gel, following the procedure we have described.[11]

Preparation of Alcohol 4. A flame-dried two-neck 50-mL round-bottom flask was flushed with N_2 and charged with 305 mg (2 mmol) of *p*-isopropylbenzyl alcohol (**1**), 930 mg (8 mmol) of TMEDA, and 14 mL of ether. The mixture was magnetically stirred in an ice/water bath and then *n*-BuLi (8 mmol) was added, the first half slowly, the last half all at once. After stirring in the ice bath 5 min, the mixture was warmed to reflux for 1 h.[12] The flask was then immersed in a saturated NaCl/dry ice bath, and 200 mg (1.1 mmol) of dried $Cu_2(CN)_2$ was added. After another 30 min of stirring, allyl chloride (765 mg, 10 mmol, in 2 mL of Et_2O) was added. After an additional 10 min of stirring, the reaction was quenched with aqueous NH_4Cl/NH_4OH solution and extracted with Et_2O. The combined organic layers were dried over anhydrous K_2CO_3 and concentrated in vacuo. The residue was chromatographed on 50 g of silica gel with 3.5% EtOAc/petroleum ether. The first 90 mL was discarded. The next 450 mL was concentrated in vacuo to give 250 mg (1.3 mmol, 67%) of **4** as a pale yellow oil, R_f (30% EtOAc/hexane) 0.55. Repeated runs on 5 times the scale, with 2 equiv of alkylating agent, worked equally well. ^{1}H NMR δ 1.25 (d, J = 7 Hz, 6 H), 1.7–1.9 (br s, 1 H), 2.8–3.0 (m, 1 H), 3.5 (d, J = 7 Hz, 2 H), 4.6 (s, 2 H), 4.9–5.1 (m, 2 H), 5.9–6.1 (m, 1 H), 7.0–7.4 (m, 3 H); ^{13}C NMR 24.0 (q), 33.9 (d), 37.0 (t), 63.1 (t), 115.8 (t), 124.6 (d), 128.2 (d), 128.7 (d), 136.2 (d), 137.8 (d), 148.9 (s) ppm IR 3610, 3420 (br), 3070, 2955, 1627, 1600, 1450, 990, 905 cm^{-1}; MS, 190 m/z (8), 172 (53), 157 (100), 147 (30), 129 (77), 117 (28), 115 (25).

Alcohol 5: R_f (30% EtOAc/hexane) 0.50; ^{1}H NMR δ 1.4 (d, J = 6.5 Hz, 3 H), 2.9–3.0 (br s, 1 H), 3.4 (d, J = 6.5 Hz, 2 H), 4.9–5.1 (m, 3 H), 5.9–6.1 (m, 1 H), 7.1–7.6 (m, 4 H); ^{13}C NMR 24.5 (q), 36.7 (t), 66.2 (d), 115.9 (t), 125.3 (d), 127.0 (d), 127.6 (d), 130.0 (d), 136.0 (s), 137.7 (d), 143.9 (s); IR 3610, 3380 (br), 3070, 2975, 1630, 1440, 1245, 1065, 990, 905, 795 cm^{-1}; MS, m/z 162 (2), 147 (29), 145 (17), 144 (64), 130 (11), 129 (100), 119 (12), 107 (13).

Alcohol 6: R_f (30% EtOAc/hexane) 0.59; ^{1}H NMR δ 0.9 (t, J = 6.5 Hz), 1.3 (br s, 10 H), 1.4 (d, J = 6.5 Hz, 3 H), 2.2–2.4 (br s, 1 H), 3.4 (d, J = 6 Hz 2 H), 5.0–5.2 (m, 1 H), 5.3–5.6 (m, 2 H), 7.1–7.6 (m, 4 H); ^{13}C NMR 14.1 (q), 22.6 (t), 24.3 (q), 28.9 (t), 29.4 (t), 31.7 (t), 32.6 (t), 35.6 (t), 66.2 (d), 125.1 (d) 126.8 (d), 127.4 (d), 128.8 (d), 129.8 (d), 132.2 (d), 137.1 (s), 143.6 (s); IR 3600, 3060, 3010, 2920, 2845, 1475, 1440, 1065, 990, 960 cm^{-1}; MS, m/z 246 (1), 231 (11), 230 (29), 229 (100), 228 (36), 157 (10), 143 (59), 131 (24), 117 (13).

Alcohol 7: R_f (30% EtOAc/hexane) 0.69; ^{1}H NMR δ 1.6 (s, 6 H), 2.0–2.2 (br s, 1 H), 3.7–3.8 (m, 2 H), 4.9–5.1 (m, 2 H), 5.95–6.1 (m, 1 H), 7.1–7.5 (m, 4 H); ^{13}C NMR 31.7 (q), 38.3 (t), 73.8 (s), 115.3 (t), 125.5 (d), 125.9 (d), 127.1 (d), 132.3 (d), 137.9 (s), 139.5 (d), 145.6 (s) ppm; IR 3600, 3060, 2970, 1630, 1120, 900 MS, cm^{-1}; m/z 176 (11), 175 (28), 159 (100), 158 (96), 143 (67), 128 (93), 115 (33), 117 (41).

Alcohol 8: R_f (30% EtOAc/hexane) 0.48; IR 3610, 3300, 3010, 2955, 1930, 1600, 1450, 995, 840 cm^{-1}; allene MS, m/z 188 (6.9), 150 (81.3), 135 (100), 132 (22.8), 119 (32.2), 117 (24.9), 107 (38.7), 105 (38.6); allene ^{1}H NMR δ 1.25 (dd, J = 3, 8 Hz, 6 H), 2.0 (s, 2 H), 2.8–2.95 (m, 1 H), 3.0–3.2 (br s, 1 H), 4.5 (d, J = 2 Hz, 2 H), 5.1 (d, J = 7.5 Hz, 2 H), 6.4 (t, J = 6 Hz, 1 H), 7.0–7.4 (m, 3 H). Anal. (allene/acetylene). Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.98; H, 8.61.

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Registry No. 1, 536-60-7; 2, 98-85-1; 3, 617-94-7; 4, 96096-44-5; 5, 82315-95-5; 6, 96096-45-6; 7, 96096-46-7; 8, 96096-47-8; BuLi, 109-72-8; Cu(CN), 544-92-3; allyl chloride, 107-05-1; 1-chloro-2-nonene, 41792-06-7; 3-chloro-1-propyne, 624-65-7; 4-(1-methylethyl)-2-propa-1,2-dienylbenzenemethanol, 96109-60-3.

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Prosthetic Group Radioiodination at "No-Carrier Added" Levels of Carbonyl-Containing Molecules

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Indirect radioiodination by attachment of prelabeled prosthetic groups of drugs, enzymes, proteins, and other biologically important molecules is a useful synthetic method.[1,2] Examples in the literature include radioiodinated aryl diazonium ions, imidates, and esters which attach to amino functions on the target molecule[3-5] or radioiodinated phenolic amines and acyl hydrazines which attach to carbonyl loci.[6,7] Many of these are difficult to use at no-carrier added radioiodine levels or, in the case of those which are iodinated phenolics, undergo rapid in vivo deiodination.[8] There is need of a nonmetabolized, prosthetic radioiodination moiety which can be prepared in high specific activity.[9,10]

A logical prosthetic group would be an acyl hydrazide directly iodinated on an aryl ring. We therefore attempted the preparation of iodobenzyl hydrazide by reaction of benzoyl hydrazide with both iodine monochloride in acetic acid and iodide/iodic acid reaction. No product was obtained even when the potential iodinating electrophiles were in excess, a condition which, even if it had been successful, would have been inconsistent with radioiodination at no-carrier added levels.

Our earlier studies with the Sandmeyer/Wallach reaction (Scheme I) showed it to be operable at no-carrier added levels of radioiodine.[11,12] Such diazotizations would, of course, be impossible on a hydrazide, and the latter function was thus protected as an oxidazole (**2**). Acid catalysis hydrolyzes the triazene and the oxadiazole to 3-iodobenzoyl hydrazide which can be prepared in 30% chemical yield and 12% radiochemical yield at no-carrier added levels (Scheme II). The meta-substituted (triazenophenyl)oxadiazole was selected because previous studies of electronic effects indicated that electron-withdrawing groups on the aryl ring in conjugation with the triazene site reduce the yield of aryl iodide.[11,12]

Three model hydrazones (3a–c) were prepared in excellent conversions at both mass level (with Na^{127}I, in 69–89% chemical yields) and at tracer level (with Na^{125}I in radiochemical yields of 58–72% based on [^{125}I]-3-iodobenzoyl hydrazide) (Scheme III). A pharmacologically important substrate, doxorubicin, was prosthetically labeled with the benzoyl hydrazide without cleavage of the aglycone residue. Acylhydrazones of anthracycline antitumor antibiotics have demonstrated impressive cytotoxic activity.[13-15] Many antitumor agents after labeling with

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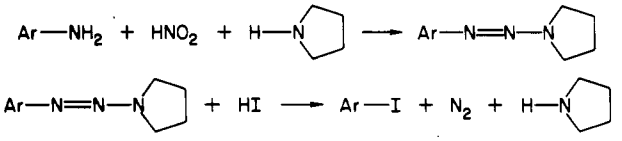
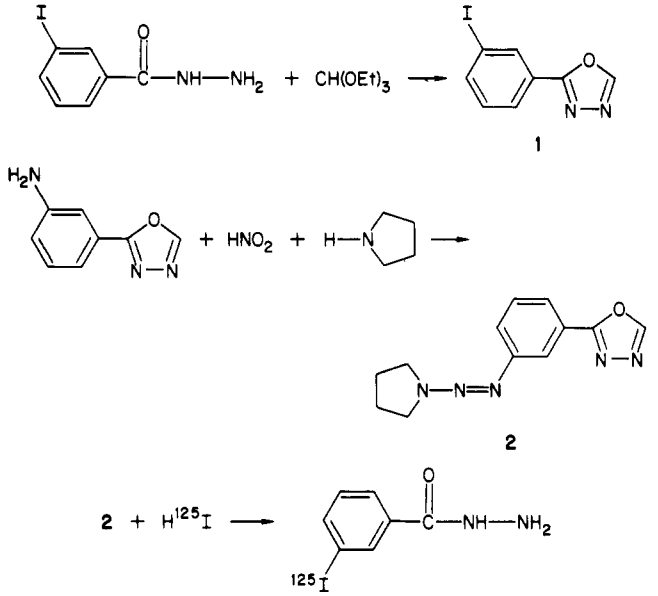
Scheme I

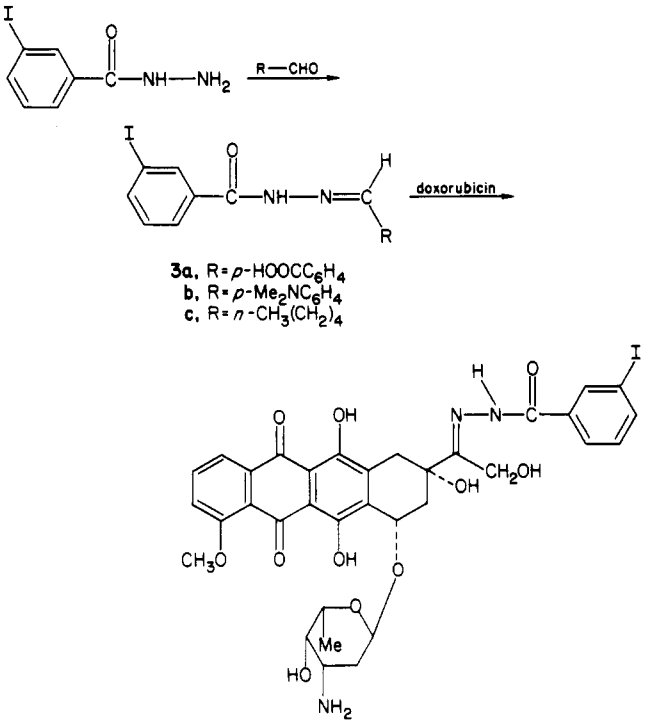


I may be iodine-127 or radioactive iodide

Scheme II



Scheme III



iodines shown can be iodine-127 or iodine-125

γ-emitting nuclides have proven useful for in vivo tumor delineation. Doxorubicin (3-iodobenzoyl)hydrazone (4) was prepared in 65% chemical yield (with iodine-127) and in 68% radiochemical yield (based on [^{125}I]-3-iodobenzoyl hydrazide).

TLC procedures were developed to permit resolution of the radioiodinated derivatives from the parent compounds. For this reason and as carrier-free Na^{125}I was used in the syntheses, the theoretical specific activity of 2175 Ci/mmol can be assumed for the resulting iodine-125 labeled compounds.[16]

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra (Me_4Si internal standard) and IR spectra (KBr disks) were recorded on JEOL-FX90Q and Perkin Elmer Model 283 spectrometers. Elemental analyses were performed by George I. Robertson Microanalytical Laboratory, Florham Park, NJ. The fast atom bombardment (FAB) mass spectrum of 4 was obtained by Dr. Douglas F. Barofsky, Oregon Graduate Center, on a CEC Du Pont 21-110B mass spectrometer.

2-(3-Iodophenyl)-1,3,4-oxadiazole (1) was prepared by reaction of 0.50 g (1.91 mmol) of 3-iodobenzoyl hydrazide[17] at reflux for 24 h in 10 mL (60 mmol) of triethyl orthoformate. The mixture was evaporated to dryness in vacuo and the residue recrystallized from 1:3 methanol/water to yield 0.45 g (87%) of shiny white flakes of 1: mp 83–85 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.29–8.28 (m, 4, ArH), 9.36 (s, 1, oxadiazole C_5H). Anal. Calcd for $C_8H_5IN_2O$: C, 35.32; H, 1.85; N, 10.30. Found: C, 35.45; H, 1.87; N, 10.08.

2-[3-(3,3-(1,4-Butanediyl)triazeno)phenyl]-1,3,4-oxadiazole (2) was prepared by diazotization at 5 °C (ice bath) of 3.0 g (19 mmol) of 2-(3-aminophenyl)-1,3,4-oxadiazole[18] in 3.0 mL of concentrated HCl treatment to the dropwise addition of 1.28 g (18.6 mmol) of sodium nitrile in 2.0 mL of water. The addition required 10 min, and the reaction mixture was then agitated for 10 min at 5 °C and poured slowly with vigorous stirring into 1.5 g (21 mmol) of freshly distilled pyrrolidine in 20 mL of 1 M aqueous KOH. The triazene precipitated as a heavy, dark-colored solid within 10 min. The solid was removed by filtration, decolorized with the aid of charcoal, and recrystallized from ethanol/water (1:1) to yield 3.25 g (72%) of 2: mp 117–118 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.96 (m, 4, pyrrolidine β-CH_2), 3.57 and 3.91 (br m, 4, pyrrolidine α-CH_2), 7.48–7.91 (m, 4, ArH), 9.31 (s, 1, oxidazole C_5H). Anal. Calcd for $C_{12}H_{13}N_5O$: C, 59.25; H, 5.38; N, 28.79. Found: C, 59.39; H, 5.30; N, 28.79.

Hydrolysis of Triazene (2) to 3-Iodobenzoyl Hydrazide. A well-stirred suspension of 0.50 g (2.1 mmol) of triazene (2), 0.34 g (2.3 mmol) of NaI, 1.3 mL of trifluoroacetic acid, and 20 mL of water was refluxed for 3.5 h, treated dropwise with a saturated aqueous solution of sodium thiosulfate undil the iodine color in the solution was bleached, adjusted to pH 10 with 1 N NaOH, and extracted with 3 × 30 mL portions of ethyl acetate. The organic phase was evaporated to an oil and 160 mg (30% yield) isolated by preparative TLC on silica plates with ethyl acetate eluent (R_f 0.24): mp 144–146 °C (lit.[17] 140–142 °C).

General Procedure for Synthesis of Hydrazones 3a–c. A solution of 0.40 g (1.5 mmol) of 3-iodobenzoyl hydrazide, 1.7 mmol of the requisite aldehyde, 20 mL of 1:1 ethanol/tetrahydrofuran, and two drops of glacial acetic acid was refluxed for 3 h and evaporated to dryness in vacuo and the residue recrystallized from the indicated solvent (below).

(3-Iodobenzoyl)(4-carboxyphenyl)hydrazone (3a): mp 300–302 °C; from 1:2 THF/water, 89% yield; IR 3200 (NH), 1675, 1645 cm^{-1} (C=O). Anal. Calcd for $C_{15}H_{11}IN_2O_3$: C, 45.70; H, 2.81; N, 7.11. Found: C, 45.46; H, 3.10; N, 7.24.

(3-Iodobenzoyl)(4-(dimethylamino)phenyl)hydrazone (3b): mp 108–110 °C; from 1:3 ethanol/water, 85% yield; IR 3170 (NH) 1640 cm^{-1} (C=O). Anal. Calcd for $C_{16}H_{16}IN_3O$: C, 48.87; H, 4.10; N, 10.69. Found: C, 48.71; H, 4.03; N, 10.45.

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(3-Iodobenzoyl)-*n*-pentylhydrazone (3c): mp 109–111 C; from 1:4 THF/petroleum ether (35–60 °C), 69% yield; IR 3200 (NH), 1645 cm^{-1} (C=O). Anal. Calcd for $C_{12}H_{15}IN_2O$: C, 43.65; H, 4.58; N, 8.49. Found: C, 43.78; H, 4.40; N, 8.63.

Doxorubicin (3-iodobenzoyl)hydrazone (4) was prepared by the general method of Cory[15] by condensation of 20 mg (0.035 mmol) of doxorubicin hydrochloride, 9.0 mg (0.035 mmol) of 3-iodobenzoyl hydrazide, and 8 mL of methanol stirred vigorously for 5 days in a light-shielded flask. The reaction mixture was filtered, evaporated to dryness in vacuo, redissolved in 50 mL of 1:4 methanol/acetonitrile, and chilled to precipitate 18.7 mg (65% yield) of dark orange crystals: mp 185–188 °C, of **4**; MS (FAB) M^+ 787 amu. A TLC analysis on Analtech preabsorbant silica plates using 20:10:1 chloroform/methanol/water as eluant and the standard pure reactants and **4** for calibration gave R_f 0.30 for doxorubicin hydrochloride, R_f 0.42 for **2**, and R_f 0.91 for 3-iodobenzoyl hydrazide. Anal. Calcd for $C_{34}H_{34}IN_3O_{11}\cdot HCl\cdot 2H_2O$: C, 47.48; H, 4.57; N, 4.91. Found: C, 47.13; H, 4.26; N, 5.37.

[^{125}I]-3-Iodobenzoyl Hydrazide. A 2-mL pointed vial was charged with 4.50 mCi of $Na^{125}I$ dissolved in 0.45 mL of distilled water, 5.0 mg (21 μmol) of **2**, 0.45 mL of tetrahydrofuran, and a micro stirring bar. The vial was sealed with a fluoropolymer-lined cap and a solution of 3.5 μL of trifluoroacetic acid in 0.1 mL of water injected by syringe through the cap.

The vial was heated in an oil bath at 100 °C for 1 h, treated to a supplemental addition of 9.5 μL of trifluoroacetic acid in 0.1 mL of distilled water, and heated for an additional 1.5 h. The product was cooled and the product isolated by addition of 0.2 mL of saturated aqueous sodium thiosulfate, pH adjustment to 10 with 1 N NaOH and extraction with 3 × 0.2 mL of ethyl acetate. The organic layer was washed once with 0.2 mL of water, dried over $MgSO_4$, and evaporated in a stream of dry nitrogen, and the residue was taken up in 0.1 mL of acetonitrile. Purified (by HPLC, radiation detection), carrier-free ^{125}I-3-iodobenzoyl hydrazide was obtained by collection of the peak eluting at 6.5 min (time at peak maximum) from a 20 cm, C-18 reverse-phase analytical column operated at a flow rate of 1 mL/min with an eluant of 7:3 acetonitrile/water. Retention time (and volume) matched that of authentic [^{127}I]3-iodobenzoyl hydrazide. Radiochemical purity was also confirmed by TLC on silica plates with ethyl acetate eluant whereon the single spot (R_f 0.24) was coincident with that observed for authentic product. A total of 0.54 mCi, 12% radiochemical yield, of [^{125}I]3-iodobenzoyl hydrazide was obtained. The product peak represented 95% of the total radioactivity eluted from the chromatograph.

([^{125}I]-3-Iodobenzoyl)(4-carboxyphenyl)hydrazone (3a). A solution of 0.5 mg of 4-carboxybenzaldehyde, 0.1 mCi of [^{125}I]-3-iodobenzoyl hydrazide, 0.3 mL of methanol, and 1 μL of 0.05 N HCl was refluxed for 3 h, evaporated under nitrogen stream, and the resulting residue taken up in 0.3 mL of water. The aqueous solution was adjusted to pH 10 with 1 N NaOH, extracted with 3 × 0.2 mL of ethyl acetate, and the organic extracts were discarded. The pH of the aqueous phase was then adjusted to 5 with 0.5 N HCl and extracted with 3 × 0.2 mL of ethyl acetate. The product was isolated by preparative TLC (reverse phase C-18, methanol eluant) of the dried ($MgSO_4$) and evaporated organic phase. A single radioactive fraction (R_f 0.73), 58 μCi, 58% radiochemical yield based on [^{125}I]-3-iodobenzoyl hydrazide eluted coincident with authentic starting material.

([^{125}I]-3-Iodobenzoyl)(4-(dimethylamino)phenyl)-hydrazone (3b) was prepared by reaction of 0.1 mCi of [^{125}I]-3-iodobenzoyl hydrazide, 0.5 mg of 4-(dimethylamino)benzaldehyde, 0.3 mL of methanol, and 1 μL of 0.05 N HCl over 3-h reflux. The cooled solution was adjusted to pH 10 with 1 N NaOH, extracted with 3 × 0.2 mL of ethyl acetate, and the dried ($MgSO_4$), evaporated extracts purified by preparative TLC (silica plates, 1:1 ethyl acetate/methylene chloride) to give 72 μCi of a single radioactive component (R_f 0.61) coincident in elution with authentic unlabeled material. Radiochemical yield was 72% calculated on [^{125}I]-3-iodobenzoyl hydrazide.

([^{125}I]-3-Iodobenzoyl)-*n*-pentylhydrazone (3c) was prepared from *n*-pentanal in a manner identical with that described above for **3b**. Preparative TLC afforded 65 μCi (65% radiochemical yield from the [^{125}I]-3-iodobenzoyl hydrazide) of **3c** migrating as a single radioactive spot coincident with authentic nonradioactive material (silica plate, diethyl ether eluant).

Dioxorubicin ([^{125}I]-3-iodobenzoyl)hydrazone ([^{125}I]-4) was prepared by 5 days of vigorous agitation in a light shielded pointed reactor vial of 0.10 mCi of [^{125}I]-3-iodobenzoyl hydrazide, 1.0 mg of doxorubicin hydrochloride, and 0.3 mL of methanol. Purification of the evaporated reaction mixture was accomplished on preparative TLC using 20:10:1 chloroform/methanol/water to yield 68 μCi, radiochemical yield 68% from I-125 3-iodobenzoyl hydrazide, with R_f 0.39, coincident with authentic **4**.

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Registry No. **1**, 31822-06-7; **2**, 96096-01-4; **3a**, 96096-02-5; **3b**, 96096-03-6; **3c**, 96096-04-7; **4**, 96096-05-8; **4** (^{125}I), 96096-07-0; $CH(OEt)_3$, 122-51-0; *m*-$H_2NC_6H_4\overline{C=NN=CHO}$. 5378-35-8; *m*-$IC_6H_4CONHNH_2$, 39115-94-1; *m*-$^{125}IC_6H_4CONHNH_2$, 96096-06-9; *p*-$CO_2HC_6H_4CHO$, 619-66-9; *p*-$Me_2NC_6H_4CHO$, 100-10-7; $CH_3(CH_2)_4CHO$, 66-25-1; pyrrolidine, 123-75-1; doxorubicin hydrochloride, 25316-40-9.

A Novel Approach to Cardenolides

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Most of the work that has been carried out over past years aimed at cardenolide synthesis has utilized pregnan-20-one derivatives as starting materials.[2]

Recent availability of efficient microbiological methods for the production of 17-oxo steroids[3] has, however, revived interest in the conversion of these intermediates into cardenolides.[4]

In this note we report a simple four-step synthesis of the cardenolides **6a** and **6b** from 3β-hydroxy-5α-androstan-17-one acetate (**1a**) and its 5-epimer **1b**, respectively.

The conversion of the cardenolide **6b** into digitoxigenin (**6c**) has already been described.[2c]

Compounds **1a** and **1b** have been transformed into 17-enol trifluoromethanesulfonates (enol triflates) **2a** and **2b** with triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine according to the procedure of Stang[5] in 55% and 46% yields, respectively.

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