1′,2′,3′,4′-Tetrahydronaphthalenespiro-2-(5-aza-7,8-benzo-4-methyl-3-thiabicyclo[4.4.0]deca-1(6),4,7-triene) (15): mp 135–137 °C; ^{1}H NMR ($CDCl_3$) δ 1.70–2.20 (m, 6 H, CH_2), 2.25 (s, 3 H, CH_3), 2.50–2.90 (m, 4 H, C=CCH_2), 7.00–7.40 (m, 6 H, aromatic CH), 7.45 (m, 1 H, aromatic CH), 7.75 (m, 1 H, aromatic CH); MS *m/e* (relative intensity) 331 (M^+, 77), 270 (M^+ – CH_3CSN, 100); IR ($CDCl_3$) ν 1605 cm^{-1}. Anal. Calcd for $C_{22}H_{21}NS$: C, 79.73; H, 6.39; N, 4.23; S, 9.66. Found: C, 79.47; H, 6.52; N, 4.16; S, 9.84.

***trans*-1-(Thiobenzamido)-2-(cyclohex-1-enyl)cyclohexane (*trans*-17)**: mp 111–113 °C; ^{1}H NMR ($CDCl_3$) δ 1.20–2.50 (m, 17 H, CH_2 and CH), 4.20–4.50 (m, 1 H, CH next to N), 5.50 (m, 1 H, vinyl H), 7.10–7.65 (m, 5 H, aromatic CH); MS *m/e* (relative intensity) 299 (M^+, 100), 121 ($C_6H_5CS^+$, 35); IR ($CDCl_3$) ν 3250, 1600, 1590 cm^{-1}; UV (hexane) λ_{max} 295 nm (ε 18500), 440 (ε 2000). Anal. Calcd for $C_{19}H_{25}NS$: C, 76.22; H, 8.42; N, 4.68; S, 10.69. Found: C, 76.03; H, 8.51; N, 4.65; S, 10.81.

Photolysis of the Thioenamide *trans*-17. A solution of the thioenamide *trans*-17 (300 mg, 5×10^{-3} M) in hexane (350 mL) was placed in a water-cooled quartz reactor equipped with a dry argon inlet and a magnetic stirrer. The solution was purged by bubbling argon through it for 2 h and then irradiated with eight Rul 3000-Å lamps in a Rayonet RPR photochemical reactor for 45 min. The solvent was removed under vacuum and the crude photoreaction product was finally purified by elution chromatography, using ethyl acetate–hexane (1:4) as eluent.

***trans*-Cyclohexanespiro-2-(5-aza-4-phenyl-3-thiabicyclo-[4.4.0]dec-4-ene) (*trans*-18)**: 255 mg, 85%; mp 123–125 °C; ^{1}H NMR ($CDCl_3$) δ 1.20–2.50 (m, 19 H, CH_2 and CH), 3.05 (m, 1 H, CH next to N), 7.20–7.75 (m, 5 H, aromatic CH); MS *m/e* (relative intensity) 299 (M^+, 11), 164 ($M^+ - C_6H_5CSN$, 100), 121 ($C_6H_5CS^+$, 22), 103 ($C_6H_5CN^+$, 34); IR ($CDCl_3$) ν 1615 cm^{-1}. Anal. Calcd for $C_{19}H_{25}NS$: C, 76.22; H, 8.42; N, 4.68; S, 10.69. Found: C, 76.28; H, 8.42; N, 4.68; S, 10.71.

Registry No. **1a**, 2227-79-4; **1b**, 5346-38-3; **2a**, 5977-82-2; **2c**, 54679-69-5; **3**, 1502-22-3; **3** (oxime), 37575-86-3; **9a**, 115464-12-5; **9b**, 115464-10-3; **10a**, 115464-13-6; **10c**, 115464-11-4; **11**, 105983-29-7; **12**, 23804-16-2; **13**, 115464-14-7; **14**, 115464-15-8; **15**, 115464-16-9; *cis*-**16**, 115464-17-0; *trans*-**16**, 115464-18-1; **17**, 115464-19-2; **18**, 115464-20-5; benzamide, 55-21-0; *cis*-1-(2-aminocyclohexyl)cyclohexene, 115464-21-6; *trans*-1-(2-aminocyclohexyl)cyclohexene, 115464-22-7; cyclohexanone, 108-94-1.

Total Synthesis of *rac*-9,11-Dehydrodigitoxigenin 3-Tetrahydropyranyl Ether

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Received March 10, 1988

There are many publications[1] dealing with partial synthesis of cardenolides. Most of these papers concern linking of the lactone ring to the steroidal skeleton and the introduction of a hydroxyl group in the 14β-position.

We present the total synthesis of the title compound in which the lactone ring was added to an earlier synthesized derivative **4** of androstane, containing a hydroxyl group in the 14β-position. Starting from racemic Mieschner–Wieland ketone **1**, which can also be obtained by asymmetric synthesis in pure enantiomeric form,[2] we obtained seco-compound **2** in five steps[3] (Scheme I). Base-catalyzed cyclization of **2** was very erratic. Control of temperature as well as pH of the reaction mixture was essential. At temperatures lower than −15 °C, the rate of cyclization was slow, whereas above −10 °C the reaction components decomposed. Under optimal conditions, the yield of **3** was 40%, and about 20% of starting compound **2** was recovered. Selective hydrogenation[3] of **3** over palladium on $SrSO_3$ furnished **4**, which served as a substrate for synthesis of the title compound. Retainment of the 14β-hydroxyl in compound **4** was an important requirement of the synthetic program. However, for continuation of the synthesis it was necessary to develop a new approach to construction of 17β-orientated lactones. Hydrogenation of ethylenic bonds in position 16–17 or 17–20 of steroids with a cis C/D ring junction is known to proceed from the less hindered β side of the molecule and furnishes products with 17α-substituents. We intended to introduce a 17β-substituent by an S_N2 type free-radical reaction of a 17α-iodo derivative. For this purpose, **4** was hydrogenated to **5**, which was converted to **6** by K-Selectride at −40 °C in a THF–toluene mixture. Compound **7** was obtained by treatment of the crude hydrazone of **6** with iodine according to a known procedure[4] (Scheme II). Hydrogenation of **7** with diimide afforded iodide **8** suitable for the substitution reaction. Direct exchange of the iodine atom for the cyano group was unsuccessful,[5] but using a procedure for protection of the 14β-hydroxyl group in the form of THP and trimethylsilyl ethers,[6] we could achieve substitution of iodine by cyanide (NaCN–DMSO, 110 °C), though only in moderate yield (40%), and complications developed during attempts to hydrolyze the protecting groups. Hence, attention was directed to free-radical reactions which do not require protection of the hydroxyl group and presumably afford a product resulting from substitution from the less hindered side. After unsuccessful attempts to attach 2-buten-1,4-olide, 3-bromo-2-buten-1,4-olide, and 3-(tributyltin)-2-buten-1,4-olide groups by a free-radical reaction[7] initiated by tributyltin hydride and AIBN, we found that reaction of iodide **8** with *tert*-butyl isocyanide in the presence of tributyltin chloride, sodium cyanoborohydride, and AIBN in boiling *tert*-butyl alcohol[8] afforded nitrile **9** in 82% yield. The β orientation of the cyano group was proved as follows. Nitrile **10** was transformed into lactone **11** (IR 1775 cm^{-1}) in 25% yield by reaction with DIBAH followed by PCC oxidation of the intermediate aldehyde.

Having on hand the nitrile **10**, we intended to prepare the corresponding derivative 21-hydroxy-20-oxopregnane and then to form the butenolide ring according to a known

(1) Wicha, J.; Kabat, M. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1601. Stork, G.; Stryker, J. M. *Tetrahedron Lett.* **1983**, *24*, 4887. Welzel, P.; Stein, H.; Milkowa, T. *Liebigs Ann. Chem.* **1982**, 2119. Marini-Bettolo, R.; Flecker, P.; Tsai, T. Y. R.; Wiesner, K. *Can. J. Chem.* **1981**, *59*, 1403.

(2) W. Ger. Pat. 2102623, Jan 21, 1970. Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. Gitzwiller, J.; Buchschacher, P.; Furts, A. *Synthesis* **1977**, 167. Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496.

(3) Daniewski, A. R.; White, P.; Valenta, Z. *Can. J. Chem.* **1979**, *57*, 1397. Daniewski, A. R.; Valenta, Z.; White, P. *Bull. Pol. Acad. Sci., Chem.* **1984**, *32*, 29.

(4) Barton, D. H. R.; O'Brien, R. E.; Sternhell, S. *J. Chem. Soc.* **1962**, 470.

(5) A similar reaction has been published by Kabat et al.: Kabat, M. M.; Kurek, A.; Masnyk, M.; Repke, K. R. H.; Schönfeld, W.; Wieland, J.; Wicha, J. *J. Chem. Res., Synop.* **1987**, 218.

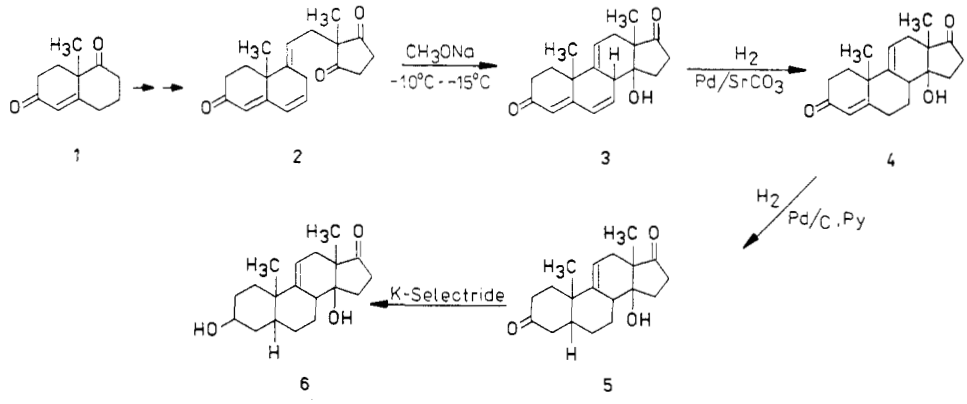
(6) The hydroxyl groups in **8** at the 3- and 14-positions were protected (in 40%) as THP ethers by using the Grieco method (*J. Org. Chem.* **1977**, *42*, 3772). The TMS ether grouping in the 3- and 14-positions in **8** was obtained in 85% yield by the reaction of **8** with TMSCN in DMF with addition of a catalytic amount of the $ZnCl_2$·Py complex.

(7) Baldwin, J. E.; Kelly, D. R.; Ziegler, C. B. *J. Chem. Soc., Chem. Commun.* **1984**, 133.

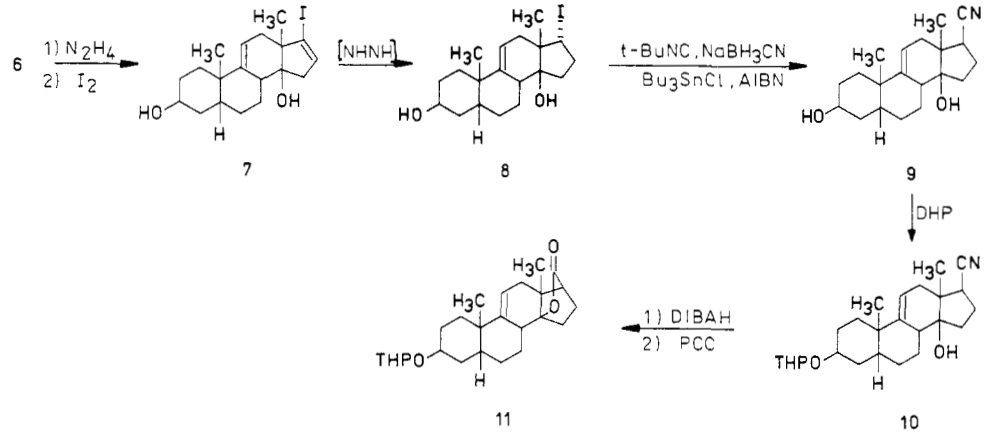
(8) Stork, G.; Sher, P. M.; Chen, H.-L. *J. Am. Chem. Soc.* **1986**, *108*, 6384.

0022-3263/88/1953-4855$01.50/0

Scheme I

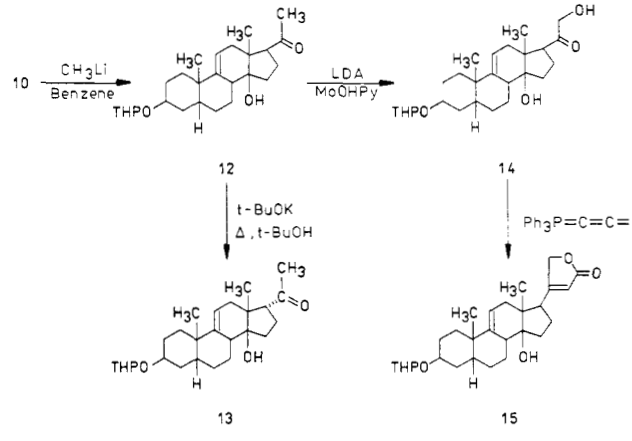


Scheme II



method.[9] Direct introduction of the hydroxymethyl[10] group by reaction of **10** with [(dimethylisopropoxysilyl)-methyl]magnesium chloride could not be achieved, although a variety of experimental conditions were investigated. However, treatment of **10** with methyllithium in benzene gave a 72% yield of **12**, whose C-17 stereochemistry was confirmed by equilibration with potassium *tert*-butoxide in boiling *tert*-butyl alcohol to form the thermodynamically more stable 17α isomer **13** (Scheme III). For introduction of the hydroxy group in the 21-position, the original procedure of Vedejs[11] utilizing lithium enolate of ketone **12** and MoOHP had to be modified owing to the low yield of product **14** (5%). Addition of HMPA to the reaction mixture containing in situ generated lithium enolate of **12** followed by addition of MoOHP furnished hydroxy ketone **14** in 27% yield together with unchanged starting material **12** (50%). Finally, treatment of **14** with (triphenylphosphoranylidene)ketene[12] in the presence of triethylamine at room temperature over 20 h yielded the desired compound **15** (52%), which was fully characterized by spectroscopic methods.

Scheme III



Experimental Section

All reactions were carried out under argon and were monitored by TLC. Melting points were measured on a micro hot plate and were not corrected. The IR spectra were taken with a Beckman 4240 spectrophotometer with the exception of compound **15**, whose IR spectrum was taken by I. M. Waseman from Rikilt Institute on a FT-IR spectrometer. The ^{1}H NMR spectra were recorded on a Bruker WP 100 FY and Bruker AM-400 spectrometer in $CDCl_3$, using TMSCl as an internal standard. The mass spectra were recorded on an LKB-9000S apparatus.

14β-Hydroxy-5β-androst-9(11)-ene-3,17-dione (5). Hydrogenation of **4** (1.5 g, 6.0 mmol) was carried out in a pyridine (20 mL) solution over 10% Pd/C (0.2 g) at room temperature under atmospheric pressure during 2 h. After removal of the catalyst by filtration, the solvent was distilled on a rotary evaporator and the residue was chromatographed on a silica gel column using hexane–ethyl acetate (3:2) as an eluent. This afforded compound **5** (1.3 g, 86.7%): mp 173–175 °C (crystallized from a chloroform–ether mixture); IR (Nujol) 3430, 1710 cm^{-1}; ^{1}H NMR (100 MHz) δ 1.027 (s, 3 H, CH_3), 1.21 (s, 3 H, CH_3), 5.56 (t, 1 H, $C_{11}H$, J = 2.6 Hz); MS (70 eV), m/e 302.

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.53; H, 8.56.

3β,14β-Dihydroxy-5β-androst-9(11)-en-17-one (6). To a stirred solution of **5** (1.3 g, 4.3 mmol) in a THF–toluene (1:1) mixture (10 mL) at −40 °C was added K-Selectride (1 M in THF,

(9) Nickisch, K.; Klose, W.; Bohlmann, F. *Chem. Ber.* **1980**, *113*, 2038.
(10) Tamao, K.; Ishida, N. *Tetrahedron Lett.* **1984**, *25*, 4245.
(11) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.
(12) Bestman, H. J.; Sanmeier, D. *Chem. Ber.* **1980**, *113*, 274.

10 mL), and the temperature −40 °C was maintained for an additional 15 min. Sodium hydroxide (3 M, 2 mL) and hydrogen peroxide (30%, 2 mL) were added, and the reaction mixture was stirred for 10 min without cooling. Then the reaction mixture was extracted with ethyl acetate, and the extract was washed with an aqueous solution of $FeSO_4$ and brine and dried over $MgSO_4$. Removal of solvent under reduced pressure furnished compound **6** (1.16 g, 88.5%), which was used for the next step. An analytical sample was obtained by crystallization from a chloroform–methanol mixture. Compound **6**: mp 220 °C dec; IR (Nujol) 3350, 1730 cm^{-1}; ^1H NMR (100 MHz) in C_5D_5N δ 1.20 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 4.40 (m, 1 H, C_3H), 5.45 (m, 1 H, $C_{11}H$); MS (70 eV), m/e 304.

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.08; H, 9.39.

3β,14β-Dihydroxy-5β-androsta-9(11),16-dien-17-yl Iodide (7). A mixture of compound **6** (1.1 g, 3.6 mmol), hydrazine hydrate (10 mL), triethylamine (12 mL), and ethanol (30 mL) was refluxed for 1 h. The solvents were removed under reduced pressure, and the white crystalline residue was dried over P_2O_5 in a vacuum desiccator. The crude hydrazone was dissolved in dry THF (30 mL) containing triethylamine (2.5 mL), and iodine (1.3 g, 10.2 mmol) in THF (10 mL was added dropwise (1 h) at room temperature; stirring was continued for an additional 0.5 h. After addition of ethyl acetate (100 mL), the reaction mixture was washed with an aqueous solution of sodium sulfite (20%, 20 mL), followed by brine washing (3 × 50 mL). The solution of **7** was dried over $MgSO_4$, concentrated under reduced pressure, and chromatographed on a silica gel column using a benzene–acetone–methanol (9:0.5:0.25) mixture as an eluent. Compound **7**: (800 mg, 53.3%); mp 165–167 °C (crystallized from a chloroform–ether mixture); IR (Nujol) 3300 cm^{-1}; ^1H NMR (100 MHz) δ 1.026 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 4.04–4.20 (m, 1 H, C_3H), 5.40–5.58 (m, 1 H, $C_{11}H$), 6.15–6.21 (t, 1 H, J = 2.5 Hz, $C_{16}H$); MS (70 eV), m/e 414, 415.

Anal. Calcd for $C_{19}H_{27}IO_2$: C, 55.07; H, 6.59. Found: C, 54.76; H, 6.49.

3β,14β-Dihydroxy-5β-androst-9(11)-en-17α-yl Iodide (8). A mixture of **7** (750 mg, 1.8 mmol) in ethanol (30 mL), hydrazine hydrate (1.6 mL), and propionic acid (1.4 mL) was refluxed for 2 h with air bubbling. The solvents were partly removed under reduced pressure, and the product was precipitated with water (8 mL). Compound **8** (650 mg, 86.25%) was separated by filtration and crystallized from an ethanol–water mixture: mp 205–207 °C; IR (Nujol) 3320 cm^{-1}; ^1H NMR (400 MHz) δ 0.86 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3), 4.06–4.1 (m, 1 H, C_3H), 4.46 (t, 1 H, J = 9.0 Hz, $C_{17}H$), 5.30–5.35 (m, 1 H, $C_{11}H$); MS (70 eV), m/e 416, 417.

Anal. Calcd for $C_{19}H_{29}IO_2$: C, 54.80; H, 7.02. Found: C, 54.76, H, 7.09.

3β,14β-Dihydroxy-5β-androst-9(11)-en-17β-yl Cyanide (9). A mixture of **8** (416 mg, 1.0 mmol), *tert*-butyl alcohol (8.0 mL), tributylin chloride (27.2 μL, 0.1 mmol), *tert*-butyl isocyanide (2.2 mL, 20 mmol), sodium cyanoborohydride (62.8 mg, 1.0 mmol), and AIBN (5.0 mg, 0.03 mmol) was refluxed under argon for 1 h. Then another portion of sodium cyanoborohydride (62.8 mg, 1.0 mmol) and AIBN (5.0 mg, 0.03 mmol) was added, and refluxing was continued for another 1 h. The solvent was removed on a rotary evaporator, and the residue was chromatographed on silica gel (20 g) by using a chloroform–acetone (95:5) mixture as an eluent. This afforded compound **9** (260 mg, 82%): mp 158–160 °C (from a chloroform–ether mixture); IR ($CHCl_3$) 3600, 2215 cm^{-1}; ^1H NMR (400 MHz) δ 1.10 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3), 2.62 (dd, 1 H, J = 5.7 Hz, $C_{17}H$), 4.05–4.10 (m, 1 H, C_3H), 5.27–5.31 (m, 1 H, $C_{11}H$); MS (70 eV), m/e 315.

Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.26; N, 4.44. Found: C, 75.98; H, 9.31; N, 4.32.

14β-Hydroxy-3β-(tetrahydropyranyloxy)-5β-androst-9-(11)-en-17β-yl Cyanide (10). A mixture of compound **9** (315 mg, 1.0 mmol), methylene chloride (10 mL), dihydropyran (0.5 mL), and pyridinium *p*-toluenesulfonate (2 mg) was left overnight at room temperature. Pyridine (two drops) was added, and the mixture was concentrated on a rotary evaporator. The residue was chromatographed on a silica gel column, affording compound **10** (280 mg, 70%): mp 130–138 °C (from ether–hexane); IR ($CHCl_3$) 3600, 2210 cm^{-1}; ^1H NMR (100 MHz) δ 1.1 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3), 2.62 (t, 1 H, J = 6.1 Hz, $C_{17}H$), 3.35–3.60 (m, 1 H), 3.74–4.00 (m, 2 H), 4.55–4.70 (m, 1 H, OCHO), 5.20–5.35 (m, 1 H, $C_{11}H$); MS (70 eV), m/e 399.

Anal. Calcd for $C_{25}H_{37}NO_3$: C, 75.14; H, 9.33; N, 3.5. Found: C, 74.66; H, 9.53; N, 3.2.

14,20-Epoxy-3β-(tetrahydropyranyloxy)-5β,14β,21-norpregn-9(11)-en-20-one (11). To a stirred solution of **10** (20 mg, 0.5 mmol) in toluene (2 mL) was added DIBAH (0.1 mL) at −78 °C. The reaction mixture was stirred for 1 h at −78 °C, and then methanol (0.2 mL) and water (0.2 mL) was added. The reaction mixture was stirred at room temperature for 2 h and then the precipitate separated by filtration. The filtrate was evaporated to dryness; its IR spectrum exhibited a band at 1720 cm^{-1}. This residue was dissolved in methylene chloride (4 mL), and PPC (50 mg) was added. The reaction mixture was stirred at room temperature for 3 h, filtered through Celite, and chromatographed on a silica gel, affording compound **11** (5 mg, 25%): IR ($CHCl_3$) 1775 cm^{-1}; ^1H NMR (100 MHz) δ 1.0 (s, 3 H, CH_3), 1.13 (s, 3 H, CH_3), 2.60 (d, 1 H, J = 3.5 Hz, $C_{17}H$), 3.35–3.60 (m, 1 H), 3.8–4.05 (m, 2 H), 4.58–4.70 (m, 1 H, OCHO), 5.30–5.50 (m, 1 H, $C_{11}H$); MS (70 eV), m/e 400.

14β-Hydroxy-3β-(tetrahydropyranyloxy)-5β-pregn-9-(11)-en-20-one (12). To a solution of compound **10** (550 mg, 1.38 mmol) in dry benzene (10 mL) was added methyllithium (1.6 M, 2.0 mL, 3.2 mmol) at room temperature, and the reaction mixture was stirred for 15 min. Acetic acid (192 μL, 3.2 mmol) was added, and the reaction mixture was washed with brine and dried over Na_2SO_4; the solvent was removed under reduced pressure. The residue was chromatographed on silica gel, affording compound **12** (420 mg, 72%): mp 138–140 °C (from ether); IR ($CHCl_3$) 3400, 1700 cm^{-1}; ^1H NMR (400 MHz) δ 0.90 (s, 3 H, CH_3), 1.1 (s, 3 H, CH_3), 2.26 (s, 3 H, CH_3CO), 2.92–2.96 (dd, 1 H, J = 4 Hz, $C_{17}H$), 3.39–3.48 (m, 1 H), 3.82–3.92 (m, 2 H), 4.6–4.7 (m, 1 H, OCHO), 5.17–5.30 (m, 1 H, $C_{11}H$); MS (70 eV), m/e 398 (M − 18); HRMS calcd 398.2821, found 398.2821.

14β-Hydroxy-3β-(tetrahydropyranyloxy)-5β,17α-pregn-9-(11)-en-20-one (13). A solution of compound **12** (20.8 mg, 0.5 mmol) in *tert*-butyl alcohol (3 mL) containing potassium *tert*-butoxide (20 mg, 0.18 mmol) was refluxed under argon for 0.5 h. TLC showed that about 50% of **12** was equilibrated into **13**, which was a little more polar (hexane–ethyl acetate, 2:1). The mixture was neutralized with acetic acid (10.8 μL), diluted with ethyl acetate (10 mL), and washed with brine. After drying over Na_2SO_4, filtration, and removal of solvent under vacuum, the residue was chromatographed, affording 8 mg of **13** and 7 mg of **12**. Compound **13**: IR (film) 3400, 3200, 1700 cm^{-1}; ^1H NMR (100 MHz) δ 1.1 (br s, 6 H, 2 CH_3), 2.18 (s, 3 H, CH_3CO) 3.15–3.60 (m, 2 H), 3.8–4.02 (m, 2 H), 4.60–4.70 (m, 1 H, OCHO), 5.25–5.35 (m, 1 H, $C_{11}H$); MS (70 eV), m/e 398 (M − 18).

14β,21-Dihydroxy-3β-(tetrahydropyranyloxy)-5β-pregn-9(11)-en-20-one (14). To s stirred solution of LDA (1.0 mmol) in THF (2.0 mL) under argon was added a solution of **12** (104 mg, 0.25 mmol) in THF (2.0 mL) at −78 °C. After 10 min, HMPA (600 μL) was added and the mixture was stirred at −78 °C for 20 min. A solution of powdered MoOHP (440 mg, 1.0 mmol) in THF–HMPA (2:1, 2.0 mL) was added, and the reaction mixture was warmed to −10 °C. Then water (1.0 mL) and ethyl acetate (5 mL) were added, and the organic layer was washed with diluted aqueous $CuSO_4$, followed by aqueous $KHCO_3$ and brine. After drying over Na_2SO_4 and removal of solvents under vacuum, the organic layer was chromatographed, affording compound **14** (30 mg, 27%) and the recovered compound **12** (50 mg, 50%). Compound **14**: mp 105–120 °C (from ether); IR ($CHCl_3$) 3570, 3450, 1700 cm^{-1}; ^1H NMR (400 MHz) δ 0.83 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 2.74–2.80 (dd, 1 H, $C_{17}H$), 3.4–3.49 (m, 1 H), 3.81–3.93 (m, 2 H), 4.24 (d, 1 H, J_{AB} = 5.9 Hz, $C_{21}H$), 4.30 (dd, 1 H, J_{AB} = 5.9 Hz, J_{BX} = 1.5 Hz, $C_{21}H$), 4.57–4.63 (m, 1 H, OCHO), 5.20–5.26 (m, 1 H, $C_{11}H$); MS (70 eV), m/e 414 (M − 18).

14β-Hydroxy-3β-(tetrahydropyranyloxy)-5β-carda-9(11),20(22)-dienolide (15). A mixture of **14** (10.8 mg, 0.025 mmol), benzene (1 mL), triethylamine (10 μL), and (triphenylphosphoranylidene)ketene (9.06 mg, 0.03 mmol) was maintained at room temperature for 20 h. After removal of solvent and chromatography on silica gel, compound **15** was obtained (6.0 mg, 52%): mp 170–180 °C (from ether–pentane); IR (KBr) 3221, 1782, 1748, 1616 cm^{-1}; ^1H NMR (400 MHz) δ 0.79 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 2.80–2.87 (dd, 1 H, $C_{17}H$), 3.41–3.49 (m, 1 H),

3.83–3.94 (m, 2 H), 4.57–4.62 (m, 1 H, OCHO), 4.82 (dd, 1 H, J_{ab} = 19.5 Hz, J_{BX} = 1.88 Hz, $C_{21}H$), 4.98 (ddt, 1 H, J_{AB} = 19.5 Hz, J_{AX} = 1.0 Hz, $C_{21}H$); UV (EtOH) λ_{max} 214.9 nm (ϵ 12500); HRMS calcd 372.2301, found 372.2307 (M – DHP).

Acknowledgment. We are thankful to the Polish Academy of Sciences for financial support (Grant CPBP 01.13.2.25). We are very indebted to I. M. Waseman from Rikilt for performing the FT–IR spectrum of compound **15**.

Registry No. **1**, 20007-99-2; **2**, 71563-68-3; **3**, 71505-07-2; **4**, 71563-69-4; **5**, 115649-62-2; **6**, 115562-13-5; **6** (hydrazone deriv), 115562-14-6; **7**, 115590-14-2; **8**, 115562-15-7; **9**, 115562-16-8; **10**, 115562-17-9; **10** (aldehyde deriv), 115562-18-0; **11**, 115590-15-3; **12**, 115562-19-1; **13**, 115649-63-3; **14**, 115562-20-4; **15**, 115562-21-5; $Ph_3P{=}C{=}C{=}O$, 15596-07-3.

A Facile and Efficient Preparative Method of Methyl 2-Arylpropanoates by Treatment of Propiophenones and Their Derivatives with Iodine or Iodine Chlorides

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Received December 7, 1987

Several 2-arylpropionic acids have been known as important pharmaceutical agents exhibiting nonsteroidal antiinflammatory activities[1] and many preparative methods of the acids have so far been developed.[1b,c] We also presented several new methods for the preparation of the acids or their alkyl esters from propiophenones **1** and related substances via 1,2-aryl group migration.[2-5]

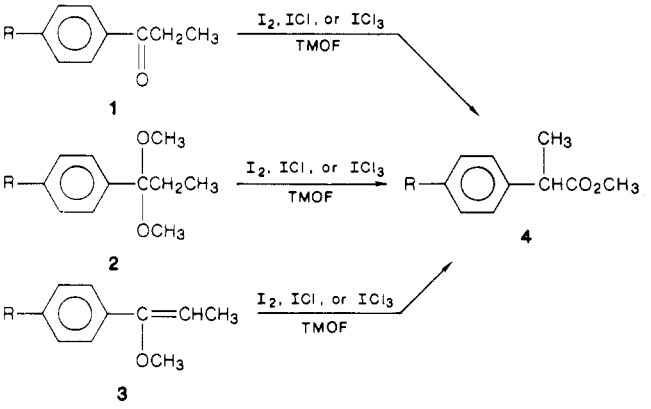
Quite recently a patent work[6] appeared which revealed the formation of methyl 2-arylpropanoates **4** by the treatment of **1** with iodine in trimethyl orthoformate (TMOF). This prompted us to report our similar work on I_2-, ICl-, or ICl_3-mediated facile preparation of **4** from **1**, its dimethyl ketals **2**, and 1-aryl-1-methoxy-1-propenes **3** via aryl migration.[7] The reagent ICl_3 was proved to be very effective for this transformation for the first time. It is worth noting that the reaction of 2-alkyl-2-phenyl-1,3-dioxolanes with ICl in dichloromethane gave 2-chloroethyl esters of 2-phenylalkanoic acids via 1,2-aryl migration.[8]

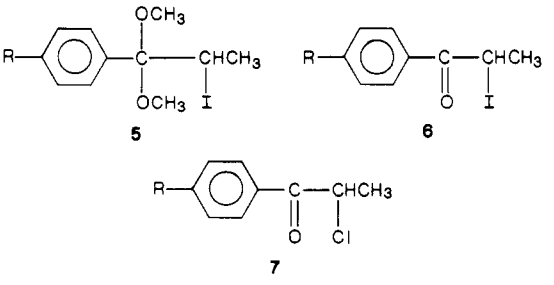
The reactions of **1**, **2**, or **3** (R = H, Bu^i, CH_3O, Br, F) with I_2, ICl, or ICl_3 were generally carried out by the addition of an iodine compound to a solution of **1**, **2**, or **3** in TMOF at 23 °C, and the mixture was stirred for 24 h at the same temperature. The esters **4**, 1-aryl-1,1-dimethoxy-2-iodopropanes **5**, and aryl 1-iodoethyl ketones **6**, or aryl 1-chloroethyl ketones **7** were the products, the amount of which depended on the reaction conditions. Typical results are shown in Table I. The reactions in other solvents such as methanol and dichloromethane were slower and gave much lower yields of **4**. The data shown in the table disclosed the following: (1) the I_2 (2 equiv to the substrate)/TMOF system is generally suitable for preparation of **4**, (2) the reactivity order of iodine compound is ICl_3 >

Table I. Preparation of Methyl 2-Arylpropanoates (4)[a]

		product and isolated yield, %			
starting compd	reagent (equiv)[b]	**4**	**5**	**6**	**7**
1 (R = H)	I_2 (2.0)	66	0	24	0
1 (R = H)	ICl_3 (1.2)	62	*d*	*d*	26
1 (R = Bu^i)	I_2 (1.2)	23	69	2	0
1 (R = Bu^i)	I_2 (2.0)	98	0	0	0
1 (R = Bu^i)	ICl (1.0)	87	0	0	*d*
1 (R = Bu^i)	ICl_3 (1.1)	97	0	0	*d*
1 (R = CH_3O)	I_2 (1.2)	85	0	0	0
1 (R = Br)	I_2 (2.0)	0	1	48[c]	0
1 (R = Br)	ICl (1.2)	9	80	*d*	*d*
1 (R = Br)	ICl_3 (1.2)	73	*d*	*d*	18
1 (R = F)	I_2 (2.0)	0[e]	0	0	*d*
1 (R = F)	ICl_3 (1.2)	52	*d*	*d*	35
2 (R = H)	I_2 (2.0)	60	0	39	0
2 (R = H)	ICl_3 (1.2)	55	*d*	*d*	32
2 (R = Bu^i)	I_2 (1.2)	30	64	0	0
2 (R = Bu^i)	I_2 (2.0)	93	0	0	0
2 (R = Bu^i)	ICl (1.2)	74	*d*	*d*	*d*
2 (R = CH_3O)	I_2 (1.2)	98	0	0	0
2 (R = Br)	I_2 (2.0)	0[f]	4	2	0
3 (R = Bu^i)	I_2 (1.0)	20	62	17	0
3 (R = Bu^i)	I_2 (2.0)	98	0	0	0
3 (R = Bu^i)	ICl (1.2)	80	*d*	*d*	*d*
3 (R = CH_3O)	I_2 (1.2)	88	0	0	0
3 (R = CH_3O)	ICl (1.0)	81	*d*	*d*	*d*

[a] Carried out using **1** (10 mmol), **2** (10 mmol), or **3** (5 mmol) in TMOF (5.3 g) at 23 °C for 24 h. [b] Equivalent to the starting compound. [c] Recovered **1**, 29%. [d] Not determined. [e] Recovered **1**, 92%. [f] Recovered **1**, 92%.





(1) See, for example: (a) Shen, T. Y. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 460. (b) Rieu, J.-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 4095. (c) Giordano, C.; Castaldi, G.; Uggeri, F. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 413.

(2) Fujii, K.; Nakao, K.; Yamauchi, T. *Synthesis* **1982**, 456. Yamauchi, T.; Nakao, K.; Fujii, K. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1433.

(3) Fujii, K.; Nakao, K.; Yamauchi, T. *Synthesis* **1983**, 444. Yamauchi, T.; Nakao, K.; Fujii, K. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1255.

(4) Uemura, S.; Fukuzawa, S.; Yamauchi, T.; Hattori, K.; Mizutaki, S.; Tamaki, K. *J. Chem. Soc., Chem. Commun.* **1984**, 426; *J. Chem. Soc., Perkin Trans. 1* **1986**, 1983.

(5) Yamauchi, T.; Hattori, K.; Nakao, K.; Tamaki, K. *Synthesis* **1986**, 1044; *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4015.

(6) Citterio, A.; Tinucci, L.; Filippini, L.; Belli, A. Eur. Pat. Appl. EP 171 840 (*Chem. Abstr.* **1986**, *105*, 6321p).

(7) (a) Yamauchi, T.; Hattori, K.; Nakao, K.; Tamaki, K. Japan Pat. Appl. 1986, 81807. (b) Presented at the 54th Annual Meeting of the Chemical Society of Japan, Tokyo, April 1987.

(8) Goosen, A.; McCleland, C. W. *J. Chem. Soc., Chem. Commun.* **1982**, 1311.

0022-3263/88/1953-4858$01.50/0