

STEREOSELECTIVE SYNTHESIS OF WITHAFERIN A AND 27-DEOXYWITHAFERIN A¹

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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 C₂₅ 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 5 β ,6 β -epoxy-4 β -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 3 β -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**.

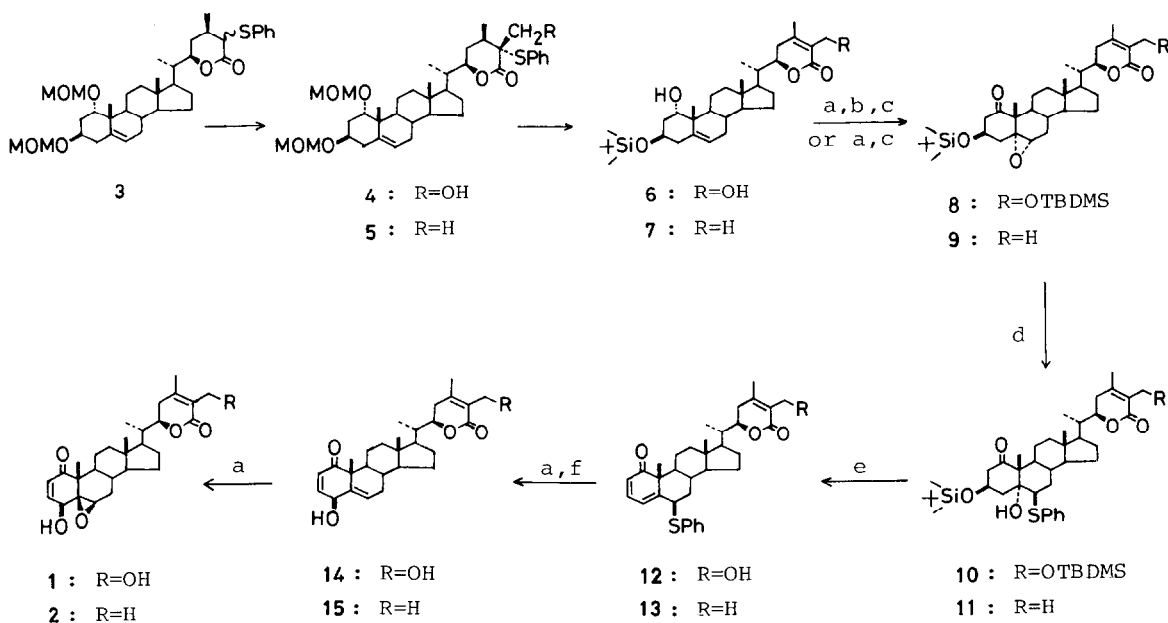
Our basic plan in controlling the functionalities involves two key stages (Scheme 1): (1) preparation of the side chain lactone compounds **6** and **7** having the desired substituents at C₂₅ by a suitable alkylation of **3** and (2) stereoselective construction of the 5 β ,6 β -epoxy-4 β -hydroxy-2-en-1-one system in the A:B rings by a facile allyl sulfoxide-sulfenate rearrangement of 6 β -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 C₂₅ 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 3 β -hydroxy group with *tert*-butyldimethylsilyl chloride (TBDMSCl)]. The desulfenylation as described earlier^{4,5} supported the S configuration at C₂₅ 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 C₂₇ with TBDMSCl was followed by oxidation with pyridinium dichromate (PDC) at C₁, to yield stereospecifically the 5 α ,6 α -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 Al₂O₃⁷ afforded the 6 β -

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



phenylthio-5 α -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·H₂O), simultaneous dienone formation and deprotection of the hydroxy group at C₂₇ occurred to give the 27-hydroxy-6 β -phenylthio-2,4-dienone **12**⁸ quantitatively. After several unfruitful experiments, a successful allyl sulfoxide-sulfenate rearrangement of the 6 β -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 4 β -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 5 α ,6 α -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 6 β -phenylthio-5 α -ol **11**⁶ (51% yield, mp 98-100°C). Upon TsOH·H₂O treatment, the 6 β -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 4 β -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 samples¹⁰ of withaferin A and 27-deoxywithaferin A, respectively.

References and notes

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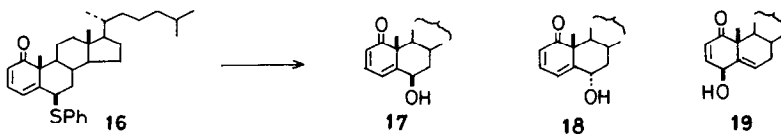
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(6) The ring opening products **10** and **11** showed the C₆ proton signals at 3.13 (W_{1/2} 6 Hz) and 3.17 (W_{1/2} 6 Hz), respectively, which indicated both of the precursors **8** and **9** were the 5 α ,6 α -epoxides.

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(8) Partial ¹H NMR: **12**; δ 4.09 (1H, br d, J=6 Hz, C_{6 α} H), 5.75 (1H, d, J=6 Hz, C₄H), 5.86 (1H, d, J=10 Hz, C₂H), and 6.71 (1H, dd, J=6, 10 Hz, C₃H). **13**; δ 4.11 (1H, br d, J=6 Hz, C_{6 α} H), 5.79 (1H, d, J=6 Hz, C₄H), 5.89 (1H, d, J=10 Hz, C₂H), and 6.75 (1H, dd, J=6, 10 Hz, C₃H). **14**; δ 4.60 (1H, d, J=4 Hz, C_{4 α} H), 5.93 (1H, d, J=10 Hz, C₂H), 5.94 (1H, m, C₆H), and 6.74 (1H, dd, J=4, 10 Hz, C₃H). **15**; δ 4.60 (1H, d, J=4 Hz, C_{4 α} H), 5.91 (1H, d, J=10 Hz, C₂H), 5.93 (1H, m, C₆H), and 6.73 (1H, dd, J=4, 10 Hz, C₃H).

(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 6 β -hydroxy compound **17** as a major product along with the 6 α -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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