, 34.3, 44.0, 60.4, 125.1, 125.8, 126.2, 127.6, 128.7, 132.7, 133.1, 140.9; MS m/z (rel intensity) 232 (M, 12), 155 (M – 77, base peak); HRMS calcd for $C_{14}H_{16}OS$ 232.0922, found 232.0926. Anal. Calcd: C, 72.37; H, 6.94; Found: C, 72.10; H, 7.40.

1-Amino-4-(2-naphthyl)-3-thiapentane (2j). In a manner similar to that described in the general procedure, the reaction of 1-(2-naphthyl)ethanol (1.03 g, 6 mmol), ZnI_2 (1.92 g, 6 mmol), and 2-aminoethanethiol hydrochloride (830 mg, 7.2 mmol) in CH_2Cl_2 (12 mL) yielded crude **2j**, which was chromatographed on silica gel (EtOAc) to afford pure **2j** as an oil (750 mg, 54%): IR (neat) 3361, 3050, 2966, 1065, 894, 858, 750, 684, 615 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.63 (br d, J = 8 Hz, 5 H), 2.35–2.50 (m, 2 H), 2.71 (t, J = 6 Hz, 2 H), 4.10 (q, J = 8 Hz, 1 H), 7.42–7.83 (m, 7 H); ^{13}C NMR δ 22.6, 35.2, 40.9, 44.1, 125.2, 125.8, 126.2, 127.7, 128.6, 132.7, 133.1, 141.2; MS m/z (rel intensity) 231 (M, 32), 202 (M – 29, 37), 155 (M – 76, base peak); HRMS calcd for $C_{14}H_{17}NS$ 231.1081, found 231.1080.

1-Amino-4,4-diphenyl-3-thiapentane (2k). In a manner similar to that described in the general procedure, the reaction of 1,1-diphenylethanol (2.97 g, 15 mmol), ZnI_2 (4.79 g, 15 mmol), and 2-aminoethanethiol hydrochloride (2.05 g, 18 mmol) in CH_2Cl_2 (30 mL) yielded crude **2k**, which was chromatographed on silica gel (EtOAc) to afford pure **2k** as an oil (2.45 g, 64%): IR (neat) 3395, 3055, 1594, 1372, 1061, 762, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.24 (s, 2 H), 2.06 (s, 3 H), 2.38 (t, J = 12.7 Hz, 2 H), 2.64 (t, J = 12.7 Hz, 2 H), 7.20–7.44 (m, 10 H); ^{13}C NMR δ 30.7, 34.6, 41.3, 56.1, 126.6, 127.9, 128.0, 146.2; MS m/z (rel intensity) 257 (M, 3), 181 (M – 76, base peak); HRMS calcd for $C_{16}H_{19}NS$ 257.3965, found 257.3967. Anal. Calcd: C, 74.03; H, 7.04; N, 5.76. Found: C, 73.80; H, 7.01; N, 5.63.

4,4-Diphenyl-3-thiabutane-1-thiol (11). In a manner similar to that described in the general procedure, the reaction of 1,1-diphenylethanol (920 g, 5 mmol), ZnI_2 (1.6 g, 5 mmol), and 1,2-ethanedithiol (0.84 mL, 10 mmol) in CH_2Cl_2 (10 mL) yielded **11** as an oil (672 mg, 52%); IR (neat) 2923, 2544, 1593, 1443, 1207, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.66 (t, J = 7.4 Hz, 1 H), 2.58–2.67 (m, 4 H), 5.19 (s, 1 H), 7.19–7.45 (m, 10 H); ^{13}C NMR δ 24.3, 36.2, 54.1, 127.3, 128.2, 128.6, 141.0; MS m/z (rel intensity) 260 (M, 3), 167 (M – 93, base peak); HRMS calcd for $C_{15}H_{16}S_2$ 260.0693, found 260.0693. Anal. Calcd: C, 69.18; H, 6.19. Found: C, 69.17; H, 6.02.

4-(4-Tolyl)-3-thiabutane-1-thiol (6c). In a manner similar to that described in the general procedure, the reaction of 1-(4-tolyl)methanol (610 mg, 5 mmol), ZnI_2 (1.6 g, 5 mmol), and 1,2-ethanedithiol (0.84 mL, 10 mmol) in CH_2Cl_2 (10 mL) yielded **6c** as an oil (672 mg, 68%): IR (neat) 2920, 2831, 2562, 1606, 1580, 1506, 1439, 1301, 1174, 1107, 1034, 833 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.65 (t, J = 9.0 Hz, 1 H), 2.32 (s, 3 H), 2.54–2.66 (m, 4 H), 3.68 (s, 2 H), 7.08–7.20 (m, 4 H); ^{13}C NMR δ 21.1, 24.4, 35.3, 35.9, 128.7, 129.3, 134.9, 136.0; MS m/z (rel intensity) 198 (M, 41), 105 (M – 93, base peak); HRMS calcd for $C_{10}H_{14}S_2$ 198.0537, found 198.0529. Anal. Calcd: C, 60.56; H, 7.11. Found: C, 60.92; H, 6.81.

4-(3-Methoxyphenyl)-3-thiabutane-1-thiol (6d). In a manner similar to that described in the general procedure, the reaction of 1-(3-methoxyphenyl)methanol (690 mg, 5 mmol), ZnI_2 (1.6 g, 5 mmol), and 1,2-ethanedithiol (0.84 mL, 10 mmol) in CH_2Cl_2 (10 mL) yielded **6d** as an oil (645 mg, 60%): IR (neat) 2923, 2832, 2560, 1661, 1594, 1259, 1152, 1044, 995, 876, 688 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.67 (t, J = 6.6 Hz, 1 H), 2.60–2.65 (m, 4 H), 3.57 (s, 2 H), 3.79 (s, 3 H), 6.76–7.25 (m, 4 H); ^{13}C NMR δ 24.4, 35.3, 36.2, 55.2, 112.7, 114.3, 121.1, 129.5, 139.6, 159.8; MS m/z (rel intensity) 214 (M, 66), 121 (M – 93, base peak); HRMS calcd for $C_{10}H_{14}OS_2$ 214.0486, found 214.0477.

4-(4-Methoxyphenyl)-3-thiabutane-1-thiol (6e). In a manner similar to that described in the general procedure, the reaction of 1-(4-methoxyphehyl)methanol (690 g, 5 mmol), ZnI_2 (1.6 g, 5 mmol), and 1,2-ethanedithiol (0.84 mL, 10 mmol) in CH_2Cl_2 (10 mL) yielded **6e** an an oil (730 mg, 68%): IR (neat) 2998, 2553,

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2070, 1607, 1509, 1174, 747 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.66 (t, J = 9 Hz, 1 H), 2.58–2.62 (m, 4 H), 3.66 (s, 2 H), 3.76 (s, 3 H), 6.82 (d, J = 11.4 Hz, 2 H), 7.20 (d, J = 11.4 Hz, 2 H); ^{13}C NMR δ 24.2, 35.0, 35.2, 55.0, 113.7, 129.5, 129.6, 158.4; MS m/z (rel intensity) 214 (M, 15), 121 (M – 93, base peak); HRMS calcd for $C_{10}H_{14}OS_2$ 214.0486, found 214.0493. Anal. Calcd: C, 56.04; H, 6.58. Found: C, 56.33; H, 6.38.

4-(2-Tolyl)-3-thiabutane-1-thiol (6f). In a manner similar to that described in the general procedure, the reaction of 1-(2-tolyl)methanol (610 mg, 5 mmol), ZnI_2 (1.6 g, 5 mmol), and 1,2-ethanedithiol (0.84 mL, 10 mmol) in CH_2Cl_2 (10 mL) yielded **6f** as an oil (647 mg, 65%): IR (neat) 2932, 2562, 1606, 1581, 1505, 1440, 1301, 1246, 1174, 1034, 831 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.66 (t, J = 8.0 Hz, 1 H), 2.39 (s, 3 H), 2.59–2.72 (m, 4 H), 3.73 (s, 2 H), 7.13–7.20 (m, 4 H); ^{13}C NMR δ 19.1, 24.6, 34.3, 35.7, 125.9, 127.5, 129.6, 130.7, 136.7; MS m/z (rel intensity) 198 (M, 61), 105 (M – 93, base peak); HRMS calcd for $C_{10}H_{14}S_2$ 198.0537, found 198,0530. Anal. Calcd: C, 60.56; H, 7.11. Found: C, 60.39; H, 7.10.

1-(3-Mercapto-1-thiapropyl)-2,2-dimethyl-1,2,3,4-tetrahydronaphthalene (9). In a manner similar to that described in the general procedure, the reaction of 2-hydroxy-3,3-dimethyltetrahydronaphthalene (880 mg, 5 mmol), ZnI_2 (1.6 g, 5 mmol), and 1,2-ethanedithiol (0.84 mL, 10 mmol) in CH_2Cl_2 (10 mL) yielded **9** an an oil (364 mg, 29%): IR (neat) 3014, 2536, 1680, 1600, 1448, 1381, 1268, 1102, 1014, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.95 (s, 3 H), 1.17 (s, 3 H), 1.39–1.50 (m, 1 H), 1.66 (t, J = 5.2 Hz, 1 H), 1.93–2.09 (m, 1 H), 2.58–3.49 (m, 6 H), 3.58 (s, 1 H), 7.04–7.23 (m, 4 H); ^{13}C NMR δ 24.9, 25.8, 26.9, 28.1, 31.6, 34.5, 37.3, 57.0, 125.5, 126.7, 129.1, 130.0, 135.3, 137.4; MS m/z (rel intensity) 252 (M, 4), 149 (M – 93, base peak). Anal. Calcd for $C_{14}H_{20}S_2$: C, 66.61; H, 7.99. Found: C, 66.39; H, 7.80.

6-(2-Naphthyl)-2,5-dithiaheptane (2f).[9] To a stirred mixture of DBU (0.18 mL, 1.2 mmol) and 4-(2-naphthyl)-3-thiapentane-1-thiol (298 mg, 1.2 mmol) in benzene (4 mL) was added MeI (0.075 mL, 1.2 mmol). The mixture was stirred at room temperature for 3 h. The precipitate was removed by filtration and the filtrate was washed with water and dried ($MgSO_4$). After evaporating the solvent in vacuo, the residue was chromatographed on silica gel (EtOAc/hex = 1/50) to give **2f** as an oil (250 mg, 80%): IR (neat) 3052, 2965, 1019, 948, 893, 857, 819, 749, 688, 615 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.64 (d, J = 8 Hz, 3 H), 1.91 (s, 3 H), 2.49–2.52 (m, 4 H), 4.11 (q, J = 8 Hz, 1 H), 7.35–7.84 (m, 7 H); ^{13}C NMR δ 12.4, 22.4, 30.7, 34.0, 44.5, 125.2, 125.8, 126.2, 127.7, 128.3, 128.8, 132.7, 133.1, 141.0; MS m/z (rel intensity) 262 (M, 51), 155 (M – 107, base peak); HRMS calcd for $C_{15}H_{18}S_2$ 262.0845, found 262.0849. Anal. Calcd: C, 71.00; H, 7.94. Found: C, 70.65; H, 7.99.

7-(2-Naphthyl)-2,6-dithiaoctane (2g). In a manner similar to that described above, the reaction of 5-(2-naphthyl)-4-thiahexane-1-thiol (382 mg, 1.46 mmol), DBU (0.22 mL, 1.46 mmol), and MeI (0.1 mL, 1.46 mmol) in benzene (5 mL) gave **2g** as an oil (365 mg, 91%): IR (neat) 3052, 2965, 1018, 948, 892, 857, 819, 749, 685, 614 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.64 (d, J = 8 Hz, 3 H), 1.71–1.91 (m, 2 H), 1.98 (s, 3 H), 2.32–2.54 (m, 4 H), 4.11 (q, J = 8 Hz, 1 H), 7.35–7.84 (m, 7 H); ^{13}C NMR δ 12.4, 22.5, 28.6, 30.1, 33.0, 44.4, 125.3, 125.7, 126.1, 127.6, 128.3, 128.5, 132.7, 133.1, 141.2; MS m/z (rel intensity) 276 (M, 32), 155 (M – 121, 48), 121 (M – 155, base peak); HRMS calcd for $C_{16}H_{20}S_2$ 276.1006, found 276.0997. Anal. Calcd: C, 69.51; H, 7.29. Found: C, 69.33; H, 7.50.

1-Hydroxy-5-(2-naphthyl)-4-thiahexane (2i). To a slurry of $LiAlH_4$ (152 mg, 4 mmol) in ether (10 mL) was added a solution of 1-(methoxycarbonyl)-4-(2-naphthyl)-3-thiapentane (822 mg, 3 mmol) in ether (12 mL). The mixture was refluxed for 8 h, quenched with aqueous NH_4Cl, and extracted with ether. The combined organic layers were dried ($MgSO_4$). The filtrate was evaporated in vacuo and the residue was chromatographed on silica gel (EtOAc/hex = 3/7) to give **2i** (650 mg, 88%): IR (neat) 3386, 3052, 2925, 1151, 918, 857, 750, 681 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.63–1.78 (m, 5 H), 2.32–2.48 (m, 3 H), 3.54 (q, J = 6 Hz, 2 H), 4.13 (q, J = 8 Hz, 1 H), 7.41–7.84 (m, 7 Hz); ^{13}C NMR δ 22.4, 27.9, 31.6, 44.3, 61.7, 125.2, 125.7, 126.1, 127.6, 128.5, 132.6, 133.1, 141.3; MS m/z (rel intensity) 246 (M, 37), 155 (M – 91, base peak); HRMS calcd for $C_{15}H_{18}OS$ 246.1077, found 246.1078. Anal. Calcd: C, 73.13; H, 7.36. Found: C, 72.42; H, 7.58.

General Procedure for the Synthesis of Benzylic Thioethers from the Reactions of Benzylic Bromides with Thiols. To a slurry of NaH (1.2 equiv) in THF was added dropwise the thiol (1.2 equiv) at 0 °C. After 15 min, benzylic bromide (1 equiv) was introduced. The mixture was stirred at room temperature for 20 h and then quenched with water, extracted with ether, and dried ($MgSO_4$). After evaporation of solvent, the residue was chromatographed on silica gel (EtOAc/hex = 1/50).

1-Amino-4-(1-naphthyl)-3-thiabutane (6g). In a manner similar to that described in the general procedure, the reaction of (1-naphthyl)methyl bromide (1.11 g, 5.0 mmol), NaH (180 mg, 7.5 mmol), and 2-aminoethanethiol hydrochloride (677 mg, 6.0 mmol) in THF (10 mL) yielded crude **6g**, which was chromatographed on silica gel (EtOAc) to afford pure **6g** as an oil (0.95 g, 88%): IR (neat) 3351, 2923, 1937, 1593, 1426, 1225, 1167, 778 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20 (s, 2 H), 2.55 (t, J = 6.4 Hz, 2 H), 2.87 (t, J = 6.4 Hz, 2 H), 4.14 (s, 2 H), 7.34–8.15 (m, 7 H); ^{13}C NMR δ 33.7, 36.1, 40.9, 123.9, 125.0, 125.8, 126.0, 127.0, 128.1, 128.7, 131.2, 133.6, 134.6, 134.0; MS m/z (rel intensity) 217 (M, 23), 141 (M – 76, base peak); HRMS calcd for $C_{13}H_{15}NS$ 217.0925, found 217.0918.

1-Hydroxy-4-(1-naphthyl)-3-thiabutane (6h). In a manner similar to that described in the general procedure, the reaction of (1-naphthyl)methyl bromide (1.11 g, 5.0 mmol), NaH (180 mg, 7.5 mmol), and 2-hydroxyethanethiol (0.42 mL, 6.0 mmol) in THF (10 mL) yielded crude **6h**, which was chromatographed on silica gel (EtOAc/hex = 3/7) to afford pure **6h** as an oil (0.99 g, 90%): IR (neat) 3393, 3044, 2917, 1937, 1684, 1593, 1225, 1060, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.25 (s, 1 H), 2.68 (t, J = 6 Hz, 2 H), 3.69 (t, J = 6 Hz, 2 H), 4.17 (s, 2 H), 7.16–8.14 (m, 7 H); ^{13}C NMR δ 33.6, 34.9, 60.3, 123.9, 125.1, 125.9, 126.2, 127.2, 128.3, 128.8, 131.1, 133.3, 134.1; MS m/z (rel intensity) 218 (M, 33), 141 (M – 77, base peak); HRMS calcd for $C_{13}H_{14}OS$ 218.0765, found 218.0760.

4-(1-Naphthyl)-3-thiabutane-1-thiol (6a). To a THF solution (20 mL) of 1-naphthylmethanethiol (1.74 g, 10 mmol) was added n-BuLi (6.25 mL, 10 mmol) at 0 °C. After the solution was stirred at 0 °C for 2 h, the reaction temperature was lowered to −78 °C and ethylene sulfide (0.6 mL, 10 mmol) was added dropwise. The mixture was stirred at −78 °C for 2 h, quenched with NH_4Cl, extracted with ether, and dried ($MgSO_4$). After evaporation of the solvent, the residue was chromatographed on silica gel (EtOAc/hex = 1/50) to give **6a** as an oil (0.5 g, 21%): IR (neat) 3042, 2920, 2560, 1935, 1683, 1593, 1506, 1395, 1269, 1243, 1167, 1048, 885, 791, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.64 (t, J = 7.7 Hz, 1 H), 2.59–2.73 (m, 4 H), 4.18 (s, 2 H), 7.34–8.14 (m, 7 H); ^{13}C NMR δ 24.5, 34.1, 35.9, 123.9, 125.1, 125.9, 126.2, 127.0, 128.3, 128.8, 133.3, 134.1; MS m/z (rel intensity) 234 (M, 37), 141 (M – 93, base peak); HRMS calcd for $C_{13}H_{14}S_2$ 234.0537, found 234.0542.

4-(2-Naphthyl)-3-thiabutane-1-thiol (6b). In a manner similar to that described above, the reaction of 1-naphthylmethanethiol (1.8 g, 10.3 mmol), n-BuLi (6.4 mL, 10.3 mmol), and ethylene sulfide (0.7 mL, 10.3 mmol) in THF (20 mL) gave **6b** as an oil (0.71 g, 29%): IR (neat) 3047, 2916, 2553, 1688, 1596, 1503, 1420, 1357, 1270, 1235, 1145, 957, 858, 818, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.64 (t, J = 7.7 Hz, 1 H), 2.62–2.68 (m, 4 H), 3.88 (s, 2 H), 7.44–7.83 (m, 7 H); ^{13}C NMR δ 24.4, 35.2, 36.4, 125.9, 126.3, 126.9, 127.2, 127.6, 127.7, 128.5, 132.6, 133.2, 135.3; MS m/z (rel intensity) 234 (M, 37), 141 (M – 93, base peak); HRMS calcd for $C_{13}H_{14}S_2$ 234.0537, found 234.0539.

General Procedure for the Nickel-Catalyzed Cross-Coupling Reactions of 2 or 6 with MeMgI. Under a N_2 atmosphere,

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to a benzene solution (10 mL) of thioether **2** or **6** (0.5 mmol) and $NiCl_2(PPh_3)_2$ (0.025 mmol) or $NiCl_2$(dppe) (0.025 mmol) was added MeMgI (4 equiv) in benzene (2 mL). The resulting mixture was stirred for 18 h and quenched with NH_4Cl. The organic layer was separated and the aqueous portion was extracted with ether. The combined organic layers were washed with NaOH (10%) and water, dried ($MgSO_4$), and filtered. After evaporation of the solvent, the residue was chromatographed on silica gel (hex) to give the product(s).

Reaction of 9 with MeMgI. In a manner similar to that described in the general procedure, a mixture of **9** (126 mg, 0.5 mmol), $NiCl_2$(dppe) (13 mg, 0.025 mmol), and MeMgI (1 M, 2 mL, 2 mmol) in benzene (10 mL) was refluxed for 18 h to afford **10** (67 mg, 84%): IR 3056, 2920, 1578, 1486, 1384, 1246, 1160, 1048, 953, 749, 718 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.83 (s, 6 H), 1.09–1.15 (m, 8 H), 1.45–1.56 (m, 2 H), 2.74–2.79 (m, 4 H), 3.11 (s, 2 H), 6.87–7.10 (m, 8 H); ^{13}C NMR δ 25.9, 30.7, 31.0, 31.1, 32.9, 53.6, 124.9, 125.4, 128.6, 130.9, 135.8, 141.4; MS *m/z* (rel intensity) 318 (M, 6), 159 (M - 159, base peak). Anal. Calcd for $C_{24}H_{30}$: C, 90.51; H, 9.49. Found: C, 90.65; H, 9.29.

Acknowledgment. This work was supported by a grant from the National Science Council of the Republic of China.

Registry No. 2a, 139277-79-5; **2b**, 139277-80-8; **2c**, 139277-81-9; **2d**, 139277-82-0; **2e**, 139277-83-1; **2f**, 139277-84-2; **2g**, 139277-85-3; **2h**, 139277-86-4; **2i**, 139277-87-5; **2j**, 139277-88-6; **2k**, 54225-34-2; **3a**, 827-54-3; **3b**, 826-74-4; **3c**, 530-48-3; **6a**, 139277-89-7; **6b**, 139277-90-0; **6c**, 139277-91-1; **6d**, 139277-92-2; **6e**, 139277-93-3; **6f**, 139277-94-4; **6g**, 106670-25-1; **6h**, 68320-91-2; **6i**, 65824-33-1; **7a**, 1127-76-0; **7b**, 939-27-5; **7c**, 622-96-8; **7d**, 10568-38-4; **7e**, 1515-95-3; **8a**, 15374-45-5; **8c**, 538-39-6; **8d**, 36707-27-4; **8f**, 952-80-7; **9**, 139277-95-5; **10**, 139277-97-7; **11**, 26926-48-7; **12**, 632-50-8; $HS(CH_2)_2SH$, 540-63-6; $HS(CH_2)_3SH$, 109-80-8; $HS(CH_2)_4SH$, 1191-08-8; $HS(CH_2)_6HS$, 1191-43-1; $HS(CH_2)_2OH$, 60-24-2; $HS(CH_2)_2NH_2$·HCl, 156-57-0; (2-Np)$CH(CH_3)OH$, 7228-47-9; (1-Np)$CH(CH_3)OH$, 1517-72-2; Ph_2CHOH, 599-67-7; 4-$MeC_6H_4CH_2OH$, 589-18-4; 3-$MeOC_6H_4CH_2OH$, 6971-51-3; 4-$MeOC_6H_4CH_2OH$, 105-13-5; 1-$NpCH_2Br$, 3163-27-7; 1-$NpCH_2SH$, 5254-86-4; $\overline{CH_2CH_2S}$, 420-12-2; MeMgI, 917-64-6; $NiCl_2(PPh_3)_2$, 14264-16-5; $NiCl_2$(dppe), 23443-96-1; 1-hydroxy-2,2-dimethyltetrahydronaphthalene, 103041-51-6; 1-(methoxycarbonyl)-4-(2-naphthyl)-3-thiapentane, 139277-96-6.

Supplementary Material Available: ^1H NMR data of **3a,b**, **7a–e**, **8c,d,f**, and **12** and ^1H NMR spectra of **2j** and **6a,b,g,h** (6 pages). Ordering information is given on any current masthead page.

Oxidation of Natural Targets by Dioxiranes. Oxyfunctionalization of Steroids†

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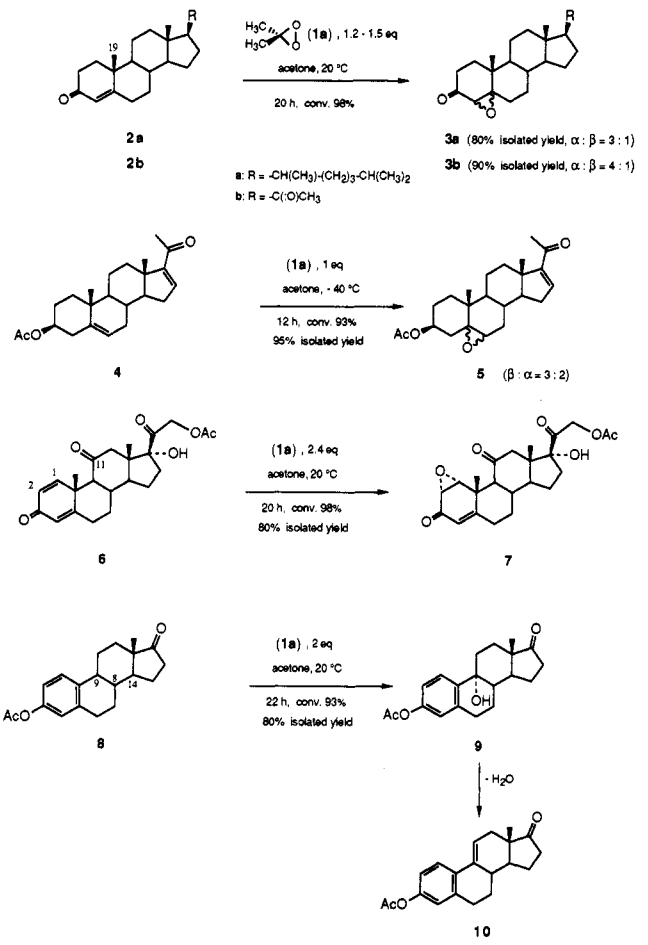
Received November 21, 1991

Dioxiranes constitute a new class of versatile oxidants, powerful in their action, yet selective and capable of performing under extremely mild conditions, which allows one to carry out an impressive variety of synthetically useful transformations.[1] Since these reagents (either in situ[2] or in their isolated form[3,4]) permit isolation of even labile oxiranes[5] and dioxaspiroalkanes,[6] epoxidation is the most frequent application of dioxirane oxidation. Nonetheless, the feat of easy O atom insertion into "unactivated" alkane C–H bonds[7,8] and the selective conversion of alcohols into carbonyls[9] count among the highlights of dioxirane chemistry. At present, while functional group selectivities attainable by using these reagents are being determined,[1,7-9] the oxyfunctionalization of nonnatural[8,10]

Scheme I



† Dedicated to professor John O. Edwards (Brown University) in the year of his 70th birthday.

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