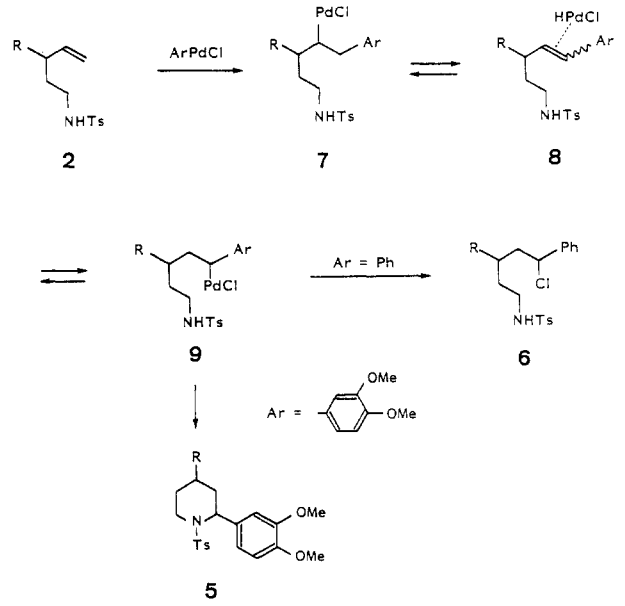
Table I. Terminal *gem*-Arylamination and Arylchlorination of *N*-3-Butenyl- and *N*-4-Pentenyl-*p*-toluenesulfonamides Catalyzed by Pd^{II}

	starting amide[a] 1 or 2	arylating agent $ArSn(n\text{-}Bu)_3$, Ar	reacn[b] conditions T, °C	reacn[b] conditions t, h	product (yield,[c] %)
1	1	C_6H_5	0	6	**3a** (65) **4a** (35)
2	1	$4\text{-}MeC_6H_4$	0	7	**3b** (72) **4b** (21)
3	1	$3,4\text{-}(MeO)_2C_6H_3$	0	8	**3c** (63) (11)[d]
4	2 (R = H)	C_6H_5	0	5	**6a** (69)
5	2 (R = H)	$4\text{-}(MeO)C_6H_4$	0	5	**5b** (70)
6	2 (R = H)	$3,4\text{-}(MeO)_2C_6H_3$	0	8	**5c** (78)
7	2 (R = Me)	C_6H_5	0	8	**6d** (65)
8	2 (R = Me)	$4\text{-}(MeO)C_6H_4$	0	7	**5e** (58)[e]
9	2 (R = Ph)	C_6H_5	0	6	**6f** (77)
10	2 (R = Ph)	$4\text{-}(MeO)C_6H_4$	0	5	**5g** (55)[f]
11	2 (R = OAc)	$4\text{-}(MeO)C_6H_4$	*h*	5	**5h** (77)

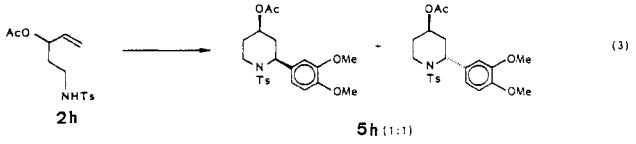
[a] For the structures of 1, 3, and 4 and for those of 2, 5, and 6, see eq 1 and 2, respectively. [b] The mixture consisting of 1 or 2 (1 mmol), $PdCl_2(PhCN)_2$ (0.05 mmol), $ArSn(n\text{-}Bu)_3$ (1.5 mmol), $CuCl_2$ (4 mmol), and dry ether (20 mL) was stirred under argon for the period indicated. [c] All the products, isolated by column chromatography, showed satisfactory spectral (^1H and ^{13}C NMR, IR) and analytical data (high-resolution MS). Yield refers to the isolated one for the spectroscopically homogeneous compound. No entry data signifies that the expected product could not be detected by ^1H NMR and TLC monitoring of the crude reaction mixture. [d] *N*-3-Chloro-4-[(3,4-dimethoxyphenyl)butyl]-*p*-toluenesulfonamide was obtained. [e] *cis*- and *trans*-*N*-tosyl-2-*p*-anisyl-4-methylpiperidines were obtained in 47% and 11% yields, respectively. [f] A mixture of stereoisomers was obtained. [g] See eq 3. [h] Room temperature.

Scheme I



phenyltin gives **6** specifically.[8]

We suggest that **5** and **6** may proceed through a common intermediate **9**, which is derived from a primary arylpalladation intermediate **7** via sequential elimination–addition of a hydridopalladium species (Scheme I). Interestingly no 1,2-regioisomers derived from **7** (e.g., *N*-(5-aryl-4-chloropentyl)-*p*-toluenesulfonamides or *N*-tosyl-2-(arylmethyl)pyrrolidines) were detected.[10] Finally, the formation of **5h** from 3-acetoxy-4-pentenyl-*p*-toluenesulfonamide (**2h**, eq 3) in high yield is noteworthy. Although the structural arrangement of **7** (R = OAc) is ready to undergo deacetoxypalladation,[11] the reaction still prefers to take the course of dehydropalladation to give **9**.



Acknowledgment. We are grateful for partial financial support from the Ministry of Education, Science and Culture, the Japanese Government (Grant-in-Aid for Special Project No. 60119002 and Scientific Research B No. 61470094).

(8) It is premature to discuss the distribution of the cyclized and noncyclized products. The mechanism of the $CuCl_2$-assisted Pd–C bond cleavage is still controversial,[9] and the distribution of products is rather complicated and dependent on the ring sizes to be formed. However, it may be suggested that the more stable the carbonium ion generated by heterolytic cleavage of the Pd–C bond in an intermediate **9** (Scheme I), the higher the proportion of cyclized products.

(9) Bäckvall, J.-E. *Acc. Chem. Res.* **1983**, *16*, 335.

(10) For the explanation about this point, see ref. 6.

(11) Arai, I.; Daves, F. D., Jr. *J. Am. Chem. Soc.* **1981**, *103*, 7683.

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Chirality Transfer in Stereoselective Synthesis. A Highly Stereocontrolled Synthesis of 22-Hydroxylated Steroid Side Chains via the [2,3]-Wittig Rearrangement[1]

Summary: An efficient approach toward 22-oxygenated steroid side chains has been accomplished utilizing the [2,3]-Wittig rearrangement of the dianion derived from the (*E*)-17(20)-ethylidene-16α-(carboxymethyl)oxy steroid.

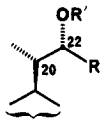
Sir: Despite the recent considerable success in the construction of steroid side chains,[2] the efficient, highly stereocontrolled synthesis of 22-hydroxylated steroids remains a formidable challenge. Interestingly, all of the known physiologically significant 22-oxygenated steroids, with the notable exception of the plant hormone brassinolides[3] (e.g., **2**), possess the C-22 configuration shown in

(1) This work was presented in part at the 190th National Meeting of the American Chemical Society, Chicago, September, 1985 (Abst ORGN 145) and at the International Symposium on Organic Chemistry of Medicinal Natural Products (IUPAC), Shanghai, November, 1985 (Abst C-50).

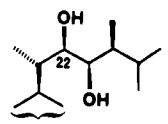
(2) Reviews: (a) Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199. (b) Redpath, B. J.; Zeelen, F. J. *Chem. Soc. Rev.* **1983**, *12*, 75. (c) Elks, J. *Nat. Prod. Rep.* **1985**, *2*, 393.

(3) Grove, M. D.; Spencer, G. F.; Rohwedder, W. K.; Mandava, N.; Worley, J. F.; Warthen, J. D., Jr.; Steffens, G. L.; Flippen-Anderson, J. L.; Cook, J. C., Jr. *Nature (London)* **1979**, *281*, 216.

0022-3263/86/1951-4090$01.50/0



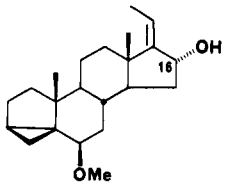
1



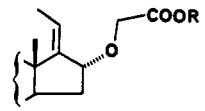
2

1. The synthesis of the C-22 structure in brassinolides (see **2**) presents no obstacles as this stereochemistry corresponds to the one produced preferentially by nucleophilic addition to the C-22 aldehyde.[4] In contrast, generation of the more prevalent C-22 hydroxy configuration (see **1**) has proven to be problematic.[5] In the following we delineate a novel, completely stereocontrolled synthesis of 22-hydroxylated steroid side chains that employs the [2,3]-Wittig rearrangement as the crucial chirality transfer step (Scheme I).

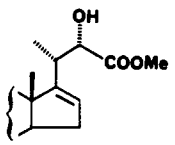
The starting allylic alcohol **3** was obtained in three steps (52%) following the literature procedure[6] from the commercially available 16α,17α-epoxypregnenolone. Treatment of **3** with ethyl diazoacetate in benzene (room tem-



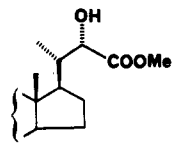
3



4 R = Et
5 R = H



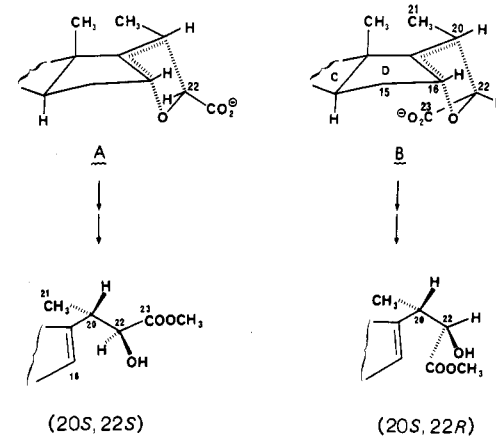
6



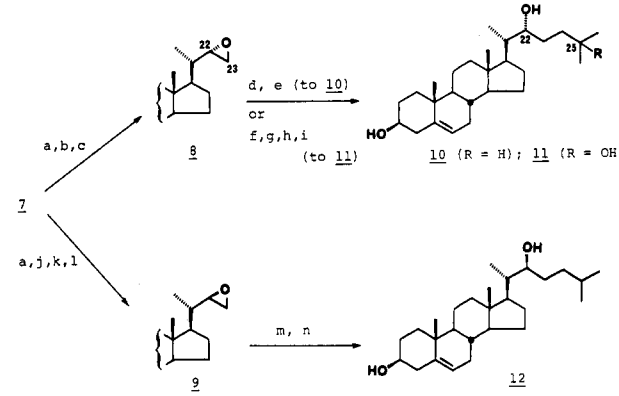
7

perature, 30 min) in the presence of a catalytic amount of $[Rh(OAc)_2]_2$[7] smoothly afforded the α-alkoxy ester **4**[8,9] (70% yield) which was subsequently hydrolyzed to the acid **5** with LiOH/MeOH–H_2O, room temperature, 20 h, in 83% yield.

Scheme I



Scheme II[a]



[a] Conditions: (a) $LiAlH_4$, Et_2O, reflux, 1 h (90%); (b) *p*-TsCl/pyr/Et_2O, room temperature, 24 h (81%); (c) NaH, Et_2O/HMPA (300:1), room temperature for 5 h, then reflux for 15 min (90%); (d) *i*-BuMgCl, CuI (cat.), THF, 0 °C, 1 h (93%); (e) *p*-TsOH, DME/H_2O (3/1), reflux, 2 h (86%); (f) $BrMgCH{=}CMe_2$, CuI (cat.), THF, 0 °C, 1 h (83%); (g) MCPBA, CH_2Cl_2, 0 °C, 2 h (85%); (h) $LiAlH_4$, Et_2O, room temperature, 10 h (93%); (i) same as e[5a] (80%); (j) pivaloyl chloride, pyr/CH_2Cl_2, DMAP (cat.), 0 °C, 24 h (91%); (k) *p*-TsCl, pyr/CH_2Cl_2, DMAP (cat.), 40 °C, 48 h (85%); (l) LiOH, dioxane/H_2O, room temperature, 8 h (92%); (m) same as d (92%); (n) same as e (85%).

The key step for the generation of the desired C-20–22 stereochemistry was effected by treating the acid **5** with 2.3 equiv of LDA in THF at –78 °C. The resulting dianion rearranged sluggishly at –78 °C, but upon warming to –56 °C a clean rearrangement reaction took place within 2 h. Aqueous quenching followed by esterification with CH_2N_2 gave rise to the α-hydroxy ester **6**[10] in 85% overall yield. Careful analysis of the crude reaction mixture with high-field ^1H (300 MHz) and ^{13}C (90.56 MHz) NMR revealed the virtual absence (i.e., less than 2%) of other C-20 and/or C-22 stereoisomers. The remarkably high diastereoselectivity observed for this [2,3]-Wittig rearrangement of the dianion of **5** is in sharp contrast to the meager stereoselectivity reported for the same reaction with the (*E*)-crotyl alcohol system.[11] In view of existing uncertainties regarding the exact transition-state structure for the

(4) (a) Fung, S.; Siddall, J. B. *J. Am. Chem. Soc.* **1980**, *102*, 6580. (b) Ishiguro, M.; Takatsuto, S.; Morisaki, M.; Ikedawa, N. *J. Chem. Soc., Chem. Commun.* **1980**, 962. (c) Mori, K.; Sakakibara, M.; Ichikawa, Y.; Ueda, H.; Okada, K.; Umemura, T.; Yabuta, G.; Kuwahara, S.; Kondo, M.; Minobe, M.; Sogabe, A. *Tetrahedron* **1982**, *38*, 2099. (d) Hayami, H.; Sato, M.; Kanemoto, S.; Morizawa, Y.; Oshima, K.; Nozaki, H. *J. Am. Chem. Soc.* **1983**, *105*, 4491. (e) Donaubauer, J. R.; Greaves, A. M.; McMorris, T. C. *J. Org. Chem.* **1984**, *49*, 2834. (f) Koreeda, M.; Tanaka, Y. *Tetrahedron Lett.*, in press.

(5) Several stereocontrolled syntheses of 22-hydroxylated steroid side chains have been reported: (a) Trost, B. M.; Matsumura, Y. *J. Org. Chem.* **1977**, *42*, 2036. (b) Midland, M. M.; Kwon, Y. C. *J. Am. Chem. Soc.* **1983**, *105*, 3725. (c) Midland, M. M.; Kwon, Y. C. *Tetrahedron Lett.* **1984**, *25*, 5981. (d) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1985**, *107*, 2138.

(6) (a) Tanabe, M.; Hayashi, K. *J. Am. Chem. Soc.* **1980**, *102*, 862. (b) Koreeda, M.; Tanaka, Y.; Schwartz, A. *J. Org. Chem.* **1980**, *45*, 1172.

(7) Paulissen, R.; Reimlinger, H.; Hayez, E.; Hubert, A. J.; Teyssié, Ph. *Tetrahedron Lett.* **1973**, 2233.

(8) Compounds 4–9 possess the same A–C ring structures as indicated in **3**.

(9) For **4**: 300-MHz ^1H NMR ($CDCl_3$) δ 0.448 (dd, 1 H, J = 5.1, 8.0 Hz), 0.664 (dd, 1 H, J = 3.9, 5.1 Hz), 0.922 (s, 3 H), 1.035 (s, 3 H), 1.296 (t, 3 H, J = 7.1 Hz), 1.756 (dd, 3 H, J = 1.0, 7.3 Hz), 2.238 (ddd, 1 H, J = 3.0, 3.5, 12.3 Hz), 2.801 (br d, 1 H, J = 2.6, 2.6 Hz), 3.342 (s, 3 H), 4.021 and 4.123 (AB q, 2 H, J_{AB} = 16.5 Hz), 4.216 (q, 2 H, J = 7.1 Hz; overlapped with another H (~4.2 ppm)), 5.761 (dq, 1 H, J = 1.3 for d, 7.3 Hz for q); 90.56-MHz ^{13}C NMR ($CDCl_3$) δ 13.21, 13.32, 18.03, 19.19, 21.44, 22.80, 24.99, 29.60, 31.42, 33.40, 35.17, 35.30, 37.42, 43.54, 44.37, 48.10, 51.57, 52.87, 56.60, 65.95, 77.39, 82.40, 82.83, 121.33, 150.49, 171.37.

(10) For **6**: 300-MHz ^1H NMR ($CDCl_3$) δ 0.450 (dd, 1 H, J = 5.1, 8.0 Hz), 0.663 (dd, 1 H, J = 3.8, 5.1 Hz), 0.780 (s, 3 H), 1.051 (s, 3 H), 1.156 (d, 3 H, J = 7.1 Hz), 2.602 (br dq, 1 H, J = 5.2 for d, 7.1 for q), 2.797 (br dd, 1 H, J = 2.6, 2.6 Hz), 3.343 (s, 3 H), 3.739 (s, 3 H), 4.225 (d, 1 H, J = 5.2 Hz), 5.632 (br s, 1 H); 90.56-MHz ^{13}C NMR ($CDCl_3$) δ 13.15, 16.34, 18.64, 19.24, 21.52, 22.46, 24.96, 29.25, 31.41, 33.24, 35.15, 35.42, 35.57, 36.70, 43.69, 47.63, 48.72, 51.97, 56.57, 57.24, 74.87, 82.43, 124.56, 155.74, 174.50.

(11) (a) Nakai, T.; Mikami, K.; Taya, S.; Kimura, Y.; Mimura, T. *Tetrahedron Lett.* **1981**, *22*, 69. (b) Mikami, K.; Fujimoto, K.; Nakai, T. *Ibid.* **1983**, *24*, 513.

[2,3]-Wittig rearrangement in general,[12] this marked difference in stereoselectivity may not be readily accountable. However, if one adopts a Rautenstrauch-type transition-state structure[13] for this reaction, it becomes immediately apparent that transition state B (Scheme II) having the quasi-axial 23-carboxylate should be considerably disfavored relative to A. Furthermore, in transition state B, there must exist the additional unfavorable steric repulsion between this metalated (and possibly solvated) carboxylate and the rigid steroid C/D ring unit. Therefore, it may be reasonable to speculate that this additional steric factor makes transition state A even more favored, accounting for the complete stereochemical control in the present case. Interestingly, the monoanion generated from the ester **4** produced a mixture of several products.

The α-hydroxy ester **6** was next reduced (H_2, PtO_2, EtOAc, 10 h; 97%) to **7** which was further converted into the known epoxides **8**[14] and **9**[15] (Scheme II), identical with authentic samples prepared following the literature procedure.[5a] These epoxides were further converted into (22*R*)-22-hydroxycholesterol (**10**)[16] (a key biosynthetic intermediate from cholesterol to pregnenolone), (22*S*)-22-hydroxycholesterol (**12**),[16] and the α-ecdysone (insect and crustacean molting hormone) side chain **11**[5a] (Scheme II).

The approach described herein, invoking the concerted, highly ordered nature of the [2,3]-Wittig rearrangement reaction, cleanly establishes in one step the stereochemistry at both C-20 and C-22 of the 22-hydroxylated steroid side chains. The product thus obtained (**6**) serves as a highly versatile intermediate for the synthesis of many 22-oxygenated steroids.[17]

Acknowledgment. We are grateful to the National Institutes of Health (Grant No. DK30025) for the support of this research and to the National Science Foundation of its contribution to the purchase of a Bruker 300-MHz NMR spectrometer.

(12) Reviews: (a) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 563. (b) Hill, R. K. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 8. (c) Nakai, T.; Mikami, K.; Sayo, N. *J. Synth. Org. Chem. Jpn.* **1983**, *41*, 100.

(13) Rautenstrauch, V. *J. Chem. Soc. D* **1970**, 4. See also: Tsai, D. J.-S.; Midland, M. M. *J. Org. Chem.* **1984**, *49*, 1843.

(14) For **8**: 300-MHz ^{1}H NMR ($CDCl_3$) δ 0.439 (dd, 1 H, J = 5.1, 7.9 Hz), 0.648 (dd, 1 H, J = 3.9, 5.1 Hz), 0.720 (s, 3 H), 0.960 (d, 3 H, J = 6.5 Hz), 1.025 (s, 3 H), 2.407 (dd, 1 H, J = 2.8, 5.0 Hz), 2.663 (dd, 1 H, J = 4.1, 5.0 Hz), 2.742 (m, 1 H), 2.773 (br dd, 1 H, J = 2.6, 2.8 Hz), 3.323 (s, 3 H); 90.56-MHz ^{13}C NMR ($CDCl_3$) δ 12.47, 13.15, 15.56, 19.31, 21.64, 22.84, 24.49, 25.06, 27.08, 30.61, 33.51, 35.19, 35.53, 38.49, 40.29, 43.22, 43.52, 44.62, 48.32, 56.30 (×2), 56.55, 57.02, 82.50.

(15) For **9**: 300-MHz ^{1}H NMR ($CDCl_3$) δ 0.440 (dd, 1 H, J = 5.1, 8.2 Hz), 0.656 (dd, 1 H, J = 4.0, 5.1 Hz), 0.708 (s, 3 H), 1.026 (s, 3 H), 1.13 (diffused d, 3 H), 2.595 (dd, 1 H, J = 2.8, 4.9 Hz), 2.63 (m, 1 H), 2.777 (br dd, 1 H, J = 2.7, 2.7 Hz), 2.800 (dd, 1 H, J = 4.9, 5.0 Hz), 3.329 (s, 3 H); 90.56-MHz ^{13}C NMR ($CDCl_3$) δ 12.47, 13.21, 16.89, 19.30, 21.64, 22.84, 24.39, 25.07, 27.37, 30.71, 33.55, 35.32, 35.51, 39.51, 40.26, 43.20, 43.58, 48.35, 48.90, 54.37, 56.33, 56.60, 57.36, 82.55.

(16) Teicher, B. A.; Koizumi, N.; Koreeda, M.; Shikita, M.; Talalay, P. *Eur. J. Biochem.* **1978**, *91*, 11.

(17) After completion of this work, we learned that Nakai and his co-workers developed a stereocontrolled synthesis of 22-hydroxy-23-acetylenic steroid side chains employing a similar [2,3]-Wittig rearrangement strategy: Mikami, K.; Kawamoto, K.; Nakai, T. *Tetrahedron Lett.* **1985**, *26*, 5799.

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Additions and Corrections

Klaus Eckart, Helmut Schwarz,* Günther Becker, and Horst Kessler*. Monitoring and Optimization of Deprotection Reactions of Peptides by Direct Sampling with Fast Atom Bombardment Mass Spectrometry.

Page 485. Table I is missing reaction number 17. The peptide for reaction number 17 is also the peptide for 18 and 19. This section of the table is shown below.

Table I. List of the Deprotection Reactions Studied

peptide	reaction number	am, mg/μmol	reacn conditions[i]	T_R,[h] min	results
(Bzl) / Boc-Tyr-O / c[(D)Ser-Gly-Gly-Phe-Leu]	17	0.8/1.0	HBr/HOAc;[f] 10 μL; RT	60	complete removal of protecting groups but partly acetylation of Tyr and elimination of TyrOH with generation of the dehydro-alanine-cyclopentapeptide
	18	0.2/0.3	HBr/HOAc;[g] 1 μL; RT	180	complete removal, only small traces of the side products found in reaction 17
	19	0.5/0.6	100% Pd/C;[d] 20 μL solvent[e]	540	almost complete deprotection within 30 min, no acetylation, after prolonged reaction small traces of the dehydro-alanine-cyclopentapeptide and further of the alanine-cyclopeptide from the side reaction described in reaction 17