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.

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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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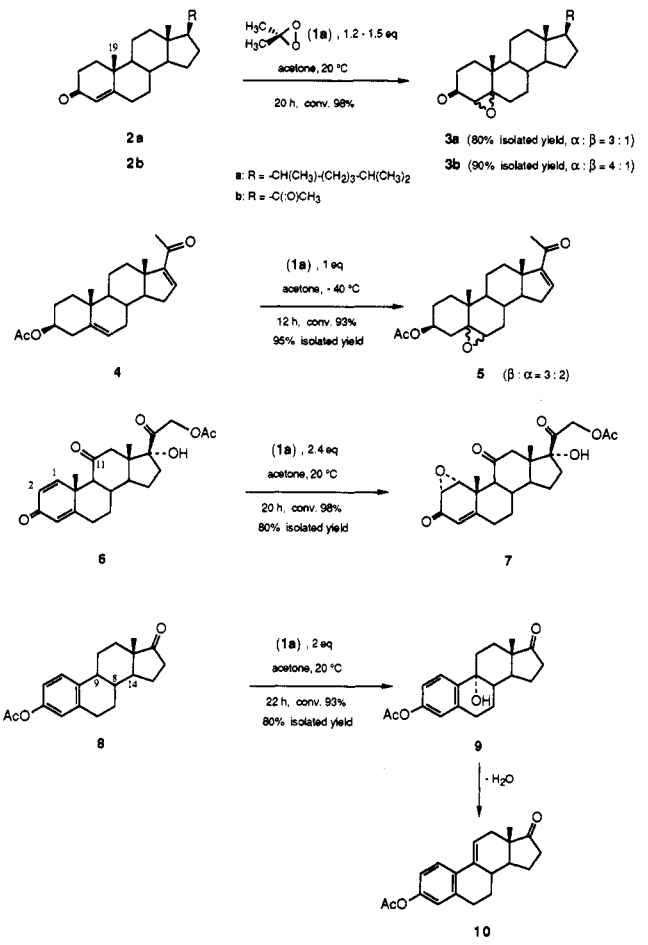
Dioxiranes constitute a new class of versatile oxidants, powerful in their action, yet selective and capable of performing under extremely mild conditions, which allows one to carry out an impressive variety of synthetically useful transformations.[1] Since these reagents (either in situ[2] or in their 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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(1) For reviews, see: (a) Curci, R. In *Advances in Oxygenated Processes*; Baumstark, A. L., Ed.; JAI: Greenwich, CT; Vol. 2, Chapter 1, 1990. (b) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. (c) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187.

(2) (a) Edwards, J. O.; Pater, R. H.; Curci, R.; Di Furia, F. *Photochem. Photobiol.* **1979**, *30*, 63. (b) Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem.* **1980**, *45*, 4758.

(3) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847.

(4) (a) Cassidei, L.; Fiorentino, M.; Mello, R.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1987**, *52*, 699. (b) Mello, R.; Fiorentino, M.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1988**, *53*, 3890.

(5) For instance, see: (a) Mello, R.; Ciminale, F.; Fiorentino, M.; Fusco, C.; Prencipe, T.; Curci, R. *Tetrahedron Lett.* **1990**, *31*, 6097. (b) Adam, W.; Hadjiarapoglou, L.; Klicic, J. *Tetrahedron Lett.* **1990**, *31*, 651. (c) Adam, W.; Hadjiarapoglou, L.; Jäger, V.; Seidel, B. *Tetrahedron Lett.* **1989**, *30*, 4223. (d) Troisi, L.; Cassidei, L.; Lopez, L.; Mello, R.; Curci, R. *Tetrahedron Lett.* **1989**, *30*, 257. (e) Chow, K.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 4211. (f) Baertschi, S. W.; Raney, K. D.; Stone, M. P.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7929.

(6) Crandall, J. K.; Rambo, E. *J. Org. Chem.* **1990**, *55*, 5929 and previous articles of the series.

(7) (a) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, *111*, 6749. (b) Murray, R. W.; Jeyaraman, R.; Mohan, L. *J. Am. Chem. Soc.* **1986**, *108*, 2470.

(8) Mello, R.; Cassidei, L.; Fiorentino, M.; Fusco, C.; Curci, R. *Tetrahedron Lett.* **1990**, *31*, 3067.

(9) Mello, R.; Cassidei, L., Fiorentino, M.; Fusco, C.; Hümmer, W.; Jäger, V.; Curci, R. *J. Am. Chem. Soc.* **1991**, *113*, 2205.

0022-3263/92/1957-2182$03.00/0

as well as natural[5e-f,11,12] target molecules[13] is beginning to be explored.

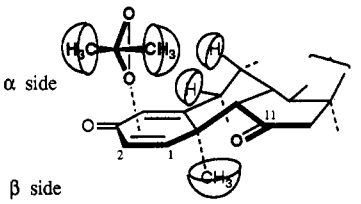
In particular, after our early example regarding β-hydroxycholesterol epoxidation by dimethydioxirane (**1a**) in situ,[11] Marples and co-workers have recently produced a study of steroidal alkene epoxidations using a number of dioxiranes.[12] This prompts us to report on our own preliminary findings concerning the dioxirane oxyfunctionalization of five different steroidal substrates, i.e., 4-cholesten-3-one (**2a**), progesterone (**2b**), 3β-hydroxy-5,16-pregnadien-20-one acetate (**4**), prednisone acetate (**6**), and estrone acetate (**8**).

The general experimental procedure was quite straightforward since it merely involved the addition of an appropriate aliquot of a ca. 0.1 M dimethyldioxirane (**1a**) solution[3,4a,14] in acetone to a stirred solution of the steroidal substrate in the same solvent (or acetone–CH_2Cl_2). Representative reaction conditions and results are summarized in Scheme I.

Akin to epoxidation by peroxy acids and oxaziridines,[15] two limiting transition-state (ts) structures can be envisaged[1a,16] for dioxirane epoxidations, i.e., spiro vs planar. Although the two arrangements might lie fairly close in energy, it was suggested[16a] that certain observations (e.g., the pronounced cis/trans selectivity given by dioxirane epoxidations) are better accommodated on the grounds of a spiro ts geometry.[16] Selectivities in dioxirane oxidation of steroids have also been rationalized on the grounds of a spiro arrangement in the ts.[12]

As for the cases presented herein, in the epoxidation of the two steroidal unsaturated carbonyls **2a** and **2b** (Scheme I, entries 1 and 2), the 19β-methyl is in no position to hinder strongly an exo spiro attack from the β face, since the thermodynamically more stable β-epoxide[17] is also formed along with the α-isomer.[18,19] Using a methyl(trifluoromethyl)dioxirane (**1b**) solution in its parent ketone (i.e., 1,1,1-trifluoropropan-2-one, hereafter TFP),[4b,7a,9] the epoxidation of **2b** in CH_2Cl_2 occurs much faster (e.g., 50% conversion during 1.5 h at −20 °C); however, the ratio of stereomeric epoxides produced does not change (i.e., α:β = ca. 4:1). Likewise, the epoxidation at the unsaturated $\Delta^{5,6}$ moiety of **4** yields a mixture of β- and α-epoxides.[20] Worthy of note, in this case complete regioselectivity could be achieved by the careful choice of reaction conditions, since just the 5,6-double bond was epoxidized while leaving intact the 16,17-unsaturated moiety (which is electron-poor due to the conjugated carbonyl). This is hardly surprising in view of the marked electrophilic character of dioxiranes.[1]

The transformation undergoing at the cyclodienone A-ring in prednisone acetate (**6**) is quite interesting, since here just the 1α,2α-epoxide is formed. Steric effects might be responsible for this unexpectedly high stereo- and regioselectivity. In fact, effective shielding by the flagpole 10β-CH_3 might force the dioxirane to attack from the α side. Also, in a spiro ts geometry, the absence of flanking α- or β-C–H interactions (and possibly a favorable dipole interaction with the C-11 carbonyl) might favor epoxidation at the $\Delta^{1,2}$ unsaturated moiety, for instance as in I.



(*I*)

Be the actual rationale beyond the unusual stereochemical course of the epoxidation of **6** as it may, its value in synthesis is unquestionable. In fact, the steroidal 1α,2α-epoxyenone **7** provides access to the important *A*-norcorticosteroids, a class of compounds possessing specific biochemical activity.[21] To our knowledge, no *direct* oxidation method allowing the transformation **6** → **7** has been reported yet. In an analogous transformation, the regioselective synthesis of 1α,2α-epoxy-17β-acetoxy-4-androsten-3-one (a key intermediate for obtaining *A*-nortestosterone in the Pfister synthesis)[22] involves three distinct steps starting with 17β-hydroxy-1,4-androstadien-3-one.

Finally, equally useful in synthesis appears to be the hydroxylation of estrone acetate (**8**) by dimethyldioxirane, allowing the oxyfunctionalization to occur selectively at C-9 (final entry, Scheme I). The 9α-hydroxyestrone acetate (**9**) easily affords the $\Delta^{9,11}$ unsaturated derivative **10**,[23] a key intermediate in the synthesis of corticosteroids and androsteroids.[21] Similar results were obtained using the more reactive methyl(trifluoromethyl)dioxirane (**1b**);[7a,8,9] the transformation is much faster, however. For instance, ^1H NMR analysis of the product resulting from the reaction of **8** in CD_2Cl_2 with 1 equiv of dioxirane **1b** in TFP[7a] at −20 °C revealed that ca. 50% conversion of the substrate **8** into **9** is attained within 2 h only; then, as the solution is allowed to warm to 20 °C, dehydration of **9** ensues at a much slower pace, yielding **10** during ca. 12 h.

Thus, the remarkable selectivity recorded for dioxirane O atom insertion into tertiary vs secondary C–H bonds of cyclic and polycyclic hydrocarbons[7a] also applies to a more complex framework such as in the steroidal substrate **8**. Normally, such site-selective oxyfunctionalizations require special methods. For instance, Grieco et al. devised synthetic Mn(III) porphyrins attached to the steroidal substrate in order to achieve selective hydroxylation at C-9 and/or C-12.[24] Therefore, the *exclusive* oxyfunctionali-

(10) For instance, see: (a) the polyoxyfunctionalization of centropolyindanes: Kuck, D.; Schuster, A.; Fiorentino, M.; Fusco, C.; Curci, R. To be published. (b) The oxyfunctionalization of: Binor-S: Pramod, K.; Eaton, P. E.; Gilardi, R.; Flippen-Anderson, J. L. *J. Org. Chem.* **1990**, *55*, 6105.

(11) Cicala, G.; Curci, R.; Fiorentino, M.; Laricchiuta, O. *J. Org. Chem.* **1982**, *47*, 2670.

(12) Marples, B. A.; Muxworthy, J. P.; Baggaley, K. H. *Tetrahedron Lett.* **1991**, *32*, 533.

(13) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1320.

(14) (a) Adam, W.; Chan, Y.-Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800. (b) Eaton, P. E.; Wicks, G. E. *J. Org. Chem.* **1988**, *53*, 5353.

(15) For instance, see: (a) Bach, R. D.; Owensby, A. L.; Gonzales, C.; Schlegel, H. B. *J. Am. Chem. Soc.* **1991**, *113*, 2338. (b) Davis, F. A. In *Advances in Oxygenated Processes*; Baumstark, A. L., Ed.; JAI: Greenwich, CT; Vol. 2, Chapter 2, 1990 and references cited therein.

(16) (a) Baumstark, A. I.; Vasquez, P. C. *J. Org. Chem.* **1988**, *53*, 3437. (b) Bach, R. D.; Owensby, A. L.; Andrés, J. L.; Schlegel, H. B. *J. Am. Chem. Soc.* **1991**, *113*, 7031.

(17) Plattner, Pl. A.; Heusser, H.; Kulkarni, A. B. *Helv. Chim. Acta* **1948**, *31*, 1822.

(18) (a) Nickon, A.; Mendelson, W. L. *J. Am. Chem. Soc.* **1965**, *87*, 3921. (b) Mihailovic, M. Lj.; Forsek, J.; Lorenc, Lj.; Maksimovic, Z.; Fuhrer, H.; Kalvoda, J. *Helv. Chim. Acta* **1969**, *52*, 459. (c) Holland, H. L.; Riemland, E.; Daum, U. *Canad. J. Chem.* **1982**, *60*, 1919.

(19) Ringold, H. J.; Batres, E.; Mancera, O.; Rosenkranz, G. *J. Org. Chem.* **1956**, *21*, 1432.

(20) Malunowicz, I.; Mironowicz, A. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1968**, *16*, 579.

(21) For instance, see: *Specialist Periodical Reports: Terpenoid and Steroids*; Overton, K. H., Ed.; Chem. Soc.: London, 1973; Vol. 3, p 426.

(22) Pfister, J.; Lehmann, C.; Wehrli, H. *Helv. Chim. Acta* **1968**, *51*, 1505.

(23) Tsuda, K.; Ohki, E.; Nozoe, S. *J. Org. Chem.* **1963**, *28*, 786.

(24) Stuk, T. L.; Grieco, P. A.; March, M. M. *J. Org. Chem.* **1991**, *56*, 2957.

zation at benzhydrylic C-9 (with none occurring at tertiary C-8 or C-14) is somewhat puzzling, and especially so because with dioxiranes insertion into $(Ph)R_2C-H$ vs R_3C-H is usually of only modest advantage.[7,25] Since one might envisage subtle steric and/or stereoelectronic effects coming into play in the dioxirane oxyfunctionalization of steroids, as well as of nonnatural target molecules,[8,10,26] further studies directed to unravel in detail the features of O atom transfer are warranted. These seem worthwhile, since it is becoming increasingly clear that dioxirane oxidations can display efficiency and selectivities that are biomimetic.[1,7a,27]

Experimental Section

Melting points and boiling points were not corrected. The NMR spectra of starting materials and products were run on a Varian Gemini XL200 instrument. The MS spectra (EI, 70 eV) were obtained using a Hewelett-Packard Model 5970 mass-selective detector connected to a Model 5890 gas chromatograph. Other equipment and methods employed have been described previously.[7a]

Materials. Commercial (Fluka) 4-cholesten-3-one (**2a**) and 4-pregnene-3,20-dione (**2b**) were purified by standard methods; 3β-acetoxy-5,16-pregnadien-20-one (**4**) [mp 172–174 °C] was synthesized by a literature[28] procedure; 21-acetoxy-17α-hydroxy-1,4-pregnadiene-3,11,20-trione (**6**) [mp 219–220 °C] and 3-acetoxy-1,3,5(10)-estratrien-17-one (**8**) [mp 122–124 °C][29] were obtained upon treatment with Ac_2O/Py of commercial (Fluka) 17α,21-dihydroxy-1,4-pregnadiene-3,11,20-trione or 3-hydroxy-1,3,5(10)-estratrien-17-one, respectively. All starting materials gave satisfactory ^1H and/or ^{13}C NMR spectra. Solutions of dimethyldioxirane (**1a**) in acetone and of methyl(trifluoromethyl)dioxirane (**1b**) in TFP were obtained by following procedures and precautions which have been described in detail.[3,4,7a]

Dioxirane Oxyfunctionalization of Steroids 2–8. An aliquot (usually from 4 to 8 mL) of standardized[3,4,14] cold solution of dimethyldioxirane (**1a**) (ca. 0.1 M in acetone) or of methyl(trifluoromethyl)dioxirane (**1b**) (ca. 0.8 M in TFP) was quickly added to a stirred solution of the steroidal substrate (100–120 mg) in solvent acetone or CH_2Cl_2 (4–6 mL) kept in a thermostat at the given temperature (20 or −40 °C, cf. Scheme I). After the reaction was carried out to a suitable conversion (GC or TLC monitoring), eventually by the addition of further dioxirane aliquots, products isolation was achieved by removal of acetone solvent in vacuo, followed by column chromatography (silica gel, *n*-hexane/AcOEt or *n*-hexane/Et_2O).

4,5-Epoxycholestan-3-one (3a) was obtained (yield 80%) as a mixture of 4β,5β-epoxide and 4α,5α-epoxide (ratio α:β = ca. 3:1). The stereomeric epoxides can be separated by column chromatography (silica gel, *n*-hexane/AcOEt (8:2):α-Epoxide, mp 123–125 °C [lit.[18a] mp 123–124 °C], β-Epoxide, mp 116–120 °C [lit.[18a] mp 118–119 °C]; ^1H NMR (200 MHz, $CDCl_3$) (α-epoxide)[18b] δ 0.65 (s, 3 H, C^{18}-*H*), 0.82 (d, *J* = 7 Hz, 6 H, C^{26}-*H* and C^{27}-*H*), 0.88 (d, *J* = 7 Hz, 3 H, C^{21}-*H*), 1.05 (s, 3 H, C^{19}-*H*), 3.00 (s, 1 H, C^4-*H*); (β-epoxide)[18b] δ 0.75–0.90 (br, 12 H, C^{18}-*H*, C^{21}-*H*, C^{26}-*H*, and C^{27}-*H*), 1.20 (s, 3 H, C^{19}-*H*), 2.95 (s, 1 H, C^4-*H*); $\{^1H\}^{13}C$ NMR (50 MHz, $CDCl_3$) (α-epoxide) δ 12.12, 16.70, 18.82, 21.61, 22.74, 22.99, 24.02, 24.41, 28.21, 28.36, 29.17, 29.30, 29.98, 33.37, 35.68, 36.00, 36.35, 36.94, 39.73, 39.95, 42.76, 50.95, 55.91, 56.50, 63.24 (C^4), 70.61 (C^5), 207.93 (C^3); β-epoxide gave values in agreement with literature data.[18c]

4,5-Epoxypregnane-3,20-dione (3b) was obtained (yield 90%) as a mixture of 4β,5β and 4α,5α stereomeric epoxides (ratio α:β = ca. 4:1): mp 121–124 °C [lit.[19] mp 122–124 °C]; ^1H NMR[18c] (200 MHz, $CDCl_3$) δ 0.60 (s, 0.6 H, C^{18}-*H*, β-epoxide), 0.61 (s, 2.4 H, C^{18}-*H*, α-epoxide), 1.02 (s, 2.4 H, C^{19}-*H*, α-epoxide), 1.12 (s, 0.6 H, C^{19}-*H*, β-epoxide), 2.08 (s, 0.6 H, C^{21}-*H*, β-epoxide), 2.09 (s, 2.4 H, C^{21}-*H*, α-epoxide), 2.95 (s, 0.2 H, C^4-*H*, β-epoxide), 3.02 (s, 0.8 H, C^4-*H*, α-epoxide).

3β-Acetoxy-5,6-epoxy-16-pregnen-20-one (5) was obtained (yield 95%) as a mixture of 5β,6β and 5α,6α epoxides[20] (ratio β:α = ca. 3:2): mp 155–158 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 0.81 (s, 1.2 H, C^{18}-*H*, α-epoxide), 0.83 (s, 1.8 H, C^{18}-*H*, β-epoxide), 1.00 (s, 1.8 H, C^{19}-*H*, β-epoxide), 1.09 (s, 1.2 H, C^{19}-*H*, α-epoxide), 1.98 (s, 1.2 H, C^{21}-*H*, α-epoxide), 2.00 (s, 1.8 H, C^{21}-*H*, β-epoxide), 2.20 (s, 3 H, CH_3CO), 2.89 (d, *J* = 4.4 Hz, 0.4 H, C^6-*H*, α-epoxide), 3.09 (d, *J* = 2.4 Hz, 0.6 H, C^6-*H*, β-epoxide), 4.66 (m, 0.6 H, C^3-*H*, β-epoxide), 4.91 (m, 0.4 H, C^3-*H*, α-epoxide), 6.62 (m, 1 H, C^{16}-*H*); $\{^1H\}^{13}C$ NMR (50 MHz, $CDCl_3$) δ 62.70, 63.23, 63.30, 65.35, 71.25, 144.32 and 144.37 (C^{16}), 155.38 and 155.49 (C^{17}), 170.49 and 170.83 (CH_3COO), 197.10 (C^{20}).

21-Acetoxy-1α,2α-epoxy-17α-hydroxy-4-pregnene-3,11,20-trione (7): yield 80%. After recrystallization from petroleum ether–acetone: mp 239–241 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 0.66 (s, 3 H, C^{18}-*H*), 1.44 (s, 3 H, C^{19}-*H*), 2.15 (s, 3 H, CH_3CO), 3.37 (dd, *J* = 4.0 and 2.0 Hz, 1 H, C^2-*H*), 4.29 (d, *J* = 4 Hz, 1 H, C^1-*H*), 4.66 (d, *J* = 18 Hz, 1 H, C^{21}-H_a), 5.08 (d, *J* = 18 Hz, 1 H, C^{21}-H_b), 5.68 (t, *J* = 2 Hz, 1 H, C^4-*H*); $\{^1H\}^{13}C$ NMR (50 MHz, $CDCl_3$) δ 15.33, 18.49, 20.28, 22.98, 32.29, 34.95, 35.87, 40.06, 49.38, 51.11, 55.02, 58.06, 60.62, 67.48 (C^{21}), 88.85 (C^{17}), 120.83 (C^4), 164.37 (C^5), 170.87 (C^{22}), 194.30 (C^3), 204.80 and 209.21 (C^{11}=O, and C^{20}=O). Anal. Calcd for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78. Found: C, 66.31; H, 6.81.

3-Acetoxy-9α-hydroxy-1,3,5(10)-estratrien-17-one (9) can be isolated (yield 80%) from reaction mixtures by careful column chromatography at 8–10 °C using *nonactivated* silica gel (Merck, 70–230 mesh; eluent *n*-hexane–Et_2O). After recrystallization from petroleum ether–acetone: mp 162–164 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (s, 3 H, C^{18}-*H*), 1.45–2.55 (complex series of m, 12 H), 2.26 (s, CH_3CO), 2.88 (br, 2 H, C^6-*H*), 6.80–6.92 (m, 2 H, C^2-*H* and C^4-*H*), 7.50 (d, *J* = 8 Hz, 1 H, C^1-*H*); $\{^1H\}^{13}C$ NMR (50 MHz, $CDCl_3$) δ 13.09, 20.13, 21.32, 21.35, 21.62, 27.81, 29.60, 32.36, 36.16, 41.35 (C^8), 43.30 (C^{14}), 47.92 (C^{13}), 70.32 (C^9), 120.02 (C^2), 122.77 (C^4), 127.05 (C^1), 138.96–139.69 (C^5 and C^{10}), 150.49 (C^3), 170.34 (CH_3CO), 221.47 (C^{17}=O); MS (70 eV) *m/z* 310 ($M^+ - 18$). Upon easy dehydration over silica gel or with $POCl_3$ in pyridine, **9** yields 3-acetoxy-1,3,5(10),9(11)-estratetraen-17-one (**10**): mp 125–126 °C;[23] the latter gave satisfactory ^1H NMR and IR spectra.

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(25) Kuck, D.; Schuster, A. *Z. Naturforsch. A.*, in press.
(26) Maynard, G. D.; Paquette, L. A. *J. Org. Chem.* **1991**, *56*, 5480.
(27) Altamura, A.; Fusco, C.; D'Accolti, L.; Prencipe, T.; Curci, R. *Tetrahedron Lett.* **1991**, *32*, 5445.
(28) Bakker, C. G.; Vrijhof, P. *Tetrahedron Lett.* **1978**, 4699.
(29) Paquet, A.; Layne, D. S. *Can. J. Chem.* **1973**, *51*, 3855.

Lithiation of 3-Aminobenzo[*b*]thiophene and 3-Aminothiophene Derivatives. Application to the Synthesis of Benzo[*b*]thienoindole and Thienoindole Derivatives

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Directed metalation of heterocycles offers attractive and highly advantageous solutions to preparative problems not readily achieved by classical chemistry.[1]

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