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(2,3)-WITTIG SIGMATROPIC REARRANGEMENTS IN STEROID SYNTHESIS. NEW STEREOCONTROLLED APPROACH TO STEROIDAL SIDE CHAINS AT C-20

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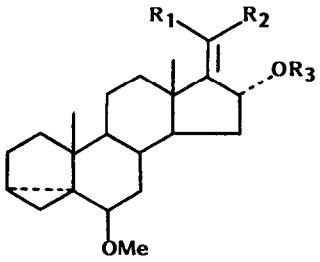
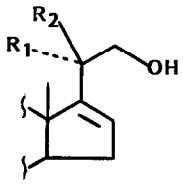
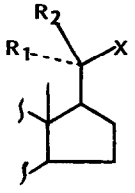
Summary: A new method which is based on (2,3)-Wittig sigmatropic rearrangements for the stereocontrolled synthesis of functionalized three-carbon side chains on the basic tetracyclic steroidal system is described.

Claisen type rearrangements have been successfully used for the stereocontrolled introduction of steroidal side chains.[1] We wish to report here an efficient and closely related alternative that relies on a primary α-oxycarbanion-induced (2,3)-Wittig sigmatropic rearrangement as the key step for the stereospecific synthesis of three-carbon side chains suitably functionalized for further elaborations. This reaction, which generally shows high stereoselectivity for Z-trisubstituted olefins in acyclic systems through a pseudoaxially substituted 5-member transition state, remains largely unexplored in rigid systems.[2]







1a, R_1=Me, R_2=H, R_3=H
1b, R_1=H, R_2=Me, R_3=H
1c, R_1=Me, R_2=H, R_3=CH_2SnBu_3
1d, R_1=H, R_2=Me, R_3=CH_2SnBu_3

2a, R_1=Me, R_2=H
2b, R_1=H, R_2=Me

3a, R_1=Me, R_2=H, X=CH_2OH
3b, R_1=H, R_2=Me, X=CH_2OH
3c, R_1=Me, R_2=H, X=CHO
3d, R_1=H, R_2=Me, X=CHO

The starting materials for this study are the known compounds 1a and 1b.[1a] These compounds were separately converted (in 89% and 85% yield) to the stannyl ether derivatives 1c and 1d[3] respectively by reaction with potassium hydride (1.5 equiv, THF, RT, 3h) followed by the addition of iodomethyltributyltin[4] (1 equiv, RT, 1h) and flash chromatography (EtOAc/hexanes).[5] Treatment of a THF solution of stannyl derivative 1c at -78 ºC with 1.1 equiv of n-butyllithium followed by stirring for 15 min afforded, after quenching with methanol at the same temperature, removal of solvents, extractive work-up (ether) and flash chromatography (EtOAc/hexanes), the homoallylic 20S-alcohol 2a (colourless oil, natural stereochemistry) in 83% yield. Under similar conditions, the n-butyllithium-induced rearrangement on 1d afforded homoallylic 20R-alcohol 2b (colourless oil, unnatural stereochemistry) in 70% yield. Neither 2a nor 2b showed cross contamination to any detectable extent on the basis of an examination of their NMR spectra[6] and TLC. Alternatively, we were able to obtain compounds 2a and 2b separately in 85% and 65% yield respectively in one pot reaction from 1a and 1b following a similar protocol and without isolating the corresponding stannyl intermediates 1c and 1d.

In order to prove the structures of the synthesized homoallylic alcohols, especially their respective configurations at C-20, the two compounds were separately hydrogenated (5% Pd-C, EtOAc, 10 PSI, 5h) to give 3a and 3b in 92% and 85% yield respectively. These synthetic alcohols were identical in all respects (250 MHz ^{1}H-NMR, 62.83% MHz ^{13}C-NMR, IR, mass spectra and TLC) with authentic samples prepared by sodium borohydride reduction on aldehydes 3c and 3d.[7]

To summarize, these results provide a remarkably simple method for stereocontrolled synthesis of steroidal C-20 stereochemistries via (2,3)-Wittig sigmatropic rearrangements under mild conditions. The synthesized alcohols and other related analogues should be of considerable value in a wide variety of transformations in the steroid field including seco-steroids. Applications of (2,3)-Wittig type sigmatropic rearrangements to the synthesis of vitamin D metabolite side chains[8] are in progress.

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References and Notes

1. (a) M. Tanabe and K. Hayashi, J. Am. Chem. Soc., 102, 862 (1980); (b) K. Mikami, K. Kawamoto and T. Nakai, Chem. Lett., 115 (1985). For general reviews on the synthesis of steroidal side chains see: c) D.M. Piatak and J. Wicha. Chem. Rev., 78, 199 (1978); (d) J. Redpath and F. Zeelen, Chem. Soc. Rev., 12, 75 (1983).

2. (a) R.W. Hoffmann, Angew. Chem., Int. Ed. Engl., 18, 563 (1979); (b) W.C. Still and A. Mitra, J. Am. Chem. Soc., 100, 1927 (1978); (c) W.C. Still, J.H. McDonald, D.B. Collum and A. Mitra, Tetrahedron Lett., 593 (1979); (d) D.G. Farnum and T. Monego, Tetrahedron Lett., 24, 1361 (1983).

3. ^{1}H-NMR (250 MHz, $CDCl_3$, δ), 1c: 5.49 (1H, dq, J=7.3 Hz, C=CH), 3.88-3.84 (1H, m, CHOR), 3.7 (2H, ABq, J=10.6 Hz, J=33.7 Hz, OCH_2Sn), 1.72 (3H, dd, J=1.2 Hz, J=7.3 Hz, C_{21}-CH_3); 1d: 5.28 (1H, dq, J=1.9 Hz, J=6.8 Hz, C=CH), 4.25-4.10 (1H, m, CHOR), 3.65 (2H, ABq, J=10 Hz, J=60 Hz, OCH_2Sn), 1.66 (3H, dd, J=0.9 Hz, J=6.8 Hz, C_{21}-CH_3).

4. Reagent prepared as per D. Seyferth and S.B. Andrews, J. Organometal. Chem., 30, 151 (1971).

5. For previous use of this methodology, see ref. 2b.

6. 2a, ^{1}H-NMR, significant signals: 5.44 (1H, m, CH=CH), 3.65-3.50 (3H, m, CH_2OH), 1.04 (3H, d, J=7.0 Hz, C_{21}-CH_3), 0.86 (3H, s, C_{18}-CH_3). ^{13}C-NMR (62.83 MHz, $CDCl_3$,δ): 157.9; 122.8; 82.3; 66.5; 57.4; 56.6; 48.6; 47.2; 43.5; 35.4; 35.2; 35.1; 31.1; 29.1; 24.8; 23.3; 21.3; 19.1; 18.0; 16.6; 13.0. m/e 344 (M+). 2b, ^{1}H-NMR: 5.46 (1H, m, C=CH), 3.56-3.40 (3H, 2 m centred at 3.52 and 3.43, CHHOH), 1.11 (3H, d, J=7.0 Hz, C_{21}-CH_3), 0.84 (3H, s, C_{18}-CH_3). ^{13}C-NMR: 157.5; 124.0; 82.3; 66.7; 57.1; 56.6; 48.6; 47.5; 43.5; 35.3; 35.2; 35.1; 34.6; 33.1; 31.2; 29.1; 24.8; 22.3; 21.3; 19.1; 18.0; 16.6; 13.0. m/e 344 (M+).

7. The aldehyde 3c (^{1}H-NMR: 9.58 (1H, d, J=3.2 Hz, CHO), 1.13 (3H, d, J=6.8 Hz, C_{21}-CH_3), 0.77 (3H, s, C_{18}-CH_3)) was easily converted to the alcohol 3a by direct $NaBH_4$ reduction in methanol. The epimeric alcohol 3b was prepared by the following sequence: epimerization of 3c (s-collidine, reflux, argon, 40h), conventional isolation and medium-pressure LC separation (EtOAc/hexanes) afforded the epimeric aldehyde 3d (^{1}H-NMR: 9.54 (1H, d, J=5.02 Hz, CHO), 1.04 (3H, d, J=3.16 Hz, C_{21}-CH_3), 0.73 (3H, s, C_{18}-CH_3)) in 50% yield. This aldehyde was easily reduced to alcohol 3b as above. Alcohols 3a and 3b are clearly distinguished by NMR. 3a: ^{1}H-NMR: 3.66-3.34 (2H, 2ABq centred at 3.36, J=7.0 Hz, J=10.5 Hz and 3.64, J=3.2 Hz, J=10.5 Hz, CHHOH), 1.05 (3H, d, J=6.65 Hz, C_{21}-CH_3), 0.74 (3H, s, C_{18}-CH_3). ^{13}C-NMR: 82.3; 67.6; 56.3; 56.1; 52.3; 47.9; 43.2; 42.7; 40.0; 38.6; 35.1; 34.9; 33.2; 30.3; 27.6; 24.8; 24.1; 22.6; 21.3; 19.1; 16.6; 12.9; 12.1. m/e 346 (M+). 3b: ^{1}H-NMR: 3.80-3.40 (2H, 2ABq centred at 3.72, J=10.6 Hz, J=3.5 Hz and 3.46, J=10.6 Hz, J=6.9 Hz, CHHOH), 0.96 (3H, d, J=6.7 Hz, C_{21}-CH_3), 0.74 (3H, s, C_{18}-CH_3). ^{13}C-NMR: 82.3; 66.8; 56.4; 56.3; 52.6; 48.0; 43.3; 42.5; 39.6; 37.8; 35.2; 35.0; 33.3; 30.4; 27.5; 24.8; 23.9; 22.6; 21.4; 19.1; 16.5; 13.0; 12.5. m/e 346 (M+).

8. For recent work in this area see: (a) J. Sardina, A. Mouriño and L. Castedo, Tetrahedron Lett., 24, 4480, (1983); (b) Findings presented at the Six Workshop on Vitamin-D. Merano (Italy), 1985. Vitamin D: Chemical, Biochemical and Clinical Update. Walter de Gruyter. 1985.

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