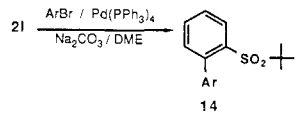
Scheme VIII



a: Ph 78%
b: p-$NO_2C_6H_4$ 52%
c: 3-pyridyl 56%

That the *tert*-butyl sulfone may act as a latent directed metalation group for the provision of meta-substituted aromatics is indicated by hydrogenolysis (Raney Ni/EtOH/reflux/15 h) of **6a** into the corresponding desulfonated product **9** (Scheme V).

Access to 2,6-disubstituted phenyl *tert*-butyl sulfones was accomplished by sequential metalation–electrophile quench procedures (Scheme VI). Thus treatment of **1** under the conditions shown involving the same or two different aromatic aldehyde electrophiles provided 2,6-dicarbinol products **10a** and **10b** as mixtures of two diasteriomers in high yields.[12] Under similar conditions, but using a 2-(methylamino)pyridine formyl transfer reagent, a low yield of the 2,6-diformylated phenyl sulfone **11** was obtained together with a greater amount of monoformylated product **2d**. Since the preparation of 2,6-dimethylphenyl *tert*-butyl sulfone **13** (Scheme VII) under these conditions is precluded by proton exchange in the monomethylated intermediate, an alternate transmetalation procedure was tested in order to obtain this compound. LiTMP metalation–stannylation of **2j** yielded **12**, which upon treatment with 2 equiv of *n*-BuLi for short reaction times followed by methylation led to a good yield of the expected product **13**.

The ready availability of the boronic acid **21** provided opportunity to test the Suzuki transition metal catalyzed cross coupling procedure,[13] whose value for the preparation of unsymmetrical biaryls and polyaryls has been recently demonstrated.[14] Clean cross coupling reactions were realized with selected aryl bromides to give biphenyls **14a–c** (Scheme VIII).

The above results demonstrate that the *tert*-butyl sulfone is a powerful directed metalation group which should prove to be of general value for the regioselective construction of polysubstituted aromatics. Its use in conjunction with other directing groups opens new and diverse methodological possibilities. Further structure–reactivity relationships vis-à-vis other directed metalation groups and applications in synthesis are currently under investigation.[15,16]

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(12) **10a**: 69:31, **10b**: 64:36 ratios, the less polar compound by TLC being indicated first. Their relative configurations have not been established.

(13) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513. For recent work, which considerably advances this methodology, see: Uenishi, J.-i.; Beau, J.-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756. Hoshino, Y.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3008.

(14) Sharp, M. J.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 5997. Sharp, M. J.; Cheng, W.; Snieckus, V. *Ibid.* **1987**, *28*, 5093. Cheng, W.; Snieckus, V. *Ibid.* **1987**, *28*, 5097.

(15) Satisfactory analytical data, MS, and ^1H NMR spectra were obtained for all new compounds.

(16) **Note Added in Proof**: Parallel studies have shown that aryl *tert*-butyl sulfoxides are similarly powerful ortho-metalation directors: Iihama, T.; Quesnelle, C.; Perrier, H.; Snieckus, V., manuscript in preparation.

Synthesis of Oogoniol

Summary: Oogoniol [(24*R*)-3β,11α,15β,29-tetrahydroxystigmast-5-en-7-one], a female-activating hormone of *Achlya*, has been synthesized from 4-androstene-3,11,17-trione. A novel step involved 1,4-addition of the magnesium cyanocuprate derivative of (*S*)-3-(1-methylethyl)-5-[(*tert*-butyldimethylsilyl)oxy]pentyl bromide to 3β-hydroxy-15β,16β-epoxy-11-oxo-(17(20)*E*)-pregna-5,17-(20)-diene 3-*tert*-butyldimethylsilyl ether. Selective hydrogenation of the resulting Δ^{16} double bond gave only the stigmastene product with the correct stereochemistry at C_{15}, C_{17}, and C_{20}.

Sir: We reported some time ago the synthesis of dehydrooogoniol **15**, a female-activating hormone of the aquatic fungus *Achlya*.[1] We now describe the synthesis of a related steroid, oogoniol (**14**) [(24*R*)-3β,11α,15β,29-tetrahydroxystigmast-5-en-7-one] also isolated from *Achlya heterosexualis* but possessing lower biological activity than **15**.[2] The starting material was commercially available 4-androstene-3,11,17-trione (**1**) (adrenosterone). Construction of the side chain involved the novel reaction of the magnesium cyanocuprate **10** of (*S*)-3-(1-methylethyl)-5-[(*tert*-butyldimethylsilyl)oxy]pentyl bromide with the steroidal intermediate 3β-hydroxy-15β,16β-epoxy-11-oxo-(17(20)*E*)-pregna-5,17(20)-diene 3-*tert*-butyldimethylsilyl ether (**9**).[3,4] Although the synthesis required many steps, these were all high yielding so that the overall yield was 7%.

Adrenosterone (**1**) was first converted to the dienol acetate **2**, which was reduced with $Ca(BH_4)_2$ in absolute ethanol at −15 °C to 3β,11β,17β-trihydroxy-5-androstene

(1) McMorris, T. C.; Le, P. H.; Preus, M. W.; Schow, S. R.; Weihe, G. R. *J. Org. Chem.* **1983**, *48*, 3370.

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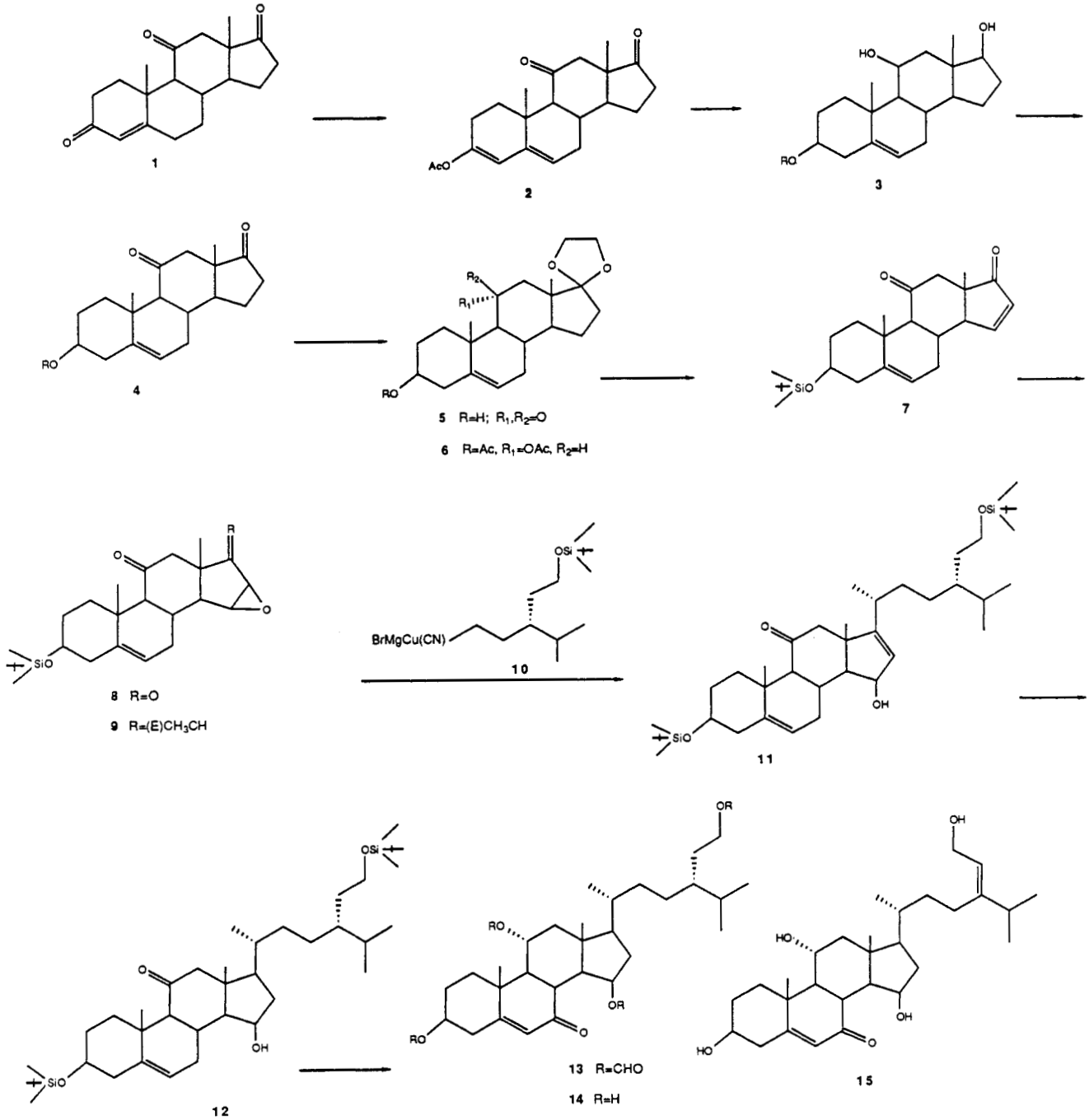
Scheme I



(3) (R = H, 84%) (Scheme I). Reduction of **2** with $NaBH_4$ was not satisfactory since sime of the Δ^4 isomer was also formed. To the triol **3** dissolved in tetrahydrofuran (THF) was added 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) and a solution of *tert*-butyldimethylsilyl chloride (TBDMSCl) in THF to give the 3β-silyloxy derivative **3** (R = *tert*-butyldimethylsilyl, TBDMS) in 85% yield. Oxidation of this derivative with pyridinium dichromate (PDC) in CH_2Cl_2 gave the diketone **4** (98%). Removal of the silyl protecting group (*p*-toluenesulfonic acid, water–acetone–methanol solution) and treatment with ethylene glycol and *p*-toluenesulfonic acid in refluxing benzene furnished the 17-acetal **5** (96% for the two steps). Reduction of the 11-ketone with sodium in 1-propanol gave the 3β,11α-diol (93%), which was converted to the diacetate **6** (97%). Bromination of **6** with pyridinium bromide perbromide gave the 16α-bromo derivative (94%), which was deacetylated (dilute KOH in DMSO–water) and subjected to dehydrobromination (potassium *tert*-butoxide in DMSO at 50 °C) to give the corresponding diene in 84% yield.[5]

Following removal of the acetal protecting group, the 3β-hydroxyl was once more protected as the *tert*-butyldimethylsilyl ether, which was oxidized with PDC to give the 11-ketone **7** (80%). The Δ^{15} double bond was selectively epoxidized with sodium hypochlorite (Chlorox) in pyridine–ethanol.[6] The 15β,16β epoxide **8** was obtained in 87% yield. This high melting compound (mp 206–208 °C) was relatively stable compared to analogous epoxides possessing an 11α-hydroxy or 11α-acetoxy function. The latter decomposed during even gentle manipulation and

(5) Fried, J.; Edwards, J. A. In *Organic Reactions in Steroid Chemistry*; Van Nostrand Reinhold: New York, 1972; Vol. 1, p 302.

(6) (a) Jakubowski, A.; Guziec, F. S., Jr.; Tishler, M. *Tetrahedron Lett.* **1977**, 2399. (b) Marmor, S. *J. Org. Chem.* **1963**, *28*, 250.

gave poor yields in the next steps of the synthesis. Wittig reaction of epoxide **8** with the ylide from ethyltriphenylphosphonium bromide and lithium diisopropylamide (LDA) gave the desired key intermediate **9**, which, however, was quite unstable. Therefore, **9** was not isolated but was added immediately to a solution of the magnesium cyanocuprate **10** derived from (*R*)-(+)-limonene in the following way. Catalytic hydrogenation of the disubstituted double bond[7] followed by ozonolysis and reductive workup gave (3*R*,6*RS*)-3-(1-methylethyl)heptane-1,6-diol.[8] Protection of the primary alcohol as the *tert*-butyldimethylsilyl ether (TBDMSCl, 4-(dimethylamino)pyridine, triethylamine in CH_2Cl_2, 92% yield) followed by oxidation with PDC afforded the corresponding ketone (98%). Reaction of the latter with 3,5-dinitroperoxybenzoic acid in CH_2Cl_2[9] gave a single ester (95%), which, on hydrolysis with methanolic potassium carbonate, gave (*R*)-5-[(*tert*-butyldimethylsilyl)oxy]-3-(1-methylethyl)pentanol (85%). Treatment with triphenylphosphine and carbon tetrabromide in THF gave the corresponding bromide (65%), which was converted to the Grignard reagent in THF, and this was added to CuCN (1 mol, previously dried over P_2O_5 for 12 h at 40 °C (in vacuo) in THF. On stirring the mixture for 1 h at room temperature a dark violet solution of the cuprate **10** was formed. The solution of **9** was then added to the cooled (−78 °C) solution of the cuprate, giving the 1,4-addition product **11** (61% from 8). Selective hydrogenation of the Δ^{16} double bond was achieved (90%) by using platinum on carbon as catalyst in ethyl acetate. Some hydrogenolysis of the 15β-hydroxyl occurred, but this could be almost completely avoided by addition of sodium carbonate to the reaction mixture.

These last three steps were highly stereoselective and none of the possible isomers of **12** (at C_{15}, C_{17}, or C_{20}) could be isolated. Reduction of the 11-ketone of **12** with sodium in propanol furnished the 11α-hydroxy product (93%). The protecting groups were then removed (*p*-toluenesulfonic acid–water) and the resulting tetrol was converted to the tetraformate with formic acetic anhydride–pyridine. Oxidation with CrO_3–3,5-dimethylpyrazole in CH_2Cl_2 at 20 °C gave the corresponding 7-ketone **13** (68%; some starting material, 13%, was recovered). Removal of the protecting groups with methanolic potassium carbonate solution yielded oogoniol **14** (46% from **12**). An analytical sample was obtained by high performance liquid chromatography (HPLC), which was also used to confirm the identity as natural oogoniol. The synthetic and natural compounds also possessed identical spectral properties.[10,11]

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(9) Rastetter, W. H.; Richard, T. J.; Lewis, M. D. *J. Org. Chem.* **1978**, *43*, 3163.

(10) HPLC analysis was performed on a Waters Associates M-45 instrument, using a 30 cm × 7.8 mm (i.d.) μ-Bondapak C-18 column. The mobile phase was methanol–water (60:40) and the flow rate was 4 mL/min at 2500 psi. The retention time for oogoniol was 19.8 min. It was isolated as a noncrystalline solid: mp 99–101 °C; high resolution MS *m/z* (rel intensity) 458.3423 ($M^+ - H_2O$, 79), 440.3300 ($M^+ - 2H_2O$, 50), 283.1717 (68), 161.0947 (100); IR ν_{max} 3400, 2950, 2870, 1660, 1470, 1058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, J = 6.6 Hz, 26-H or 27-H), 0.86 (d, J = 7.2 Hz, 27-H or 26-H), 0.95 (d, J = 6.6 Hz, 21-H), 0.98 (s, 18-H), 1.35 (s, 19-H), 3.60–3.80 (m, 3-H and 29-H), 4.08–4.20 (m, 11-H), 4.65–4.73 (m, 15-H), 5.82 (m, 6-H); ^{13}C NMR ($CDCl_3$) δ 201.9, 167.8, 125.6, 70.6, 70.5, 68.8, 62.0, 56.2, 55.9, 55.3, 51.9, 43.1, 42.5, 40.6, 40.4, 39.7, 38.8, 38.0, 35.5, 33.8, 33.5, 31.4, 29.2, 27.2, 19.6, 18.9, 18.4, 17.3, 14.9.

(11) Synthesis of oogoniol has recently been accomplished by Koreeda et al., personal communication to T.C.M.