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STEREOSELECTIVE SYNTHESIS OF WITHAFERIN A AND 27-DEOXYWITHAFERIN A[1]

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Summary: The first stereoselective synthesis of withaferin A and 27-deoxywithaferin A was described. The key steps in the synthesis involve introduction of the desired substituent at C_{25} and stereoselective construction of the A:B rings by a facile allyl sulfoxide-sulfenate rearrangement.

Among the naturally occurring withanolides,[2a] withaferin A[2b] (1) has been paid the most attractive attention because of its unique structure and its interesting biological activity, e.g. antitumor.[2c] Its structural feature of a 5β,6β-epoxy-4β-hydroxy-2-en-1-one system in the A:B rings and an unsaturated-δ-lactone in the side chain has stimulated the synthetic efforts,[3] although a total synthesis of 1 has not yet been reported. In the previous communication,[4] we reported the synthesis of jaborosalactone A, B, and D via the α-phenylthio lactone 3 from 3β-hydroxy-22,23-bisnorchol-5-enoic acid. We wish to report here the first stereoselective synthesis of withaferin A (1) and 27-deoxywithaferin A[2d] (2) from intermediate 3.

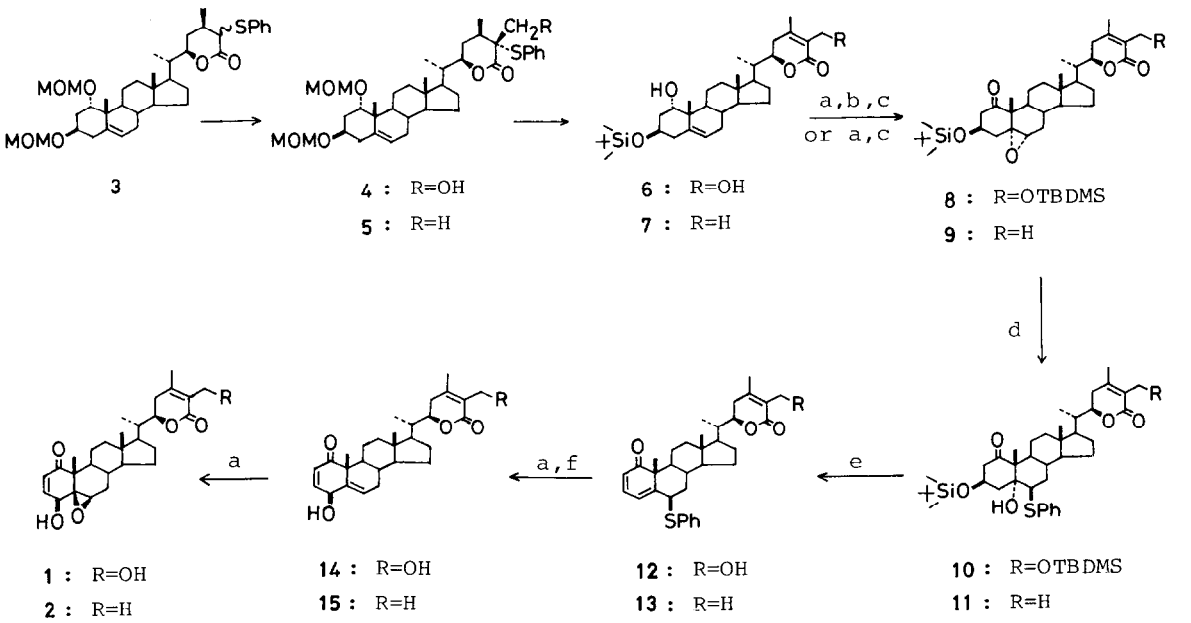
Our basic plan in controlling the functionalities involves two key stages (Scheme 1): (1) preparation of the side chain lactone compounds 6 and 7 having the desired substituents at C_{25} by a suitable alkylation of 3 and (2) stereoselective construction of the 5β,6β-epoxy-4β-hydroxy-2-en-1-one system in the A:B rings by a facile allyl sulfoxide-sulfenate rearrangement of 6β-phenylthio-2,4-dien-1-ones 12 and 13 followed by epoxidation.

Synthesis of the side chain lactone compound 6 from 3 was reported in the previous communication.[4] The deoxy analog 7 could be obtained from 3 by a simi-

lar method. Introduction of the methyl group at C_{25} was accomplished by treatment of the enolate of 3 with methyl iodide, to give a sole product 5. Compound 5 was converted into the desired unsaturated lactone 7 in three steps [desulfenylation,[5] cleavage of the 1,3-bis(methoxymethyl)(MOM) ethers by acid, and selective silylation of the 3β-hydroxy group with tert-butyldimethylsilyl chloride (TBDMSCl)]. The desulfenylation as described earlier[4,5] suported the S configuration at C_{25} of 5.

Introduction of the same functionalities as those of withaferin A into the A:B rings of 6 was carried out as follows. After epoxidation of 6 with m-CPBA, selective protection of the hydroxy group at C_{27} with TBDMSCl was followed by oxidation with pyridinium dichromate(PDC) at C_1, to yield stereospecifically the 5α,6α-epoxy-1-one 8[6] (49% yield, mp 173-174°C). Regio- and stereospecific ring opening of epoxide 8 with thiophenol in the presence of Al_2O_3[7] afforded the 6β-

Scheme 1. Synthesis of Withaferin A (1) and 27-Deoxywithaferin A (2)



a) m-CPBA,$CHCl_3$; b) TBDMSCl, imidazole-DMF; c) PDC, DMF; d) PhSH, Al_2O_3, ether; e) $TsOH \cdot H_2O$, C_6H_6, 60°C; f) excess $P(OMe)_3$, MeOH-THF.

phenylthio-5α-ol 10[6] (37% yield, amorphous solid). Fortunately, upon heating 10 at 60°C in benzene in the presence of p-toluenesulfonic acid hydrate ($TsOH \cdot H_2O$), simultaneous dienone formation and deprotection of the hydroxy group at C_{27} occurred to give the 27-hydroxy-6β-phenylthio-2,4-dienone 12[8] quantitatively. After several unfruitful experiments, a successful allyl sulfoxide-sulfenate rearrangement of the 6β-phenylthio-2,4-dienone system could be accomplished by suitable reaction conditions.[9] Thus, oxidation of 12 with m-CPBA followed by quick treatment of the resulting sulfoxide with excess trimethyl phosphite (10 equiv) at room temperature for 16 hr under nitrogen in a dark room afforded the desired 4β-hydroxy-2,5-dien-1-one 14[8] (52% yield, mp 198-199°C). Epoxidation of 14 with m-CPBA gave stereoselectively withaferin A (1).

On the basis of the same methodology, 27-deoxywithaferin A (2) was also synthesized as follows. Compound 7 was converted to the 5α,6α-epoxy-1-one 9[6] (60% yield, mp 170-172°C) in two steps (epoxidation and oxidation). Ring opening of epoxide 9 with thiophenol afforded the desired 6β-phenylthio-5α-ol 11[6] (51% yield, mp 98-100°C). Upon $TsOH \cdot H_2O$ treatment, the 6β-phenylthio-2,4-dien-1-one 13[8] was obtained from 11. Similar treatment of 13 with trimethyl phosphite as that of 12 furnished the 4β-hydroxy-2,5-dien-1-one 15[8] (64% yield, mp 64-66°C). Epoxidation of 15 with m-CPBA afforded stereoselectively 27-deoxywithaferin A (2).

By direct spectral and chromatographic comparison, these synthetic materials 1 and 2 were identical with authentic samples[10] of withaferin A and 27-deoxywithaferin A, respectively.

References and notes

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(6) The ring opening products 10 and 11 showed the C_6 proton signals at 3.13 ($W_{1/2}$ 6 Hz) and 3.17 ($W_{1/2}$ 6 Hz), respectively, which indicated both of the precursors 8 and 9 were the 5α,6α-epoxides.

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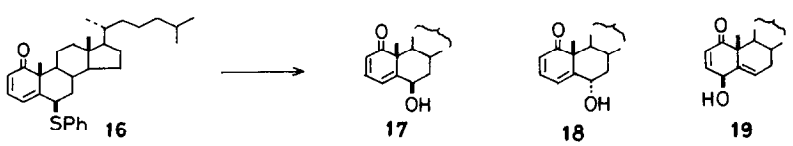
(8) Partial ^{1}H NMR: 12; δ 4.09 (1H, br d, J=6 Hz, $C_{6\alpha}$H), 5.75 (1H, d, J=6 Hz, C_4H), 5.86 (1H, d, J=10 Hz, C_2H), and 6.71 (1H, dd, J=6, 10 Hz, C_3H). 13; δ 4.11 (1H, br d, J=6 Hz, $C_{6\alpha}$H), 5.79 (1H, d, J=6 Hz, C_4H), 5.89 (1H, d, J=10 Hz, C_2H), and 6.75 (1H, dd, J=6, 10 Hz, C_3H). 14; δ 4.60 (1H, d, J=4 Hz, $C_{4\alpha}$H), 5.93 (1H, d, J=10 Hz, C_2H), 5.94 (1H, m, C_6H), and 6.74 (1H, dd, J=4, 10 Hz, C_3H). 15; δ 4.60 (1H, d, J=4 Hz, $C_{4\alpha}$H), 5.91 (1H, d, J=10 Hz, C_2H), 5.93 (1H, m, C_6H), and 6.73 (1H, dd, J=4, 10 Hz, C_3H).

(9) There have been many reports on the synthesis of allyl alcohols by [2,3]-sigmatropic allyl sulfoxide-sulfenate rearrangement in an isolated double bond but only a few reports in a conjugated double bond. See, for example, J. P. Corbet and C. Benezra, J. Org. Chem., 46, 1141 (1981). However, there has been no report on the rearrangement in a conjugated 2,4-dienone such as 12. An interesting result was observed in the rearrangement of a model compound 16. In a presence of light and oxygen, treatment of the sulfoxide of 16 with either trimethyl phosphite or piperidine gave the 6β-hydroxy compound 17 as a major product along with the 6α-hydroxy isomer 18. In order to obtain the normal rearrangement product 19, it was necessary to avoid light and oxygen. Detailed investigation on this interesting rearrangement is in progress.



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