Tetrahedron Letters,Vol.27,No.40,pp 4899-4902,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

APPLICATION OF [2,3]WITTIG AND [3,3]CLAISEN REARRANGEMENTS IN STEROID SIDE CHAIN SYNTHESIS. A HIGHLY STEREOCONTROLLED ENTRY TO EITHER (22S)- OR (22R)-HYDROXY-23-CARBOXYLIC ACID

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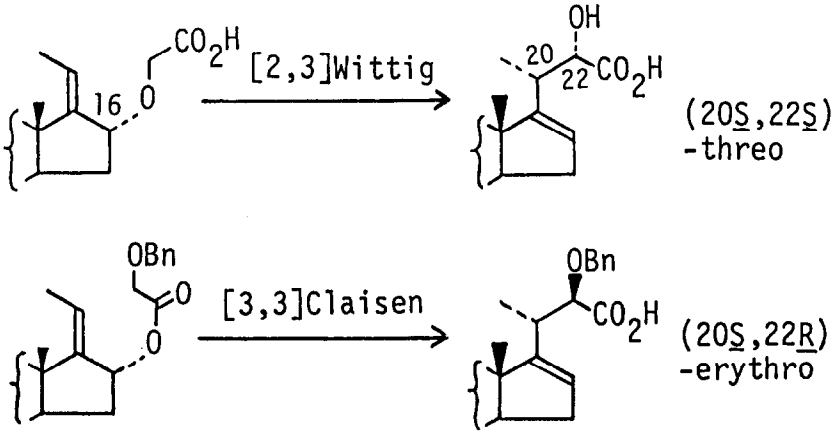
SUMMARY: An efficient approach to either (22S)- or (22R)-hydroxy-23-carboxylic acid side chain is described which relies on the stereochemical transmission via [2,3]Wittig or [3,3]Claisen sigmatropic rearrangement, respectively.

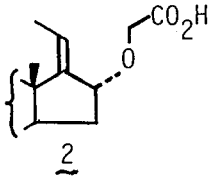
Importance of a number of biologically active steroids possessing a hydroxy functionality at the C-22 position, such as brassinolides[1] and ecdysones,[2] has currently facilitated synthetic efforts toward the stereocontrolled synthesis of (22S)- and (22R)-hydroxy steroid side chains.[3] Recently we have reported a unified approach to either (22S)- or (22R)-hydroxy-23-acetylenic side chain via the [2,3]Wittig sigmatropic rearrangement.[4] In a continuation of the study, we now wish to report a new and efficient approach for the stereocontrolled synthesis of either (22S)- or (22R)-hydroxy-23-carboxylic acid side chain which relies upon the proper use of the [2,3]Wittig and [3,3]Claisen rearrangements as the stereo-directing process (Scheme I). The key feature is that the readily available C-16α chirality is completely and specifically transmitted to the two new chiral centers at C-20 and C-22 with an extremely high degree of either threo or erythro selectivity according to a proper choice of the sigmatropic rearrangement employed.

Scheme I



The requisite acid (2) was prepared in 76% yield from the readily available alcohol (1)[5] via etherification with bromoacetic acid using potassium hydride as the base in 25% hexamethylphosphoramide-tetrahydrofuran (THF). The benzyloxyacetate (3) was easily prepared in 93% yield from 1 via usual acylation with benzyloxyacetyl chloride.

The α-face [2,3]Wittig process of 2 leading inherently to the "natural" 20S/β chirality[6] was carried out under the standard conditions [lithium diisopropylamide (LDA) (2.5 equiv), THF, -78 °C].[7] The dianionic [2,3]-rearrangement was found to afford, after methylation (CH_2N_2), the (22S)-threo product 4 as a single stereoisomer[8,9] in 82% isolated yield. The (E→threo)-selection in this [2,3]Wittig variant is quite surprising in view of the (E→erythro)-selection reported for the crotyloxyacetic acid system[7] (vide infra). On the other hand, the ester enolate [3,3]Claisen process[10] of 3 [(1) LDA (1.5 equiv), THF, -78 °C; (2) trimethylsilyl chloride (1.8 equiv), -78~25 °C] was found to afford, after methylation (CH_2N_2), the (22R)-erythro product 5 as a single stereoisomer[12] in 88% isolated yield. The Claisen product (5) is clearly distinguishable by NMR analysis from its 22-epimer (6) derived from the [2,3]Wittig product (4) ($PhCH_2Br$, Ag_2O, Et_2O).[13] The most definitive distinguishing features are the signal of the benzylic protons: δ 4.40 and 4.66 (AB, J=12.0 Hz) for 5 and δ 4.33 and 4.70 (AB, J=12.0 Hz) for 6.



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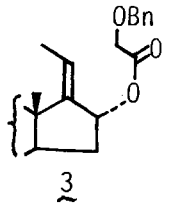

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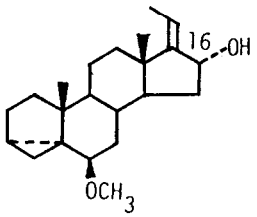

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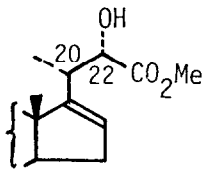

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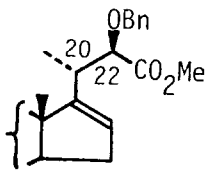

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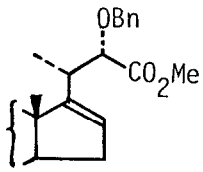

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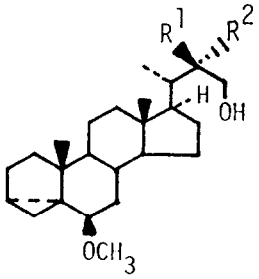
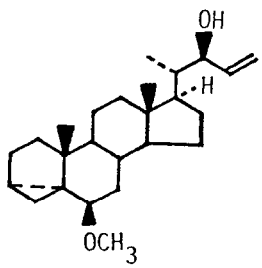


7 : R^1= OCH_2Ph , R^2= H

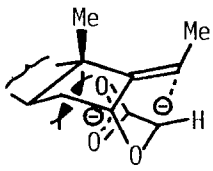
8 : R^1= H , R^2= OCH_2Ph



9

The (22S)-threo configuration of 6 was assigned as follows. Thus, the reduction of 6 ($LiAlH_4$, Et_2O) followed by α-face hydrogenation (H_2, Pd-C, EtOH) afforded the (22S)-alcohol 8 with R configuration at C-17. The alcohol 8 was, in turn, distinguished by TLC and NMR[14] from an authentic (22R)-erythro isomer 7 which was independently prepared from the (22R)-alcohol 9[15] via the benzylation, ozonolysis, and reduction ($NaBH_4$).

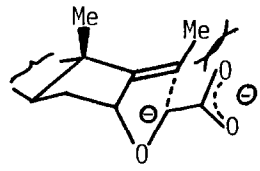
Of mechanistic interest is that the (E→threo)-selectivity observed in the present [2,3]Wittig shift of 2 is in direct contrast to the (E→erythro)-selectivity reported for the genuinely acyclic system (vide supra).[7] We suggest that the unusual threo selection may well reflect the steroidal situation that the conformer A suffers a large pseudo-1,3-diaxial repulsion of the carboxylate group with the cyclopentane ring, which prevails over the gauche repulsion of the carboxylate group with 20-methyl group in B.[16] On the other hand, the observed erythro-selectivity of the [3,3]Claisen rearrangement of 3 can be reasonably understood in terms of the chair-like transition state (C) advanced for the enolate Claisen process of glycolate esters.[10]



A

↓ [2,3]

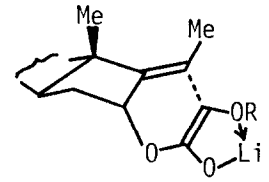
(20S, 22R)-erythro



B

↓ [2,3]

(20S, 22S)-threo



C

↓ [3,3]

(20S, 22R)-erythro

In conclusion, we have now established an efficient sigmatropic approach to either (22S)- or (22R)-hydroxy-23-carboxylic acid side chain from the single alcohol. The rearrangement products can undoubtedly serve as key intermediates for the synthesis of many important side-chain modified steroids.[1,3] Further work along this line is in progress in our laboratory.

Acknowledgment: This research was generously supported in part by the Grant-in-Aid from Ministry of Education, Science and Culture, Japan.

References and Notes

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(2) For the review on ecdysones: K. Nakanishi, "The Chemistry of Natural Products", Butterworths, London, Vol. 7, p 167 (1971).

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(8) 4: NMR ($CDCl_3$) δ 0.44-0.67 (cyclopropyl 3H), 0.79 (Me-18), 1.04 (Me-19), 1.15 (d, J=6.9 Hz, Me-21), 2.75 (m, 6-H), 3.34 (6-OMe), 3.72 (CO_2Me), 4.18 (d, J=5.4 Hz, 22-H), 5.59 (m, 16-H); TLC (silica gel, hexane/EtOAc=2 : 1), R_f=0.42.

(9) M. Koreeda and his co-workers have independently observed essentially the same stereochemical outcome: M. Koreeda, I. A. George, and D. J. Ricca, The 190th ACS Meeting, Chicago, 1985, Abstr. ORG-145.

(10) S. D. Burke, W. F. Fobare, and G. J. Pacofsky, J. Org. Chem., 48, 5221 (1983); J. Kallmerten and T. J. Gould, Tetrahedron Lett., 24, 5177 (1983), We also found that a similar Claisen rearrangement of the methoxy counterpart of 3 provided, after methylation, the corresponding (22R)-erythro ester as a single stereoisomer (ref 11) in 50% yield.

(11) NMR ($CDCl_3$) δ 0.33-0.67 (cyclopropyl 3H), 0.77 (Me-18), 1.00 (Me-19), 1.03 (d, J=6.3 Hz, Me-21), 2.75 (t, J=3.0 Hz, 6-H), 3.33 (6-OMe), 3.38 (22α-OMe), 3.69 (CO_2Me), 3.71 (d, J=6.3 Hz, 22-H), 5.41 (m, 16-H); TLC (silica gel, hexane/EtOAc=2 : 1), R_f=0.50. The 22S-epimer was prepared via methylation (MeI, Ag_2O) of 4; NMR ($CDCl_3$) δ 1.00 (d, J=6.9 Hz, Me-21), 3.67 (d, J=12.6 Hz, 22-H), 3.72 (CO_2Me), 5.50 (m, 16-H); TLC, R_f=0.50.

(12) 5: NMR ($CDCl_3$) δ 0.30-0.67 (cyclopropyl 3H), 0.75 (Me-18), 1.02 (Me-19), 1.11 (d, J=6.9 Hz, Me-21), 2.77 (m, 6-H), 3.32 (OMe), 3.64 (CO_2Me), 3.95 (d, J=7.8 Hz, 22-H), 4.40 and 4.66 (AB, J=12.0 Hz, CH_2Ph), 5.46 (m, 16-H), 7.33 (s, C_6H_5); TLC (silica gel, hexane/EtOAc=4 : 1), R_f=0.50.

(13) 6: NMR ($CDCl_3$) δ 0.30-0.67 (cyclopropyl 3H), 0.83 (Me-18), 1.04 (d, J=8.7 Hz, Me-21), 1.07 (Me-19), 2.77 (m, 6-H), 3.33 (OMe), 3.71 (CO_2Me), 3.94 (d, J=7.8 Hz, 22-H), 4.33 and 4.70 (AB, J=12.0 Hz, CH_2Ph), 5.48 (m, 16-H), 7.32 (s, C_6H_5); TLC (silica gel, hexane/EtOAc=4 : 1), R_f=0.50.

(14) 7: NMR ($CDCl_3$) δ 0.30-0.67 (cyclopropyl 3H), 0.73 (Me-18), 0.94 (d, J=6.9 Hz, Me-21), 1.02 (Me-19), 2.78 (m, 6-H), 3.31 (OMe), 3.60 (m, 22-H and 23-H), 4.64 (s, CH_2Ph), 7.32 (s, C_6H_5); TLC (silica gel, hexane/EtOAc=2 : 1), R_f=0.37. 8: NMR ($CDCl_3$) δ 0.30-0.67 (cyclopropyl 3H), 0.73 (Me-18), 0.97 (d, J=6.9 Hz, Me-21), 1.04 (Me-19), 2.77 (m, 6-H), 3.31 (OMe), 3.56 (br.s, 22-H and 23-H), 4.40 and 4.66 (AB, J=11.7 Hz, CH_2Ph), 7.34 (s, C_6H_5); TLC, R_f=0.44.

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(16) For a general discussion of the transition state model for genuinely acyclic [2,3]Wittig process: K. Mikami, Y. Kimura, N. Kishi, and T. Nakai, J. Org. Chem., 98, 279 (1983).

(Received in Japan 22 July 1986)