4.3-g (0.02 mol) quantity of this material dissolved in 20 mL of warm (<50 °C) methanol was treated with 1.4 g (0.02 mol) of cyclobutanone, added by syringe to the septum-covered 50-mL recovery flask. The reaction mixture which soon deposited crystals was allowed to stand at room temperature for several hours and then refrigerated for 1 h to give 4.6 g (86%) of product, mp 118–120 °C. Recrystallization from methanol (83% recovery) gave the analytical sample, mp 122–124 °C.

^{13}C NMR Study. Arenesulfonylhydrazines were dissolved or suspended in methanol-d_4 or tetrahydrofuran-d_8 (tosyl and trimyl, 4.00 mmol/2.0 mL of solvent; trisyl, 2.00 mmol/2.0 mL of solvent) in septum-sealed 10-mm NMR tubes. The trisylhydrazine was recrystallized from ether immediately before use. Tetramethylsilane (0.1 mL) was added as an internal reference. Distilled *n*-butanal (1.00 mol equiv) was injected into each tube, which was then placed in a shaker at ambient temperature. Proton-decoupled spectra were accumulated after 2, 24, and 168 h. The accumulation parameters were as follows: pulse width, 29 μs; pulse delay, 58.8 s; number of scans, 60. Increasing the pulse delay to 300 s or decreasing the pulse width to 14 μs did not significantly affect the results. For the other THF data in Table III, the tosyl and trimyl experiments were run at 1.0 M and the trisyl at 2.0 M.

Registry No. 1, 20208-71-3; 2, 83477-63-8; 3, 34266-29-0; 4, 83477-64-9; 5, 75938-54-4; 6, 75938-55-5; 7, 5362-74-3; 8, 52718-79-3; 9, 36432-88-9; 10, 83477-65-0; 11, 63883-82-9; (*Z*)-12, 83486-40-2; (*E*)-12, 83477-72-9; (*Z*)-13, 83477-66-1; (*E*)-13, 83477-73-0; 14, 83477-67-2; 15, 83477-68-3; 16, 83477-69-4; 17, 2524-51-8; 18, 83477-70-7; 19, 83477-71-8; 20, 54211-17-5; isobutyraldehyde, 78-84-2; cyclohexanecarboxaldehyde, 2043-61-0; 3-methylpentanal, 15877-57-3; 2,4-dimethylhexanal, 20514-48-1; pivaldehyde, 630-19-3; *n*-heptanal, 111-71-7; 4-heptanone, 123-19-3; 3-heptanone, 106-35-4; 2-heptanone, 110-43-0; cyclohexyl methyl ketone, 823-76-7; cyclobutanone, 1191-95-3; cyclopentanone, 120-92-3; bicyclo[4.2.0]octan-7-one, 54211-18-6; tosylhydrazine, 1576-35-8; trisylhydrazine, 39085-59-1; trimylhydrazine, 16182-15-3.

Preparative and Stereochemical Features of the Sulfoxide–Sulfenate [2,3] Sigmatropic Rearrangement in 17-Vinyl-17-hydroxy Steroids

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Received May 27, 1982

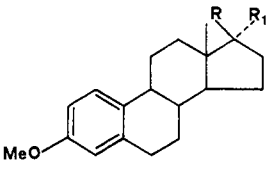
Attempts to achieve configurational inversion of tertiary allylic alcohols by the "classical" approach comprising S_N2-type displacement of suitable derivatives are invariably thwarted by the almost exclusive formation of allylic rearrangement and/or elimination products,[1] nor does the diethyl azodicarboxylate–triphenylphosphine system work with tertiary substrates.[2]

Sparse reports suggest that the allyl sulfoxide–sulfenate rearrangement could be advantageously exploited to this end, although in one direction only. Illustrations on this concern are provided by the conversion of prostaglandin (13*Z*,15*R*)-PGE$_1$ into the 13*E*,15*S* analogue[4] and a new route to the dihydroxyacetone side chain from a 17α-ethynyl-17β-hydroxy steroid.[5]

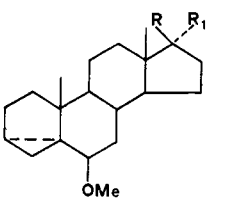
In this paper we report (a) that an effective "one-pot" epimerization procedure of 17α-vinyl-17β-hydroxy steroids to the rather inaccessible 17-epimers[6] can be assembled by the use of the above rearrangement and (b) some stereochemical observations on this process.

Results and Discussion

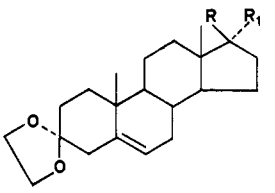
Treatment of **1a** with phenylsulfenyl chloride according to the procedure of Mislow[7] afforded the sulfoxide **4a** as a single isomer. The stereohomogeneity of **4a** was indicated by the sharp singlet for the angular methyl group in both $CDCl_3$ and C_6D_6.



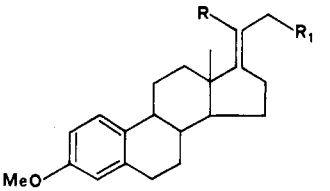
1a, R = OH; R1 = CH=CH2
b, R = CH=CH2; R1 = OH
c, R = OSPh; R1 = CH=CH2
d, R = CH=CH2; R1 = OSPh



2a, R = OH; R1 = CH=CH2
b, R = CH=CH2; R1 = OH



3a, R = OH; R1 = CH=CH2
b, R = CH=CH2; R1 = OH



4a, R = H; R1 = (S)-S(=O)Ph
b, R = H; R1 = (R)-S(=O)Ph
c, R = H; R1 = SO2Ph

The 17,20 double bond was assigned the *E* geometry on comparison of the chemical shift of the 13-Me group to other related compounds of known stereochemistry.[5,8]

Consideration of the relative energies of model transition states (see below) led to allocation of configuration at sulfur as depicted.

Exposure of **4a** to the highly efficient thiophile trimethyl phosphite[9] in refluxing methanol provided a mixture of **1b** and **1a** in a 73:27 ratio (88% overall yield). An analogous result was obtained when the two-step sequence was performed without isolating **4a**. Reaction of **1b** with phenylsulfenyl chloride gave the sulfoxide **4b**, again as a single isomer.

A 1:1 mixture of **4a** and **4b** was oxidized with *m*-chloroperbenzoic acid to the sulfone **4c**, confirming that these compounds differ only with respect to chirality at sulfur. Furthermore, each isomer was equilibrated to a 1:1 mixture by heating in C_6D_6 at 65 °C for 4 h. At 80 °C the equilibration was complete within 1 h. According to the Mislow's observations,[7] isomerization of **4a** and **4b** in refluxing methanol was appreciably slower (26% isomerization after 5 h). A considerably higher diastereoselectivity was obtained in the reaction of **4b** with the thiophile,

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(2) O. Mitsunobu, *Synthesis*, 1 (1981).
(3) D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, **7**, 147 (1974); R. W. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **18**, 563 (1979).
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resulting in a practically exclusive formation of **1b**. Only trace amounts of **1a** could, in fact, be detected.

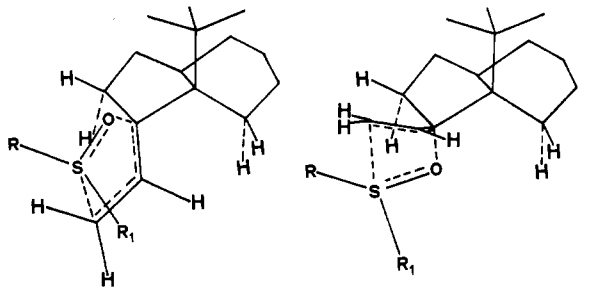
Information on the relative rates of rearrangement–cleavage of **4a** and **4b** stemmed from the observation that **4b** gave **1b** in 63% yield after 5 h at reflux in methanol–trimethyl phosphite, whereas after this time **4a** has undergone only a 29% conversion to a mixture of **1a** and **1b**. Similarly, the percent conversions were 47 and 14%, respectively, after 3 weeks at room temperature.

Evans and Andrews reported in a kinetic study of the treatment of [(4-*tert*-butylcyclohexylidene)ethyl]phenyl sulfoxide with trimethyl phosphite that the cleavage of the intermediate sulfenates occurred much faster than their rearrangement to the parent sulfoxide.[9]

This proved not to be so in our case. In fact, in both the above runs the recovered **4b** was found to be extensively isomerized into **4a**. No detectable isomerization was conversely observed in the recovered **4a**, but the discrepancy seems easily reconcilied in view of the faster rearrangement–cleavage of **4b** in comparison with **4a**. We consider it unlikely that the presence of trimethyl phosphite can induce a noticeable difference between the rates of isomerization of **4a** and **4b**.

As anticipated, assignment of configuration at sulfur to **4a** and **4b**, as well as a rationale of their behavior with the thiophile, follows from a comparison of the four cyclic transition states involved in their formation and rearrangement–cleavage.[10]

The transition state **5a** connecting the sulfenate **1c** to the sulfoxide **4a** should be of lower energy than the diastereomeric one **5b** leading to the sulfoxide **4b**, owing to



5a, R = Lone pair; R_1 = Ph
5b, R = Ph; R_1 = Lone pair

6a, R = Lone pair; R_1 = Ph
6b, R = Ph; R_1 = Lone pair

the minor phenyl-annular proton interactions. Analogously, the transition state **6a** should be preferred over **6b** for the rearrangement of the sulfenate **1d**.

Turning to the reverse process, rearrangement–cleavage of **4a** into **1a** and **1b** requires that **5a** or **6b** be transversed. From models, their energies can be conceivably estimated on a comparable level because of the balance between stabilizing and destabilizing factors. The minor phenyl-annular proton interactions of the former are, in fact, outweighed by the unfavorable attachment of the sulfoxide oxygen to C-17 from the more hindered β side, while the reverse holds for the latter.

In the absence of concurrent isomerization into **4b**, a low, if any, diastereoselectivity would then be expected. A similar comparison of the transition states **5b** and **6a** involved in the **4b** to **1b** conversion indicates **6a** to be highly favored over **5b**. Indeed, the least favorable **5d** probably fails to play any significant role in our rearrangements.

The following stability order can thus be given: **6a** > **5a** ≈ **6b** ≫ **5b**, and both the observed diastereoselectivities and relative rates are believed to be determined primarily by this order.

The incursion of a preference factor for the formation of axial vs. equatorial C–O bonds in the obtention of **1a** and **1b** cannot be completely ruled out, although it should be, in any case, much less influent in our model than in the six-membered rings examined by Hoffmann.[11]

For preparative purposes, the epimerization of **1a** can be most profitably performed by isomerizing crude **4a** in boiling benzene before subjecting it to the final treatment with the thiophile. In this way, a 86:14 ratio of **1b** to **1a** was obtained (88% overall yield). The whole sequence could be carried out in the same reaction flask.

To further demonstrate the usefulness of our method, we next used as substrates **2a** and **3a**. As expected, the epimerization procedure afforded **2b** and **3b**, respectively, in ≥70% isolated yields.

Although the main purpose of the vinylic organometallic reactions on 17-keto steroids has been for the preparation of 21-substituted pregn-17(20)-enes,[12] thus rendering synthetic efforts toward 17β-vinyl-17α-hydroxy steroids unnecessary, the present "one-pot" method promises to be useful for solving problems of "unnatural" sterochemistry that vinylic organometallic reactions might originate in biassed carbonyl compounds.

Experimental Section

Melting points were determined on a Kofler apparatus and are uncorrected. Optical rotations were measured with a Schmidt–Haensch polarimeter (1-dm cell) in 1% $CHCl_3$ solutions. ^1H NMR spectra were obtained on a Varian EM-390 spectrometer, with $CDCl_3$ as solvent, unless otherwise specified, and Me_4Si as internal standard. Column chromatographies were carried out with Merck silica gel 60 (230–400 mesh ASTM), unless otherwise indicated. THF and trimethyl phosphite were distilled over lithium aluminium hydride and sodium, respectively.

(*E*)-3-Methoxy-(*S*)-21-(phenylsulfinyl)-19-norpregna-1,3,5(10),17(20)-tetraene (4a). Utilizing the procedure of Mislow et al.,[7] we added dropwise to a stirred solution of **1a**[12] (0.62 g, 2 mmol) in THF (8 mL) at −20 °C 1.6 M *n*-butyllithium in hexane (1.37 mL, 2.2 mmol), under nitrogen. After 0.5 h at −20 °C, the solution was cooled at −78 °C, and 0.32 g (2.2 mmol) of phenylsulfenyl chloride[13] in 2 mL of THF was added dropwise. The reaction mixture was kept at −78 °C for 15 min and then allowed to warm slowly to room temperature, and the THF was removed in vacuo. Purification of the residue by chromatography on silica gel (19 g) utilizing benzene–ethyl acetate (9:1) as eluant gave 0.77 g (92%) of **4a**: mp 106–107 °C (from acetone–hexane); $[\alpha]_D$ +52°; ^1H NMR δ 0.72 (3 H, s, 13-Me), 3.44 and 3.64 (2 H, AB of ABX, 8 lines, J = 12 and 8 Hz, C-21 H_2), 3.77 (3 H, s, 3 -OMe), 5.02 (1 H, tt, J = 8 and 2 Hz, C-20 H), 6.63–7.74 (3 H, m, aromatic protons); ^1H NMR (C_6D_6) δ 0.61 (13-Me), 3.28 (d, J = 8 Hz, C-21 H_2), 3.43 (3-OMe), 5.00 (tt, J = 8 and 2 Hz, C-20 H), 6.70–7.65 (aromatic protons).

Anal. Calcd for $C_{27}H_{32}O_2S$ (420.7): C, 77.10; H, 7.67; S, 7.62. Found: C, 77.00; H, 7.68; S, 7.52.

Rearrangement–Cleavage of 4a in Methanol–Trimethyl Phosphite. A solution of **4a** (0.42 g, 1 mmol) and trimethyl phosphite (1.2 mL, 10 mmol) in methanol (4 mL) was refluxed for 40 h, after which time TLC analysis indicated that practically all **4a** had reacted. Methanol and excess phosphite were evaporated, and the residue (0.34 g) was chromatographed on silica gel (10 g). Elution with benzene–ethyl acetate (99:1) afforded **3-methoxy-19-nor-17β-pregna-1,3,5(10),20-tetraen-17-ol (1b**; 203 mg, 65%): mp 102.5–103.5 °C (from hexane); $[\alpha]_D$ −1°; ^1H NMR δ 0.71 (3 H, s, 13-Me), 3.77 (3 H, s, 3-OMe), 5.16 (1 H, dd,

(10) For other work on the stereochemistry of steroidal allyl sulfoxides, see D. Neville Jones, J. Blenkinsopp, A. C. F. Edmons, E. Helmy, and R. J. K. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 2602 (1973), and ref 5.

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J = 10.5 and 1.5 Hz, C-21 H), 5.32 (1 H, dd, J = 17 and 1.5 Hz, C-21 H), 6.11 (1 H, dd, J = 17 and 10.5 Hz, C-20 H), 6.67–7.30 (3 H, m, aromatic protons).

Anal. Calcd for $C_{21}H_{28}O_2$ (312.4): C, 80.73; H, 9.03. Found: C, 80.80; H, 9.06.

Further elution with benzene-ethyl acetate (99:1) gave the alcohol **1a** (73 mg, 23%).

Treatment of **4a** under the same conditions for 5 h afforded by elution with benzene–ethyl acetate (99:1) **1b** and **1a** (90 mg, relative yields 21 and 8%). Elution with benzene–ethyl acetate (9:1) gave the starting sulfoxide **4a** (286 mg, 68%).

Repetition of the procedure at room temperature for 3 weeks gave **1b** and **1a** in 11 and 3% yields, respectively, and unchanged **4a** (86%).

The preparation and rearrangement–cleavage of **4a** were repeated as described above, except that the second step was carried out directly on the residue of the THF evaporation to give **1b** and **1a** in 64 and 24% yields, respectively.

(*E*)-3-Methoxy-(*R*)-21-(phenylsulfinyl)-19-norpregna-1,3,5(10),17(20)-tetraene (4b) was prepared in the same manner as **4a** from **1b** in 55% yield after column chromatography: mp 100–101.5 °C (from acetone–hexane); $[\alpha]_D$ +10°; ^{1}H NMR δ 0.70 (3 H, s, 13-Me), 3.54 (2 H, d, J = 8 Hz, C-21 H_2), 3.76 (3 H, s,3-OMe), 5.00 (1 H, tt, J = 8 and 2 Hz, C-20 H), 6.63–7.73 (3 H, m, aromatic protons); ^{1} H NMR (C_6D_6) δ 0.57 (13-Me), 3.18 and 3.37 (AB of a ABX, 8 lines, J = 12 and 8 Hz, C-21 H_2), 3.44 (3-OMe), 4.98 (tt, J = 8 and 2 Hz, C-20 H), 6.67–7.63 (aromatic protons).

Anal. Calcd for $C_{27}H_{32}O_2S$ (420.7): C, 77.10; H, 7.67; S, 7.62. Found: C, 77.02; H, 7.82; S, 7.57.

Rearrangement–cleavage of 4b in methanol–trimethyl phosphite under the same conditions as for **4a** resulted in the formation of **1b** in 63% yield after 5 h at reflux. Only trace amounts (~1%) of **1a** were observed. The recovered sulfoxide (27%) consisted of a mixture of **4b** and **4a** in a 63:36 ratio.

Repetition of the procedure at room temperature for 3 weeks again afforded almost exclusively **1b** (47%), together with a 82:18 mixture of **4b** and **4a** (47%).

Equilibration of the sulfoxides 4a and 4b in C_6D_6 at 65 °C in an NMR tube was followed by measuring the relative intensities of the signals due to 13-Me protons at intervals. Equilibration to a 1:1 mixture was complete after 4 h with a first-order rate constant (k) of 1.64×10^{-4} s^{-1}.[14] At 80 °C, the equilibration was complete within 1 h. Equilibration in refluxing methanol was monitored by withdrawing samples at intervals and substituting C_6D_6 for methanol. A mixture containing 74% of the starting sulfoxide was obtained after 5 h.

(*E*)-3-Methoxy-21-(phenylsulfonyl)-19-norpregna-1,3,5-(10),17(20)-tetraene (4c). A solution of a 1:1 mixture of **4a** and **4b** (0.42 g, 1 mmol) and *m*-chloroperbenzoic acid (90%, 0.21 g, 1.1 mmol) in ether (20 mL) was stirred at room temperature for 1 h. The ether was evaporated, and the residue was chromatographed on a column of deactivated (grade IV) Woelm basic alumina (13 g). Elution with CH_2Cl_2 gave **4c** (380 mg, 87%): mp 130.5–132 °C (from methanol); $[\alpha]_D$ +30°; ^{1}H NMR δ 0.67 (3 H, s, 13-Me), 3.77 (3 H, s, 3-OMe), 3.78 (2 H, d, J = 8 Hz, C-21 H_2), 5.10 (1 H, tt, J = 8 and 2 Hz, C-20 H), 6.62–7.99 (3 H, m, aromatic protons).

Anal. Calcd for $C_{27}H_{32}O_3S$ (436.6): C, 74.27; H, 7.39; S, 7.34. Found: C, 74.27; H, 7.40; S, 7.30.

6β-Methoxy-3α,5-cyclo-5,17α-pregn-20-en-17-ol (2a). Treatment of a solution of 6β-methoxy-3α,5-cyclo-5α-androstan-17-one[15] (2.06 g, 6.82 mmol) in 20 mL of THF with 2 M vinyllithium in THF (11 mL, 22 mmol) at room temperature for 0.5 h using experimental conditions similar to those described by Olsen and Babler[12] afforded crude **2a**, which was freed from hydrocarbon impurities by chromatography on silica gel (150 g). Elution with benzene–ethyl acetate (97:3) and crystallization from hexane afforded 0.97 g (43%) of pure **2a**: mp 126–127 °C; $[\alpha]_D$ +35°; ^{1}H NMR δ 0.95 (3 H, s, 13-Me), 1.02 (3 H, s, 10-Me), 2.75 (1 H, m, 6α-H), 3.33 (3 H, s, 6β-OMe), 5.12 (1 H, dd, J = 10.5 and 1.5 Hz, C-21 H), 5.16 (1 H, dd, J = 17 and 1.5 Hz, C-21 H), 6.08 (1 H, dd, J = 17 and 10.5 Hz, C-20 H).

Anal. Calcd for $C_{22}H_{34}O_2$ (330.5): C, 79.95; H, 10.37. Found: C, 79.79; H, 10.50.

3,3-(Ethylenedioxy)-17α-pregna-5,20-dien-17-ol (3a) was prepared in the same manner as **2a** from 3,3-(ethylenedioxy)-androst-5-en-17-one[16] and crystallized from acetone–hexane: mp 184.5–186 °C; $[\alpha]_D$ –55°; ^{1}H NMR δ 0.91 (3 H, s, 13-Me), 1.02 (3 H, s, 10-Me), 3.94 (4 H, s, 3-ketal), 5.11 (1 H, dd, J = 10.5 and 1.5 Hz, C-21 H), 5.15 (1 H, dd, J = 17 and 1.5 Hz, C-21 H), 5.35 (1 H, m, C-6 H), 6.07 (1 H, dd, 17 and 10.5 Hz, C-20 H).

Anal. Calcd for $C_{23}H_{34}O_3$ (358.5): C, 77.05; H, 9.56. Found: C, 77.07; H, 9.50.

Typical "One-Pot" Epimerization Procedure of Alcohols 1a, 2a, and 3a. Compound **1a** (0.31 g, 1 mmol) was sequentially treated with *n*-butyllithium and phenylsulfenyl chloride as previously described. THF was evaporated, and the residue was refluxed in benzene (5 mL) for 1 h. The solvent was removed *in vacuo* and the residue was refluxed in methanol (4 mL) containing 1.2 mL (10 mmol) of trimethyl phosphite for 40 h. The mixture was diluted with water and extracted with ether. The extract was washed with water and dried (Na_2SO_4). The residue (0.35 g) was chromatographed on silica gel (10 g). Elution with benzene–ethyl acetate (99:1) afforded 237 mg (76%) of **1b**, followed by 37 mg (12%) of **1a**.

Repetition of this procedure on **2a** (0.33 g, 1 mmol) gave by elution with benzene–ethyl acetate (98:2) 241 mg (73%) of **6β-methoxy-3α,5-cyclo-5α,17β-pregn-20-en-17-ol (2b)**: mp 143–144 °C (from hexane); $[\alpha]_D$ +6°; ^{1}H NMR δ 0.74 (3 H, s, 13-Me), 1.02 (3 H, s, 10-Me), 2.77 (1 H, m, 6α-H), 3.34 (3 H, s, 6β-OMe), 5.13 (1 H, dd, J = 10.5 and 1.5 Hz, C-21 H), 5.29 (1 H, dd, J = 17 and 1.5 Hz, C-21 H), 6.08 (1 H, dd, J = 17 and 10.5 Hz, C-20 H).

Anal. Cald for $C_{22}H_{34}O_2$ (330.5): C, 79.95; H, 10.37. Found: C, 79.90; H, 10.39.

Further elution with the same eluant afforded 40 mg (12%) of **2a**.

In a similar fashion, **3a** (0.54 g, 1.5 mmol) afforded a residue of 0.64 g, which was rapidly chromatographed on silica gel (16 g). Elution with benzene–ethyl acetate (97:3) gave **3a** (91 mg, 17%), followed by **3,3-(ethylenedioxy)-17β-pregna-5,20-dien-17-ol (3b**; 377 mg, 70%): mp 170.5–172 °C (from methanol); $[\alpha]_D$ –85°; ^{1}H NMR δ 0.70 (3 H, s, 13-Me), 1.02 (3 H, s, 10-Me), 3.93 (4 H, s, 3-ketal), 5.12 (1 H, dd, J = 10.5 and 1.5 Hz, C-21 H), 5.27 (1 H, dd, J = 17 and 1.5 Hz, C-21 H), 5.36 (1 H, m, C-6 H), 6.07 (1 H, dd, J = 17 and 10.5 Hz, C-20 H).

Anal. Calcd for $C_{23}H_{34}O_3$ (358.5): C, 77.05; H, 9.56. Found: C, 77.12; H, 9.54.

Registry No. **1a**, 6885-48-9; **1b**, 83915-64-4; **2a**, 83845-62-9; **2b**, 83915-65-5; **3a**, 83845-63-0; **3b**, 83915-66-6; **4a**, 83845-64-1; **4b**, 83845-65-2; **4c**, 83845-66-3; 6β-methoxy-3α,5-cyclo-5α-androst-17-one, 14425-92-4; 3,3-(ethylenedioxy)androst-5-en-17-one, 3754-63-0; phenylsulfenyl chloride, 931-59-9; vinyllithium, 917-57-7.

(14) Determined graphically in the usual manner; see A. A. Frost and R. G. Pearson, "Kinetics and Mechanism", 2nd ed., Wiley, New York, 1961, pp 13 and 186.
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A Simple and Convenient Method for Esterification of Tryptophan and Other Amino Acids

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Received June 7, 1982

Esterification of amino acids is very important in peptide synthesis.[1,2] In most cases, the esters can be prepared by acid-catalyzed esterification.[1-8] However, acid-sensitive

0022-3263/83/1948-0121$01.50/0