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STEREOCONTROLLED SYNTHESIS OF EITHER (22S)- OR (22R)-HYDROXY-23-ACETYLENIC STEROID SIDE CHAINS VIA [2,3]-WITTIG SIGMATROPIC REARRANGEMENT

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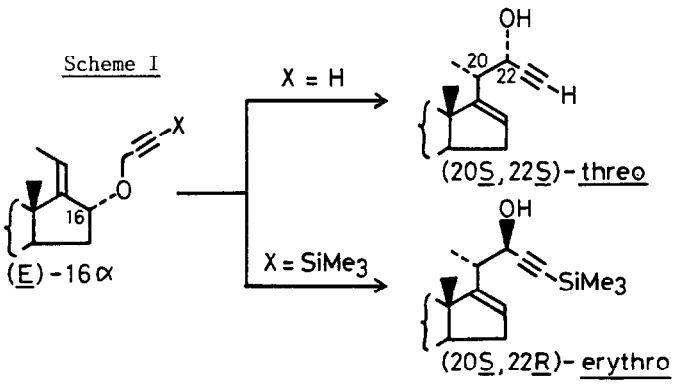
SUMMARY: A unified approach to either (22S)- or (22R)-hydroxy-23-acetylenic steroid side chains is described which relies on the concept of the stereochemical transmission via the [2,3]-Wittig sigmatropic rearrangement.

Recently considerable attention has been focused on the development of methodology for the stereocontrolled synthesis of steroid side chains, particularly the 22-hydroxylated side chains that appear in the insect hormone ecdysones and the plant growth regulator brassinolides.[1,2] We now report a new strategy for the stereocontrolled synthesis of either (22S)- or (22R)-hydroxy-23-acetylenic steroid side chains which relies on the concept of the stereochemical transmission via the [2,3]-Wittig sigmatropic rearrangement.[3] The most significant feature in this strategy is that the readily available C-16α chirality is specifically transmitted to the two new chiral centers at C-20 and C-22 with a high degree of either threo or erythro selectivity, depending on the absence or the presence of the silyl group (Scheme I).

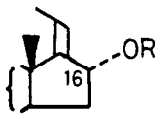
Scheme I



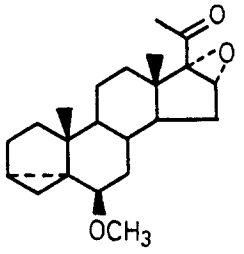
The key starting allylic alcohol (2) was obtained from the 3α, 5α-cyclo ether derivative (1) of the commercially available 16α, 17α-epoxypregnenolone according to the literature

procedure.[4] The propargyl ether 3 was prepared in 83% yield by phase-transfer reaction of 2 with propargyl bromide (n-Bu_4NHSO_4, aq. NaOH). Silylation of 3 (n-BuLi, Me_3SiCl, THF) afforded the silylated ether 4 in 91% yield.

The α-face [2,3]-Wittig process of 3 and 4 leading inherently to the "natural" 20S/β chirality[5] was carried out under the standard conditions[6] [n-BuLi (2.2 equiv for 3 and 1.2 equiv for 4), THF, -78 °C]. The dianion rearrangement of 3 was found to afford in 75% isolated yield the rearranged (22S)-product 5 as a single stereoisomer.[7] In sharp contrast, the monoanion rearrangement of 4 exhibited the changeover in configuration at C-22 to result in the quantitative formation of (22R)-product 6,[8] which was converted to the (22R)-epimer 7[7] via protiodesilylation (n-Bu_4NF, aq. THF). The two epimers 5 and 7 are clearly distinguishable by TLC and NMR analysis;[7,9] The most definitive distinguishing features are the R_f-value on TLC and the 22-H NMR signal: for 5, R_f=0.14; δ 4.39 (dd, J=8.4 and 2.4 Hz) and for 7, R_f=0.17; δ 4.44 (dd, J=6.0 and 2.4 Hz).



2, R = H
3, R = $CH_2C{\equiv}CH$
4, R = $CH_2C{\equiv}CSiMe_3$



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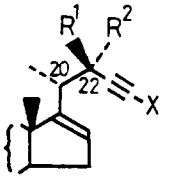
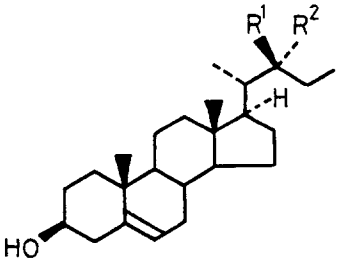
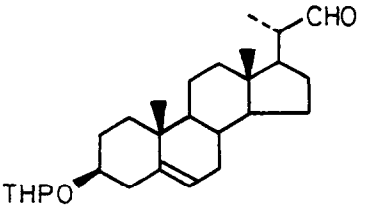


5, R^1 = H, R^2 = OH, X = H
6, R^1 = OH, R^2 = H, X = $SiMe_3$
7, R^1 = OH, R^2 = H, X = H



8, R^1 = H, R^2 = OH
9, R^1 = OH, R^2 = H



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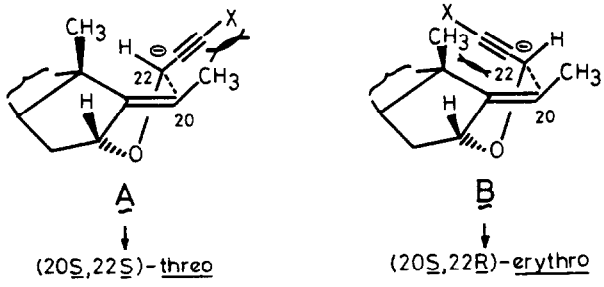
The (22S)-threo configuration of 5 was assigned by its conversion to the known compound 8. Thus, the α-face hydrogenation of 5 (H_2, PtO_2, MeOH) followed by deprotection of the cyclo ether linkage (p-TsOH, aq. dioxane) afforded 70% yield of the (22R)-diol 8 with the desired 17R chirality. The diol 8 was, in turn, identical on TLC[10] with the minor (22R)-threo isomer obtained from the (20S)-aldehyde 10 via the reaction with ethylmagnesium bromide[11], thereby confirming the (20S,22S)-configuration of 5. Likewise, the side chain stereochemistry of 7 was assigned to (20S, 22R)-erythro. Thus, either C-22 epimeric product is now available from the single alcohol precursor 2.

Particularly noteworthy is the dramatic changeover in diastereoselection observed by the introduction of the silyl group. We suggest that the dianion rearrangement of 3 proceeds preferentially via the envelope transition state A (X=Li) as expected, since conformer B (X=Li) suffers a large pseudo-1,3-diaxial interaction of the ethynyl moiety with the existing cyclopentane ring.[12] On the other hand, the unusual erythro-selection of the rearrangement of 4 may well reflect the special situation that the introduction of the silyl group would greatly enhance the gauche interaction between the ethynyl and 20-methyl group in A (X=$SiMe_3$) which prevails over the 1,3-repulsion in B (X=$SiMe_3$).[13]



In conclusion, this work has convincingly demonstrated the utility of our [2,3]-Wittig strategy as an efficient and highly stereoselective entry to either (22S)- or (22R)-hydroxy-23-acetylenic steroid side chains[14] from the single precursor. The rearrangement products can undoubtedly serve as key intermediates for the synthesis of many important side-chain modified steroids; e.g., the (22S)-epimer 5 could be converted to ecdysones by the known procedures[15] and the (22R)-epimer 6 could serve as a key brassinolide intermediate.[16] More generally, this strategy can be envisioned as a unique approach to attach an acyclic side chain in a stereocontrolled fashion onto a ring system. The applications of our strategy to natural products synthesis will be the subjects of future reports from these laboratories.

REFERENCES AND NOTES

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(2) For a list of more recent works in this area, see: Schmuff, N. R.; Trost, B. M. J. Org. Chem. 1983, 48, 1404.

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(5) For [3,3]-sigmatropic rearrangements from the α-face leading to "natural" 20R/β-chirality, see: ref. 4; Koreeda, M.; Tanaka, Y.; Schwartz, A. J. Org. Chem. 1980, 45, 1172; Mikami, K.; Kawamoto, K.; Nakai, T. Chem. Lett. 1985, 115.

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(7) 5: NMR ($CDCl_3$) δ 0.30-0.67 (cyclopropyl 3H), 0.94 (Me-18), 1.12 (Me-19), 1.23 (d, J=6.9 Hz, Me-21), 2.49 (d, J=2.4 Hz, 24-H), 2.80 (m, 6-H), 3.37 (OMe), 4.39 (dd, J=8.4 and 2.4 Hz, 22-H), 5.57 (m, 16-H). 7: NMR ($CDCl_3$) δ 0.30-0.67 (cyclopropyl 3H), 0.90 (Me-18), 1.07 (Me-19), 1.18 (d, J=6.9 Hz, Me-21), 2.42 (d, J=2.4 Hz, 24-H), 2.79 (m, 6-H), 3.37 (OMe), 4.44 (dd, J=6.0 and 2.4 Hz, 22-H), 5.71 (m, 1H, 16-H).

(8) 6: NMR ($CDCl_3$) δ 0.30-0.67 (cyclopropyl 3H), 0.93 (Me-18), 1.13 (Me-19), 1.20 (d, J=6.9 Hz, Me-21), 2.83 (t, J=3.0 Hz, 6-H), 3.38 (OMe), 4.40 (d, J=6.3 Hz, 22-H), 5.64 (m, 16-H).

(9) TLC analysis was made on a 5715 DC-Fertigplatten Kieselgel $60F_{254}$ (Merck Co.) using hexane-ethyl acetate (5 : 1) as an eluent.

(10) Five times developed TLC (5-cm length of a 5554 DC-Alufolien Kieselgel $60F_{254}$ purchased from Merck Co.): R_f=0.20 for 22S-alcohol 9 and 0.33 for 22R-alcohol 8. It should be noted that the R,S convension changes on going from 5 to 8 beacause of the change in priority upon saturation of the triple bond.

(11) Earlier work has established that the Grignard reaction of (20S)-aldehydes with "saturated" alkylmagnesium halides afford the (22S)-alcohol as the major diastereomer [Poyser, J. P.; Ourisson, G. J. Chem. Soc., Perkin Trans. 1 1974, 2061].

(12) For a general discussion of the transition-state model for acyclic [2,3]-Wittig process: Mikami, K.; Kimura, Y.; Kishi, N.; Nakai, T. J. Org. Chem. 1983, 48, 279.

(13) A similar changeover by the introduction of the silyl group has been reported for the [2,3]-Wittig shift of (E)-crotyl propargyl ether system, although the degree is much lower (cf. ref 6).

(14) 22-Hydroxy-23-acetylenic steroids have often been used as key intermediates in side chain construction (ref.1); Quite recently, the stereoselective synthesis of either (22R)- and (22S)-isomer has been reported using R-Alpine-Borane and L-selectride to reduce 22-keto steroid: Midland, M. M.; Kwon, Y. C. Tetrahedron Lett. 1984, 25, 5981.

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