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APPLICATION OF [2,3]WITTIG REARRANGEMENT IN STEROID SIDE CHAIN SYNTHESIS. A NEW ENTRY TO (22R)-HYDROXY-23-ACETYLENIC SIDE CHAINS VIA THE β-FACE REARRANGEMENT

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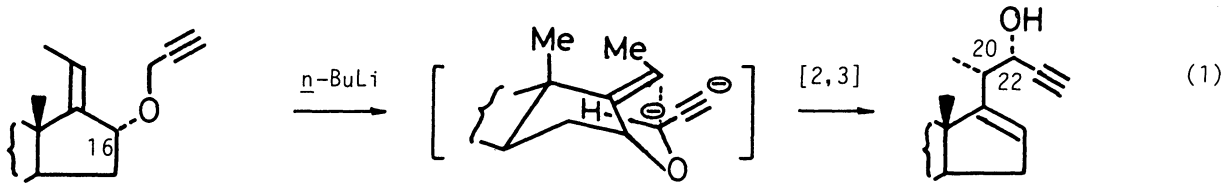
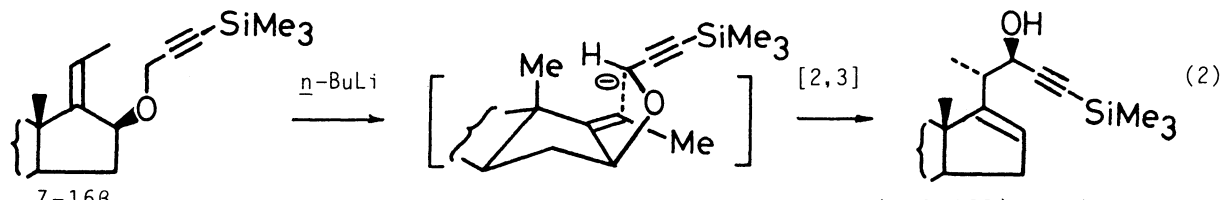
A new entry to (22R)-hydroxy-23-acetylenic steroid side chains is described which relies on the concept of chirality transfer via the unprecedented β-face [2,3]Wittig process. The key feature is that the C-16β chirality is completely transmitted to the two new chiral centers at C-20 and C-22 with a high erythro-selectivity.

Recently considerable attention has been focused on 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] Recently we have reported a highly stereocontrolled synthesis of (22S)-hydroxy-23-acetylenic side chain (ecdysone-type) by employing the concept of the stereochemical transmission[2] via the α-face [2,3]Wittig variant with a high threo-selectivity (Eq. 1).[3] In view of the well-defined stereochemistry of the [2,3]Wittig process of Z-crotyl (γ-trimethylsilyl)propargyl ether,[4] on the other hand, we reasoned that a similar rearrangement of Z-$\Delta^{17(20)}$-16β-(γ-trimethylsilyl)propargyloxy steroid should proceed with complete chirality transfer on the β-face and a high erythro-selectivity, resulting in access to the (22R)-hydroxy-23-acetylenic side chain (brassinolide-type)[5] (Eq. 2). The keys to this idea are the accessibility of the starting Z-16β-alcohol and, more crucially, the feasibility of the sigmatropic shift on the sterically more congested β-face.[6] Disclosed herein is the realization of this strategy which offers the first success in the β-face [2,3]Wittig rearrangement.



E-16α (1)

(20S, 22S)-threo



Z-16β (2)

(20S,22R)-erythro

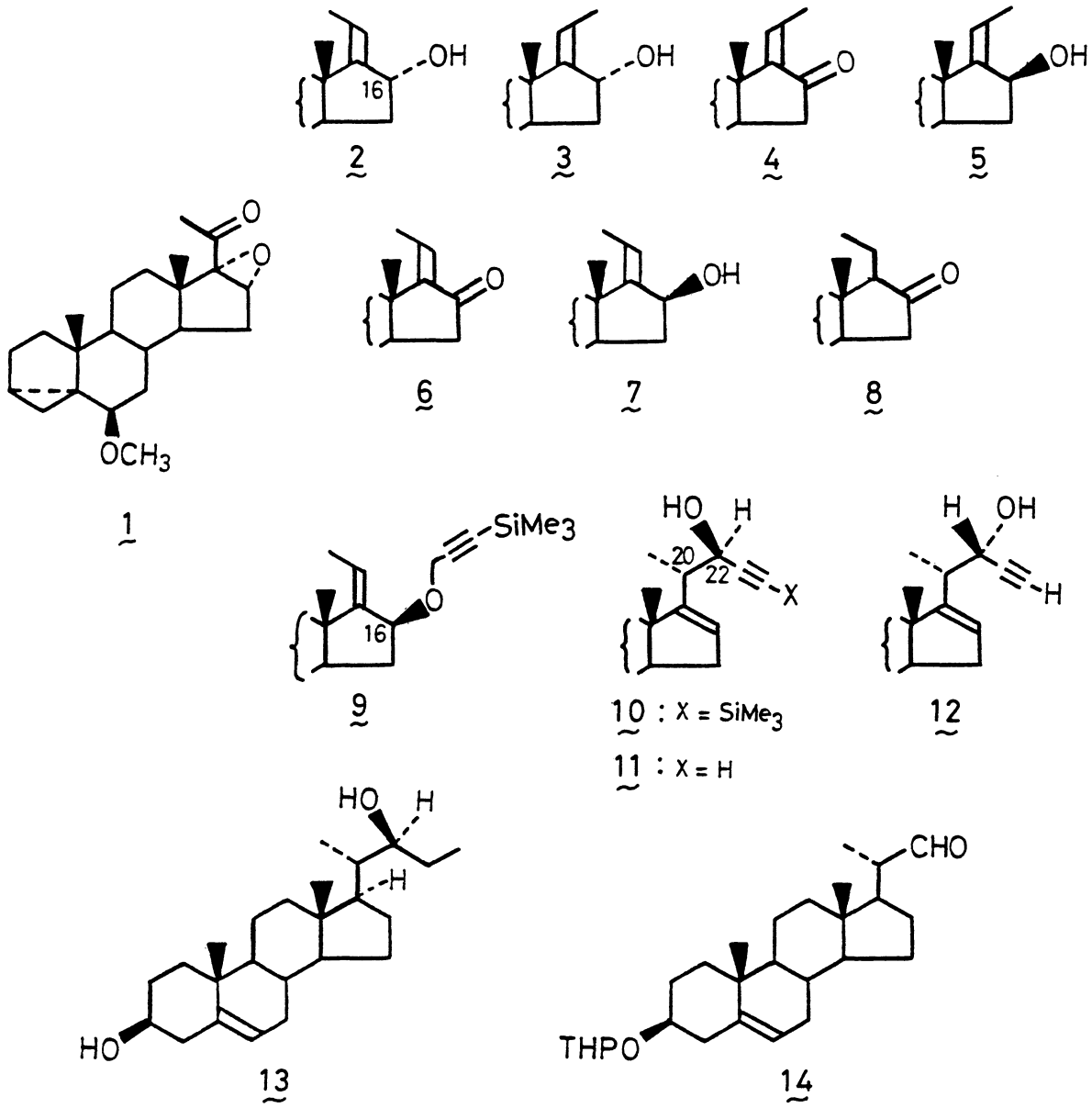
At the outset, our effort was directed to the stereocontrolled preparation of the requisite Z-16β-alcohol (5) starting with the E-16α-alcohol (2) readily derived from the 3α, 5α-cyclo ether derivative (1) of the commercially available 16α, 17α-epoxypregnenolone.[7] The geometrical isomerization of 2 was best carried out under the free radical condition.[8] Thus, 2 was refluxed in benzene for 45 min[9] in the presence of benzenethiol (2 equiv.) and azobisisobutyronitrile (a catalytic amount) to give a Z-rich mixture containing 2 (18%) and the saturated ketone (8) (8%). Column chromatographic purification of the mixture afforded the Z-16α-alcohol (3) in 63% yield. Interestingly enough, similar isomerizations of the E-enone (6) and the E-16β-alcohol (7) which are easily derived from 2[6a] gave unsatisfactory results; the former gave a 1 : 1 mixture of 4 and 6, whereas the latter resulted in the exclusive formation of the ketone (8). The Z-16α-alcohol (3) thus obtained was oxidized with activated manganese dioxide to give quantitatively the Z-enone (4) which was then reduced with lithium aluminum hydride to give in 92% yield the desired Z-16β-alcohol (5) as a single stereoisomer.[10] Etherification with propargyl bromide (KOH/n-Bu_4NI, aq. CH_3CN) followed by silylation (n-BuLi, Me_3SiCl, THF) afforded the requisite ether 9 in 91% yield.[11]

The crucial carbanion rearrangement of 9 was carried out under the standard conditions [n-BuLi (1.2 equiv.), THF, -78 °C].[4] Very fortunately, we found that the β-face rearrangement proceeded quite smoothly[12] to afford in 85% isolated yield the [2,3]-rearranged product (10) as a single stereoisomer.[13] Protodesilylation of 10 (n-Bu_4NF, aq. THF) gave the (20S, 22R)-alcohol (11) which was clearly distinguished from the (20S, 22S)-isomer (12)[3] by TLC[14] and NMR analysis (300 MHz). The most definitive distinguishing features are the R_f-value on TLC and the 22-H NMR signal: for 11, R_f= 0.17; δ 4.44 (dd, J=6.0 and 2.4 Hz) and for 12, R_f= 0.14; δ 4.39 (dd, J=8.4 and 2.4 Hz).

The (20S, 22R)-erythro configuration of 11 was confirmed by its conversion to the known compound 13. Thus, the hydrogenation of 11 (H_2, PtO_2, MeOH) followed by deprotection of the cyclo ether linkage (p-TsOH, aq. dioxane) afforded the diol 13 with the desired 17R chirality in 70% yield. The diol 13 was identical on TLC with the (20S, 22S)-erythro isomer[15] which was independently obtained as the major stereoisomer via the reaction of the 20S-aldehyde (14) with ethylmagnesium bromide,[16] thereby confirming the (20S, 22R) stereochemistry of 11.

In conclusion, this work has demonstrated for the first time that the [2,3]Wittig rearrangement is also feasible even on the sterically congested β-face within the context of the synthesis of (22R)-hydroxy-23-acetylenic steroid side chain. Undoubtedly the rearrangement product 11 could serve as a key intermediate for brassinolide synthesis.[17] Further application of our [2,3]Wittig strategy to steroid side chain synthesis is in progress in our laboratory.

The authors thank Prof. N. Ikekawa and Dr. Y. Fujimoto for providing an authentic mixture of derivatives of 13 and its (22R)-epimer. We are also grateful to Mr. K. Kushida (Analytica Corp.) for the 300-MHz NMR measurement. This work was generously supported in part by the Grant-in-Aid for Special Project Research from Ministry of Education, Science and Culture, Japan.



References

1) For recent reviews, see: D. M. Piatak and J. Wicha, Chem. Rev., 78, 199 (1978); J. Redpath and F. J. Zeelen, Chem. Soc. Rev., 12, 75 (1983).

2) N. Sayo, K. Azuma, K. Mikami, and T. Nakai, Tetrahedron Lett., 25, 565 (1984); D. J.-S. Tsai and M. M. Midland, J. Org. Chem., 49, 1842 (1984).

3) K. Mikami, N. Sayo, and T. Nakai, 46th National Meeting of the Chemical Society of Japan, Kyoto, April 1983, Abstr. No. 4E14: Submitted for publication.

4) K. Mikami, K. Azuma, and T. Nakai, Tetrahedron, 40, 2303 (1984).

5) The side chain of brassinolide possesses the absolute configuration of 20S (CH_3), 22R (OH), 23R (OH), and 24S (CH_3).
6) To our best knowledge, only two reports dealing with β-face sigmatropic shifts have appeared so far: a) [3,3]Claisen rearrangement: K. Mikami, K. Kawamoto, and T. Nakai, Chem. Lett., 1985, 115; b) Mislow-Evans [2,3]-rearrangement: B. M. Trost and N. R. Schmuff, J. Am. Chem. Soc., 107, 396 (1985). However, the [2,3]-shift has been shown to proceed with great difficulty to afford only 26% yield of the rearranged sulfoxide.
7) M. Tanabe and K. Hayashi, J. Am. Chem. Soc., 102, 862 (1980).
8) P. E. Sonnet, Tetrahedron, 36, 557 (1980), and references therein.
9) Prolonged isomerization led to an increased formation of the undesired ketone (8), although the Z/E ratio was increased. For example, the reaction for 90 min afforded a mixture containing of 2 (7%), 3 (68%), and 8 (25%).
10) 5: NMR ($CDCl_3$) δ 0.30-0.67 (cyclopropyl 3H), 0.97 (Me-18), 1.04 (Me-19), 1.74 (d, J=6.9 Hz, Me-21), 2.77 (t, J=3.0 Hz, 6-H), 3.33 (OMe), 4.72 (t, J=6.6 Hz, 16-H), 5.29 (q, J=6.9 Hz, 20-H).
11) 9: NMR ($CDCl_3$) δ 0.30-0.67 (cyclopropyl 3H), 0.83 (Me-18), 0.97 (Me-19), 1.63 (d, J=6.9 Hz, Me-21), 2.65 (m, 6-H), 3.19 (OMe), 4.06 (d, J=4.2 Hz, CH_2-≡), 4.57 (t, J=6.9 Hz, 16-H), 5.23 (q, J=6.9 Hz, 20-H).
12) It should be noted that a similar but dianion rearrangement of the Z-16β-propargyloxy counterpart (without the silyl group) did not proceed under the same conditions.
13) 10: 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).
14) TLC analysis was made on a 5715 DC-Fertigplatten Kieselgel $60F_{254}$ (Merck Co.) using hexane-ethyl acetate (5 : 1) as an eluent.
15) Five times developed TLC: R_f=0.20 for (22S)-alcohol 13 and 0.33 for its 22R-epimer. It should be noted that the R,S convension changes on going from 11 to 13 because of the change in priority upon saturation of the triple bond.
16) It has been well-established that the Grignard reactions of (20S)-aldehydes with "saturated" alkylmagnesium halides afford the (22S)-alcohol as the major diastereomer: J. P. Poyser and G. Ourisson, J. Chem. Soc., Perkin Trans. 1, 1974, 2061.
17) H. Hayami, M. Sato, S. Kanemoto, Y. Morizawa, K. Oshima, and H. Nozaki, J. Am. Chem. Soc., 105, 4491 (1983).

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